Public Consultation on Proposed Amendments to the Poisons Standard (codeine)

Notice under subsections 42ZCZL of the Therapeutic Goods Regulations 1990 (the Regulations)

The delegate of the Secretary to the Department of Health publishes herein all valid public submissions made in response to the invitation for public submissions on the proposed amendments to the Poisons Standard. In order to give due consideration to the submissions received in the interim decision public consultation period and to seek further advice from the Advisory Committee on Medicines Scheduling (ACMS) at its March 2016 meeting, the medicines scheduling delegate on 18 November 2015 deferred a final decision on the proposed codeine re-scheduling. The TGA then sought further advice and public comment on several options for codeine re-scheduling via an additional consultation period that was open from 10 December 2015 through 29 January 2016. These submissions were considered by the medicines scheduling delegate when making their final decision.

In accordance with the requirements of subsection 42ZCZL of the Regulations these submissions have had their confidential information removed.

Materials claimed to be commercial-in-confidence were considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015), issued by the Australian Health Ministers' Advisory Council. The SPF is accessible at https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.

[redacted] [redacted]
To: Medicines Scheduling
Subject: Proposed Amendments to the Poisons Standard (Medicines) - Codeine, ACMS March 2016
Date: Thursday, 14 January 2016 4:28:47 PM
[redacted] [redacted]

Please find below my submission to the proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS), March 2016.

I strongly oppose both proposals to amend the schedule 3 codeine entry. I oppose both reducing the reduce the pack size to not more than 3 days' supply and I also oppose the interim decision to up-schedule to Schedule 4. However if given the choice I would prefer reducing the pack size instead of changing to Schedule 4.

I do not support a real-time monitoring system as I don't believe that privacy would be assured, but I see it as a lesser of two evils.

I would prefer that the pack size instead be increased to its former levels (not restricted to 5 days). It has already been demonstrated that this reduction to 5 days was not efficacious in its goals so there is no reason to keep this reduction. By reducing it further to three days you are essentially doing the same thing and expecting different results.

The TGA submission site at https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-codeine suggested that respondents assess the likely benefits and costs and attempt to quantify them. I have attempted to quantify the cost of changing codeine to schedule 4 below.

GP visit: $42.95 out of pocket, net after medicare rebate ($80 gross fee)

Approximate cost of 1.5 hours of work forgone due to having to attend a GP (includes waiting time and transit): $63

Total cost to my household: $105.95 per visit

Cost to medicare: $37.05 rebate (not including processing fees and staff FTE).

At a rate of 6 visits per year (a visit every two months):

$635.70 annual cost to my household

$222.30 annual cost to Medicare

This is assuming that it only takes 6 GP visits per year to manage this condition, when in my experience it takes a lot of time, distress and GP visits due to cycling through various medications and treatments to treat pain conditions.

Any changes to codeine scheduling is likely to impact negatively on the more vulnerable members of the community. For example:

"Women are more likely to seek treatment for chronic pain, but are also more likely to be inadequately treated by health-care providers, who, at least initially, discount women's verbal pain reports."[1]

On other matters, I disagree with the amount of personal information you now require for submissions. Several people like myself are likely to have made multiple submissions over this issue and may not have noticed the change in submission policy between this consultation and the previous one. The new measures seem to disproportionately affect the common consumer's motivation to make a submission. It seems designed to evoke the response the TGA would prefer e.g. nil comment from concerned consumers who seem to be the majority opposing this proposed amendment. Any changes in submission policy should not have been made in the middle of an continuing issue.

Please find my cover sheet attached.

Sincerely Yours

Concerned Australian citizen.

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[1] Diane E. Hoffnann and Anita J. Tarzian, "The Girl Who Cried Pain: A Bias Against Women in the Treatment of Pain," The Journal of Law, Medicine & Ethics, 29:1.

[redacted]

8 Feb 2016

Medicines.Scheduling@tga.gov.au

Re: Consultation: Proposed amendments to the Poisons Standard (Codeine)

[redacted]

[redacted] believes that any changes to the scheduling of medicines should be driven by evidence and underpinned by the principles of patient safety.

[redacted] supports:

- option (c) for Schedule 2 (cough and cold medicine preparations); and
- option (b) for Schedule 3 (including, but not limited to codeine containing analgesics).

[redacted] believes if the final decisions are to not up-schedule products containing codeine to Schedule 4, and reduce the pack sizes to not more than 3 days' supply, we suggest the following additional requirements:

- these products are supplied as pharmacist only medicines and are dispensed, individually labelled and recorded by the pharmacist; and
- are included in a national *Electronic Recording and Reporting of Controlled Drugs* (ERRCD) system.

[redacted]

[redacted]

16th January 2016

To the TGA submissions officer,

Re: 'Proposed Amendments to the Poisons Standard (Medicines)'

I am writing to register my disagreement with aspects of the Proposed amendments to the Poisons standard: Codeine.

I disagree making otc codeine products a prescription only drug, this is based on several reasons;

I am a migraine sufferer, these migraines are based around my menstrual cycle and have not been affected nor controlled by standard migraine medication, dietary changes nor other therapies. Symptomatic treatment for acute pain is currently my only option.

Panadeine, one of the over the counter (otc) drugs that will be affected by the proposed changes has been the only medication that reduces the severe pain associated with migraine for me. Making this medication prescription only will be a huge inconvenience as attending doctors appointments is already incredibly difficult on my schedule ([redacted]).
My story is not unique, millions of busy Australians manage acute pain using similar products and utilise these products responsibly. It is unreasonable that responsible persons using otc codeine medication will be burdened so heavily by needing a doctors appointment for acute pain relief.

I have 2-3 migraines a month with photophobia, phonophobia and nausea (without aura) lasting around 16 hours each and use maximum of 8 tablets per migraine. This equates to around 24 tablets a month. If I cannot get to a doctor, rescheduling otc codeine means the potential of suffering 16 hours of severe pain where I can barely function.

Rescheduling this medication due to the very few people that abuse this medication does not make sense. Whilst I do not belittle those affected negatively by overconsumption of otc codeine medications it is well established that prescription only does not stop nor reduce addiction nor overdose.

The [redacted] previous submission on this topic states that those who chose to abuse these medications will simply doctor shop as they already do with stronger codeine medications that are already prescription only. Once at a GP it is not unreasonable to believe they may request stronger medication than required since the effort has already been made to see a GP, why settle for a relatively weak medication such as Panadeine for example.

The Australian Bureau of statistics reports that 82% of intentional and accidental overdose deaths are already due to prescription medication. Dobbin, 2014 reports that oxycodone is now the seventh leading drug prescribed in general practice. The number of opioid prescriptions subsidised by the Pharmaceutical Benefits Scheme (PBS) increased from 2.4 million in 1992 to 7 million in 2007 and will continue to rise as more medications are rescheduled.

Amanda Roxburgh, Wayne D Hall, Lucinda Burns, Jennifer Pilgrim, Eva Saar, Suzanne Nielsen and Louisa Degenhardt, in their paper "Trends and characteristics of accidental and intentional overdose deaths in Australia" report that:

- The 83.7% codeine related deaths between 2000-2013 were attributed to *multiple drug toxicity including injecting drug use.*

The large proportion of deaths noted above will not be reduced by rescheduling otc codeine to prescription only medication. These persons already had access to multiple prescription and illicit drugs and it is not unreasonable to assume they will find other sources or drugs where one is not easily available.

- 8.5% of codeine related deaths in this study were attributed to *underlying health causes such as heart disease.*

- 7.8% of deaths were actually attributed to codeine toxicity

Australian Bureau of statistics date suggest that 82% (i.e. 6.4%) of the 7.8% codeine deaths were from prescription medications, leaving a very small number of deaths primarily related to over the counter medications (1.4%).

The rise in accidental overdose via otc codeine products needs to be dealt with via better education at point of sale and by the more practical suggestion of a real time monitoring system for pharmacists to be able to realistically reduce over consumption.

As the statistics clearly show prescription medications are already the major source of medications used in intentional and accidental overdose.

The proposed rescheduling of otc codeine products to prescription only to reduce harm is a fallacy. It is unlikely to achieve the intended goal and consequently place a huge burden on responsible persons using this medication and on an already heavily burdened Medicare system. This burden is of great concern at a time when the government is continuing to cut funding to health.

Please, for the sake of the millions of Australians using over the counter codeine products responsibly, do not reschedule otc codeine medications, instead introduce a real time monitoring system for pharmacists.

Yours sincerely,

[redacted]

References

Dobbin, M., Pharamceutical drug misuse in Australia, Australian Prescriber, 2014; 37:79-81

Roxburgh. A., Hall, W.D., Burns. L., Pilgrim. J., Saar. E., Nielsen. S., and Degenhardt. L., "Trends and characteristics of accidental and intentional overdose deaths in Australia" MJA, 2015

[redacted]

15/01/2016

Therapeutic Goods Administration
136 Narrabundah Lane
SYMONSTON ACT 2609
By email: medicines.scheduling@tga.gov.au

To whom it may concern

Re: Proposed amendments to the Poisons Standard (Codeine)

Currently codeine is provided virtually unmonitored or unregulated in pharmacies while other opioids are only legally accessible through prescriptions from medical practitioners.

As a GP and opioid substitution therapy prescriber I frequently see people getting into trouble with over-the counter (OTC) codeine, and it is difficult to treat patients with codeine dependence because codeine is easily available. I do not think many people are aware of the risk of dependence or other drug-associated harms associated with codeine.

The current scheduling structure deters pharmacists from refusing to supply opioids regardless of whether or not they feel compromised or pressured. The TGA can thus make it easier for health care providers to protect people from opioid-related harms.

For these reasons I support regulatory restrictions on access to codeine, which may include clearer labelling of the risks on the packaging and/or codeine's rescheduling to an S4 medication.

Yours sincerely

[redacted]

21 January 2016

To Whom It May Concern:

While it is most certainly tragic that ill-informed, misguided, or intellectually challenged individuals have harmed themselves (including death) by abusing over-the-counter products that contain codeine, the current plans by the TGA will not help stop those's same individuals from further harming themselves. Codeine is not a new drug and the effects and side effects of it s overuse/ abuse are well-known and understood by the general populace; especially those of us who have taken products containing codeine as necessary for conditions which afflict them.

The current legislation changes proposed by the TGA will do little to actually prevent those mentioned in the first paragraph above from harming themselves. What will happen though is that those of us who do not abuse products with codeine in them will be forced to go to the doctor for other pain relief medications and/or more frequent trips to the chemist for those products containing codeine. For that matter, what is a "three-day supply”? Is at 12? Is that 24? Is is 36? This is so subjective that it's almost laughable.

I strongly urge the TGA to consider the harm that these currently proposed decisions will foist those of us in the public who do not abuse these drugs and how that this action being considered will also cost the system more, not less money than it does now (in more frequent trips to the one’s GP and chemist).

I strongly urge the TGA to stay with the system as it is today (available over the counter upon request) which meets the needs of the many who do not abuse drugs with codeine in them as opposed to the few who don't seem to be able to control themselves or are incapable understanding the potential danger of abuse.

[redacted]

Submission on Proposed Amendments to the Poison Standard regarding Codeine

[redacted]

[redacted]

Codeine dependence has become an increasing part of my workload over the past ten years. I generally now have 5-6 patients on a buprenorphine maintenance program at any one time for codeine dependence (out of a total of 180 pharmacotherapy patients).

[redacted] 15 of my codeine patients [redacted] 5 were male, 10 were female. They obtained their codeine compounds over the counter at pharmacies- most commonly buying Mersyndol . 40% of this group had coexisting psychiatric diagnosis of depression requiring treatment, 27% had an anxiety disorder. Some of these patients admitted that that codeine gave them some relief of these symptoms. Similar high rates of mental health problems were found in other studies of codeine dependent people in Australia (Nielson S, Cameron J et al 2010; Nielson S, Murnion B, Dunlop et al 2015).

In my daily work with drug addicted people I try to apply harm reduction strategies whenever possible, as these generally have a strong evidence base to back them up.

The TGA has recommended that codeine be rescheduled as a S4 drug, requiring a doctor's prescription. I recognise that some people abuse codeine and as a result suffer serious medical consequences. But I have some doubts that rescheduling of codeine is a sound public health policy and is necessarily a harm reduction strategy. This concern is based on:

By far the majority of the population, I think, uses codeine compounds appropriately for short term relief of moderately severe pain eg occasional severe headache, dental pain, a flare up of arthritis. (? data source) . If these codeine compounds were rescheduled, I believe that many would not make time to get an appointment to see their GP for a script, and would put up with the pain or use other less effective treatments. If they did see their doctor, it is quite possible that the doctor would feel that further tests including scans are necessary to rule out other rare causes of such a pain. All this would lead to under treatment, over investigation and undue concern of medicolegal risk.

There is also a risk I believe that if codeine compounds are made more difficult to obtain that some at-risk patients will turn to other drugs for pain relief, especially alcohol which is widely available or perhaps cannabis or even psychostimulants. The high coexistence of mental health disorders in this patient group makes this drug seeking a possibility, with a high risk of an outcome of more severe adverse effects than even codeine can cause.

I prefer to see greater restriction on quantities of supply of codeine (eg to a three day supply), labelling of boxes with a warning of risk of addiction and bowl inflammation and better monitoring at the point of sale by the pharmacist, similar to that which occurs for ephedrine compounds.

Submission on Proposed Amendments to the Poisons Standard (Codeine)

January 2016

Introduction

[redacted] opposed the proposal to reschedule all codeine at currently are on Schedules 2(S2) and 3(S3) which went to the August meeting of Advisory Committee on Medicines Scheduling (ACMS). We also opposed the interim delegate's decision to accept the recommendations from ACMS to reschedule those products.

We welcome the opportunity to provide comments on the new options that will be considered by ACMS in March 2016.

Issues

[redacted] in response to the delegate's interim decision – [redacted] for different treatment for the Schedule 2 codeine products which are used in preparations for coughs and colds and those on Schedule 3. We are pleased to see that the current proposals make that distinction.

Schedule 2 (cough and cold medicine preparations)

a. ***Proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; or***
b. ***Proposal to upschedule Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; or***
c. ***Retain the interim decision to upschedule to Schedule 4.***

[redacted] believes that Option b is the best option in terms of balancing the need to minimise risk of harm and addiction whilst still ensuring reasonable access and an affordable price.

We agree that these products have low dosages of codeine and the potential for them to do harm is less than with the S3 analgesics. However there is still some risk and we think consumers need a higher level of protection than that offered by Schedule 2. We do not think that any products containing codeine should be freely available for consumers to just pick up off the shelf.

We support the addition of warning labels on front of pack for such products but believe that is not sufficient information for consumers. By moving these products to S3 we ensure that the consumers need for and suitability for such a product is assessed by a pharmacist. This would give the pharmacist the opportunity to explain that there are other non-codeine products that are available and also go over the potential problems with using a codeine product.

By moving the products to Schedule 3 they would also come under the advertising requirements for Schedule 3 which preclude advertising directly to consumers except for some well-defined exceptions. Given the concerns about addiction and potential harm [redacted] believes that products containing codeine should not be advertised directly to consumers and think the move to Schedule 3 gives some added protections in that regard.

Limiting pack size to 3 days has merit because it makes it clear to consumers that the products should only be used for a short period of time. However people could still purchase larger quantities buy going to multiple pharmacies and there is no way of tracking this. This will change when the real time recording system for Schedule 3 products which has been developed by the Pharmacy Guild is rolled out nationally.

Schedule 3 Analgesics containing codeine

a. ***Proposals to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; or***
b. ***Retain the interim decision to upschedule to Schedule 4***

[redacted] believes Option a is the better option in terms of balancing the need to minimise risk of harm and addiction whilst still ensuring reasonable access and an affordable price.

We believe the majority of users of codeine analgesics, particularly those using it for ongoing or chronic pain, are using responsibly and as part of a pain management plan. There is a real shortage of comprehensive pain management services in Australia and we think that making it more difficult for people to access this pain relief is not acceptable.

We support the move to restrict supply to 3 days as it goes some way to addressing the fears about misuse and addition. [redacted] acknowledges that there is a significant body of evidence that shows the problems that can arise from the use of OTC codeine analgesics, particularly when it is misused. We share the Faculty of Pain Medicine's and other clinicians concerns about this being a growing problem. Whilst people will still be able to shop around to get larger supplies, the introduction of real time recording and reporting will allow pharmacists to see if the consumer has bought from other pharmacies and so make a decision on whether or not to supply at that time.

We also know that misuse is not restricted to over the counter purchases as we know people also misuse prescription products. We do not believe rescheduling on its own will address the issue of codeine misuse and are concerned that Government might think that it will ~~and so not~~neglect to resource other efforts to reduce harm and addiction.

It is possible that moving these products to Schedule 4 could actually encourage their use as it is likely for concessional patients that the PBS co-payment will be lower than the current OTC price.

As with the cough and cold medicines we think it is it important that all codeine products have warnings on the packages about the potential harm of codeine and the risk of addiction.

Conclusion

[redacted] does not support the rescheduling all codeine products to ~~o~~ Schedule 4. We support limiting products size and putting warnings on all packets along with moving current Schedule 2 products to Schedule 3.

[redacted]

The Delegate
Therapeutic Goods Administration
medicines.scheduling@tga.gov.au

Dear Sir/Madam

Thank you for the opportunity to provide comment on the proposed scheduling change to codeine. It has been a useful exercise to consider ramifications for [redacted] and the general public.

The case for removing codeine products from over the counter (OTC) Schedules 2 and 3 is clearly laid out in the record of reasons from the Advisory Committee Medicines Scheduling (ACMS) meeting and the Delegate's interim decision.

Salient points from the Interim decision webpage of 1 October 2015 are:

- OTC products are intended for acute self- limiting pain, but they are clearly being used inappropriately for chronic pain.
- Codeine shares the properties of other opioid analgesics and is capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.
- The potential for severe adverse effects at 'usual' doses in ultra-rapid metabolisers is such that codeine appears to be an unsuitable candidate for OTC availability, with either S2 or S3 scheduling. The Australian population possesses a highly variable ability to metabolise codeine into morphine and very few individuals are aware of their own metaboliser status. I note the increased migration of persons from North Africa and the Middle East in recent years which leads to the conclusion that there is now an increased number of people at potentially at risk from codeine products.
- There is no convincing evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen.
- However it is known that Codeine is emerging as an increasingly commonly used drug of abuse internationally and in Australia.

[redacted]

[redacted]

- Codeine is a prescription only medicine in at least 13 European countries, and other significant jurisdictions such as the USA, Hong Kong, Iceland, India, Japan, Russia and the United Arab Emirates.

I understand Codeine containing analgesics (CCAs) were up-scheduled to Schedule 3 in 2010, but there has been no initiative to include CCAs into Project Stop prior to the application to up-schedule codeine to S4. This leaves community pharmacists without means to check on prior purchases of codeine products by customers, and consequently unable to monitor objectively for potential dependence.

It is expected that there will be additional demand on general practitioners, drug and alcohol services and pain services consequent to removal of OTC codeine. Education is needed at the level of general practice to reduce harms associated with codeine use, and to assist GPs assess this client group and appropriately treat or refer.

Yours sincerely

[redacted]

[redacted]

[redacted]

Therapeutic Goods Administration
Medicines.Scheduling@tga.gov.au

28 January, 2016

Dear Sir/Madam,

re: Consultation: Proposed amendments to the Poisons Standard (Codeine). Proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS), March 2016.

The following [redacted] submission addresses the proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS), March 2016, specifically, the proposed amendments to the Poisons Standard (Codeine), dated 11 December, 2015.

Sincerely,

[redacted].

Proposed amendments

I strongly oppose the Schedule 2 (cough and cold medicine preparations) proposals for codeine:

a. Proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
b. Proposal to up-schedule the Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
c. Retain the interim decision to up-schedule to Schedule 4.

I strongly oppose the Schedule 3 (including, but not limited to codeine containing analgesics) proposals for codeine:

a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR
b. Retain the interim decision to up-schedule to Schedule 4.

Assessed impact

The arguments against rescheduling low dose codeine to Schedule S4 are the increase in time and money cost when seeking to visit a general practitioner. This has been manifestly articulated in a number of submissions against proscription of OTC codeine: when one has pain and stands in need of treatment, it beneficial to obtain access immediately to options for pain relief.

The inconvenience of having to schedule an appointment to visit a general practitioner and the cost involved in that action, adds a burdensome time and monetary cost which is currently not incurred. One has to book an appointment out of hours for a full-time employed person, pay an above Medicare cost for a non-bulk-billed practitioner, then travel to and visit the practitioner to obtain a source of pain relief. By then the need is over. It may prove difficult to persuade a practitioner, when one does not have pain, on the need for codeine for future occasions. The doctor may require fees of about $50 or more, and the cost of codeine may increase under such a regime. In addition there is the non-quantifiable cost of one's time and the inconvenience to book and visit a doctor and then a pharmacist. This will increase the cost and reduce the standard of living to responsible users of codeine. Responsible users of codeine will have to suffer from untreated pain, if the cost and time to access codeine is increased.

[redacted] resulted in a fractured skull, broken arm and damaged sternum, the latter, a long-term illness, creates ongoing back pain, due the inability of the sternum to hold the ribs in place. It causes a twisting of vertebrae and back pain. Years of osteopathic and chiropractic help has not resolved the problem. A couple of visits to an orthopaedic surgeon suggested that the result from an operation to resolve the problem may be worse than the current problem. Pain management for life was the suggested solution. Over the last [redacted] years, a combination of aspirin (or similar) and (8 mg) codeine has been immensely beneficial, in addition to regular exercise [redacted] Migraines were common in the years after this accident, [redacted]. In more recent years, prescription [redacted] has assisted when the pain relief sought from codeine, due to pain caused by skeletal or structural

twisting, has not been sufficient.

The time and money cost of having to visit a general practitioner to obtain [redacted] is too much of a cost for one who uses the product responsibly. Add to this another appointment for obtaining access to codeine and the time and money cost would increase.

This proscription would create unintended consequences. A self-interested person, seeking relief via codeine at the time when pain is paramount, would seek alternatives. Some of these could be illicit drugs which could be used to self-medicate; others would utilise emergency departments for pain relief; or the worst case scenario is to suffer with pain, which impacts a person's wellbeing. Intense, persistent pain has deleterious effects. More time off work adds costs to an employer.

In my case, [redacted] The real benefit is access to codeine – sometimes just one 8mg tablet – which relieves tension and pain, and allows me to continue to operate with reduced or minimal pain. Without that I would be literally bed-ridden, not for hours, but at a minimum one day, or more. It provides the capacity to continue to function at close to normal due bouts of pain. Writ large, the social impact of pain will introduce economic penalties to the lives of employees and their employers.

Suggested improvements

As noted, I do not support the amendments. In particular, I reject the interim decision to up-schedule Schedule 2 (cough and cold medicine preparations) to Schedule 4. I reject the interim decision to up-schedule Schedule 3 (including, but not limited to codeine containing analgesics) Schedule 4.

The *status quo* is acceptable. The existing constraints are adequate.

The arguments against rescheduling low dose codeine to Schedule S4, or rescheduling it, for the almost 100 per cent of people who responsibly use both (1) cold medicine preparations and (2) codeine containing analgesics include the increase in inconvenience, time and money cost when seeking to visit a general practitioner. It will also increase the cost of medication. Schedule S3 codeine is currently an effective treatment for those with chronic pain; limiting access for genuine users will decrease the standard of living and quality of life.

The point of issue does not include the responsible users who it seems are being targeted to receive the penalty for the miniscule number of irresponsible, excess users of codeine. The intent then is to punish the responsible and in so doing through proscriptive regulation to limit access to those who abuse the system. It seems that even with S3 pharmacy only access to codeine, anecdotal evidence indicates that the same minimal number of abusers continue to gain access to it and abuse its use. Thus it is illogical.

Proscriptive regulation that imposes a heavy burden on the many to somehow and only probably preclude the few from abusing codeine is also unjust. It shifts the burden of

responsibility for abuse from those individuals via the TGA to the responsible many. Thus is it unjust and unfair.

The focus should be on the irresponsible abusers. It is easy to perceive that such excessive and proscriptive regulation on access to codeine is designed as a probable solution. There is no guarantee that it will preclude access. Thus the proposal fails to address the cause of the problem.

If the evidence indicates that there are users who access and abuse codeine, then these parties should be treated as they are, addicts, and treated as such. If it becomes apparent that there is evidence, then they can be treated at the point when evidence of their abuse is obvious. Precluding access to codeine will lead to ways and means for the abusers to shop around for doctors who would be willing to prescribe their access to codeine, as they currently do now with pharmacists.

A study into irresponsible doctors who abuse their office by providing access to prescription only drugs who currently doctor shop to feed their current addition to prescription-only drugs would be enlightening. The [redacted] presents itself in this debate as those on the side of the angels, whose members morally and comprehensively discharge their office, who will no doubt ensure this problem is solved, at a significant pecuniary benefit to their members and economic and social cost to a responsible public.

The social equation to prohibit over the counter access to codeine involves weighing the current benefits to the many responsible against the benefits that possibly and may come from restricting access to potential abusers. The social and economic cost impact on the responsible many outweighs the benefits to the irresponsible few.

The decision of those who abuse codeine is intentional. Addicts know that they abuse the drug and undertake many of the deceitful methods to gain access to excess quantities of codeine: the use of multiple pharmacies; purchase of a number of days use at a time; note those pharmacies where there are individual staff members who allow easy access to purchase; limit access to the same pharmacies too often; buy lower quantities; avoid internet purchases due to record keeping; and opportunistically purchase. None of this will change under rescheduling.

In the extreme, no state-imposed bureaucratic system will preclude an individual's attempt to undertake action which may be physically harmful. An argument to suggest that the effort to do so will be worthwhile is fallacious. It does not capture and deal with the original cause, the intentional person.

The rational alternative should be to assist help those with an addiction. This could come in the form of increased education to alert those who abuse codeine as well as more available access to treatment for those with such addictive conditions.

To whom ever it may concern,

i wish to add my voice to the tide of objections to the modification of the over the counter availability of codeine combination products. As it seems there are many Australians who responsibily use codeine products, of which I am one, why would we need to be restricted in our pain relief of choice by a few who's choice it is to abuse this product? As the public is already questioned and vetted by the pharmacist, I feel that trips to the Dr for a script is only a means to revenue raise for the Drs, and it will cost the tax payer many millions, as medicare must fund increased trips to the Dr by those who choose codeine.

This is a move by the committee at the TGA who wish to "nanny" us further in our daily life choices, and approved by the AMA as it will inevitably mean more income for their members. The only winners here will be the doctors.

Broken down into component parts, and assessed in this way, it is difficult to see who else will benefit. Those that already choose to abuse codeine will find something else to abuse. Are you going to lock all drugs up as prescription only?

Yours sincerely,

[redacted]

[redacted]

[redacted]

Email: medicines.scheduling@tga.gov.au

RE: Proposed Amendments to the Poisons Standard (Medicines)

[redacted] I strongly support the deletion of codeine from schedule 3 and rescheduling to schedule 4 due to potential issues of morbidity, toxicity and dependence while being of limited analgesic benefit.

I will outline my reasons below; such a reclassification would also bring Australian legislation into line with those of other countries such as the United States, Sweden and Germany, where all codeine containing medications appropriately are scheduled as prescription-only by a medical practitioner.

The current Australian classification (which as far I know is only similar to the Canadian one among all developed countries) is enabling provision of a drug of abuse over the counter and therefore unacceptable from a public health, from a harm minimisation and from a drug safety point of view, while not offering the public any advantages with regard to access to effective analgesics for mild to moderate pain.

- **Codeine is a poor analgesic with unpredictable efficacy and risks associated even with its appropriate use**

Codeine (methylmorphine) is the inactive prodrug of morphine and requires metabolic conversion to morphine by Cytochrome P450 2D6 to be an active analgesic[1]. This metabolism is dependent on the phenotype of the individual patient with a range from practically no analgesic effect in extreme slow metabolisers to achieving high plasma concentrations of morphine in fast metabolisers. This means that in such fast metabolisers potentially toxic morphine concentrations can be reached; deaths have been reported in children who are fast metabolisers and babies of fast-metabolising mothers who are breast-feeding. These finding have appropriately led to major restrictions on the use of codeine in such high-risk groups. As fast metabolisers are much more common among patients of Asian and even more so North African descent, the risk for the rising number of such patients in the Australian population increases. This is further complicated by the fact, that nearly nobody in the population knows their phenotype of CYP 450 2D6.

[1] Lotsch J (2005) Opioid metabolites. *J Pain Symptom Manage* **29**(5 Suppl): S10-24.

This is increased risk of toxicity is unnecessary as codeine on its own is a poor analgesic (and the efficacy depending on the phenotype of CYP 450 2D6 as outlined above); 12 patients need to be treated for one to achieve a 50% reduction in post-operative pain with a single (high dose!) of 60 mg (NNT 12)[2].

While this fact alone justifies already rescheduling of all codeine containing preparations to Schedule 4, it might even be appropriate for the TGA to consider removal of all codeine containing preparations from the Australian market; most pain clinics and services I know do no longer use any codeine containing preparations.

- **Poor analgesic efficacy of combinations of low dose codeine with paracetamol and ibuprofen**

While the combination of codeine with non-opioids such as paracetamol or ibuprofen enhances the analgesic efficacy of these non-opioids, this requires combinations containing typically paracetamol 500 mg with codeine 30 mg per tablet such as in Panadeine forte™, already now a Schedule 4 drug. Combinations with lower doses of codeine such as the ones currently under consideration for rescheduling offer only minor advantages with regard to efficacy over the non-opioids paracetamol and ibuprofen on their own. There are no data supporting combinations of paracetamol with 8 or 15 mg codeine in the world literature; improved NNTs have only been shown for higher doses of codeine in combination with paracetamol.

- **The rescheduling of codeine containing preparations to Schedule 4 will not impair access of Australians to effective non-opioid analgesics for mild to moderate pain without a prescription**

Combinations of ibuprofen plus paracetamol provide superior analgesic efficacy to OTC codeine combination analgesics: One 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 compared to ibuprofen 200 mg/codeine 12.8 mg and one tablet was found noninferior to this combination[3].

Such combinations would continue to provide access to good and safe OTC analgesic if codeine-containing preparations would be rescheduled to Schedule 4 as proposed in this submission.

- **Dependence on opioid analgesics is a significant concern in Australia and OTC codeine contributes to this by providing unmonitored access to a prodrug of morphine.**

Dependence and abuse of opioid analgesics are a significant health problem in Australia with numbers of abusers and deaths similar to the ones in the USA and Canada. Current strategies to reduce this abuse have failed and new attempts need to be made to address these issues including education of medical practitioners, prescribing guidelines and implementation of the national dispensing monitoring system as already done in Tasmania and available through the Commonwealth to the

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[2] 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

[3] 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; Ong CK, Seymour RA, Lirk P et al (2010) Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg* **110**(4): 1170-9.

states, but not yet realised. Codeine under Schedule 3 contributes to this problem, by providing completely unmonitored access to an opioid, which is a prodrug to morphine. National and international media have focused attention on the significant and damaging impacts of codeine dependence on the community through featuring individual stories of the effects of codeine[4] [5] [6].

- **Combinations of codeine with non-opioids tempt patients to use overdoses of these combinations with cause serious and potentially life-threatening adverse effects (including documented fatalities)**

The dependence on and abuse of codeine containing combination preparations leads to significant organ toxicity due to the resulting consumption of excessive overdoses of the non-opioids paracetamol and ibuprofen in these combinations.
With regard to paracetamol, use of paracetamol containing codeine preparations exceeds the safe threshold of 4 g paracetamol in many abusers with high risk of liver toxicity of the excessive paracetamol doses consumed (80 tablets/day in one of my recent patients, who visited 4 pharmacies daily to obtain these amounts).
With regard to ibuprofen, life threatening hypokalaemia from renal tubular acidosis, acute kidney failure as well as non-healing gastric ulcers unresponsive to treatment and with significant risks of perforation and bleeding occur with overdoses; again we see patients using up to 80-100 tablets/day.

- **Under current arrangements (Schedule 3 Pharmacist Medicine) the easy and widespread availability of these opioid medicines is not limited and/or monitored.**

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 [7] [8] [9]. It is unreasonable to expect a pharmacist will be able to detect codeine dependence based solely on a customer's their appearance. Therefore the current status of codeine as a Schedule 3 medication results in poorly limited and unmonitored access to a drug of abuse.

In conclusion the current listing of codeine containing combinations with non-opioids as schedule 3 medications fails to protect the Australian community from the harmful side effects of these combination preparations with marginal analgesic benefit.

Therefore the only appropriate measure to contain this significant problem is the rescheduling of all codeine containing preparations to Schedule 4, as proposed by the Advisory Committee on Medicines Scheduling of the TGA.
This proposal has my full support.

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4 Yang, J. Star investigation: Canada's invisible codeine problem http://www.thestar.com/news/canada/2015/01/17/star-investigation-canadas-invisible-codeine-problem.html [accessed April 24, 2015].

5 The Hoopla. Codeine addiction destroyed my family http://thehoopla.com.au/counter-addiction/ [accessed April 24, 2015].

6 Marie Claire, National. Why addiction has never been so easy. 2015 pp42 – 46.

7 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

8 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;

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

Yours sincerely

[redacted]

[redacted]

28 January, 2016

The Secretary
Communications and Secretariat
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Re: Invitation for public comment — Proposed amendments to the Poisons Standard (Codeine)

[redacted]

Interim decision to up-schedule all codeine-containing products to Schedule 4:

In most instances, there is little distinction between the handling of Schedule 2, 3 and 4 products in [redacted] hospitals. If the interim decision to up-schedule all codeine-containing products to Schedule 4 is retained, the following implications for hospital pharmacy practices and medication handling in [redacted] hospitals are anticipated:

- The removal of all codeine-containing products from Nurse Initiated Medicines (NIMs) protocols. The impact of this change in workflow may be greater for rural and remote hospitals.
- Potential for increases in discharge prescriptions and associated expenditure for codeine-containing products, where previously patients may have been advised to obtain an over-the-counter (OTC) preparation
- Delays in discharge for patients requiring codeine-containing products to be dispensed by hospital pharmacies
- Storage and handling implications if [redacted] or Local Health Districts develop policy that mandates codeine-containing products must be considered Schedule 4 Appendix D medicines.

Amendment of Schedules 2 and 3 with pack size reductions for codeine-containing products

In most instances, [redacted] hospital pharmacies are unlikely to stock cough and cold medicine preparations containing codeine. It is common practice, however for [redacted] hospital pharmacies to stock codeine-containing analgesics such as paracetamol/codeine and ibuprofen/codeine combination products. Amendments to Schedules 2 and 3 to reduce pack sizes for codeine containing products are supported in principle, however [redacted] recommends that there be made available larger pack sizes for "hospital pharmacy use only". This is due to limited storage space for smaller pack sizes in hospital pharmacies and ward imprest cupboards being anticipated.

Evidence for change

[redacted] suggests deferring the final decision concerning the re-scheduling of codeine-containing products, pending collection of evidence that will inform decision making. [redacted] notes that the Pharmacy Guild of Australia and community pharmacies will commence a pilot study of real-time monitoring of codeine-containing products in February 2016, and suggests that prospective/concurrent data should also be collected from hospital emergency department presentations, drug and alcohol treatment units and Poisons Information Centres across Australia.

In summary, [redacted] initiatives to reduce the harmful use of codeine-containing medicines in the community, and supports an evidence-based approach to decision making regarding the re-scheduling of codeine-containing products. Pack size reductions are supported in principle.

Contact details:

[redacted]

SUBMISSION ABOUT PROPOSED AMENDMENTS TO SCHEDULING OF S3 AND S2 CODEINE PRODUCTS FOR CONSIDERATION OF THE MARCH 2016 ACMS MEETING

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I support retaining the interim decision to up-schedule all current Schedules 2 and 3 medicines containing codeine (methylmorphine) to *Prescription Only* (Schedule 4).

OTC codeine cold and flu medications: codeine has no advantage over placebo for cough suppression, and the maximum permitted dose of codeine 10 mg provides a sub-therapeutic dose of 0.5-1 mg morphine for some, making little contribution to analgesia in cold and flu preparations.

Cough, cold and flu medicines are widely abused and illicitly trafficked in many other countries.

If OTC CACCs are made *Prescription Only* those codeine seekers currently misusing them or addicted will seek to substitute them with OTC cough, and cold and flu medications.

In the absence of evidence that a product is effective, no amount of toxicity or risk of abuse and addiction is acceptable.

OTC CACCs. The addition of sub-therapeutic doses of codeine to over-the-counter combination analgesics containing codeine (OTC CACC) provides little benefit, but provides a risk of addiction, escalation of dose, harm from high doses of the non-narcotic analgesic with which it is combined.

Codeine (methylmorphine) is the only opiate available without a prescription.

New knowledge about: pharmacogenomics; contribution to rare but catastrophic outcomes of medical use in infants and children and adolescents; and reports of misuse and serious harm from combination product misuse from many countries has led to calls to review codeine use. Many hospitals have removed it from their formulary.

Even if the risk of addiction is low, widespread and easy availability exposes a large number of vulnerable people to risk, resulting in a large number of people at risk.

- Hundreds of thousands of Australians use OTC CACCs non-medically to induce or enhance a drug experience, 209,080 in 2013 alone.
- Drug treatment for codeine dependence in AOD treatment centres has increased 4-fold from 683 in 2003-04 to 2,593 in 2013-14,
- Several hundred people are treated with pharmacotherapy each year for opioid dependence on codeine.
- OTC CACCs contributed to a substantial number of deaths described in a study describing the doubling of Australian overdose deaths involving codeine
- More than 250 Australian and New Zealand cases of serious harm are described in publications, and several reports of multiple cases from single hospitals and clinics suggest that serious harm is widespread and largely undocumented.

Misuse and addiction lead to escalation of dose, and exposure to very high doses of non-opioid drugs with which the opiate codeine is combined in OTC CACCs, with consequent serious harm.

High dose OTC codeine-ibuprofen misuse results in a number of characteristic NSAID adverse effects:

- gastric and duodenal ulcer with complications – haemorrhage and perforation, gastric outlet obstruction,
- NSAID enteropathy affecting the small bowel and colon, with diaphragm disease, strictures, bowel obstruction, and small bowel ulceration and perforation, peritonitis, chronic occult blood loss, hypoalbuminaemia, colon perforation, and unnecessary surgery
- renal tubular acidosis, dialysis

- life-threatening hypokalaemia, intensive care unit admission
- rhabdomyolysis, and
- iron deficiency anaemia, transfusion.

The balance between benefits and harms is a critical factor influencing scheduling decisions: the minimal benefit of adding sub-therapeutic doses of codeine, an addictive opiate, to non-opioid analgesics toxic at high dose has to be balanced against the evidence of an unacceptable level of harm and in this case the inability of existing scheduling to control misuse, harm and healthcare costs.

Codeine-seekers describe techniques to avoid detection and report rarely being refused supply.

Pharmacists:

- Are uncertain about how to manage problematic requests for OTC CACCs over the counter in public with little information and little opportunity to ask difficult questions
- Express concern about 'codeine road trips' (travelling long distances shopping for OTC CACCs from multiple pharmacies)
- Describe aggressive behaviour and 'codeine tantrums' when supply is refused
- Are concerned about consequences of misuse, and
- In a recent survey, 30% supported rescheduling despite the strident opposition and public relations campaign of the pharmaceutical industry and pharmacy organisations.

The need for an extra and more intensive level of assessment and management of the risk of addiction and harm by up-scheduling to *Prescription Only* is evident.

Pharmacists have never before been exposed to such a high level of information and support about any *Pharmacist Only* medication, and particularly about what must now be the single most problematic and dangerous products in this category so it is unlikely that any pharmacist would be unaware of these serious problems.

In the months following the early April 2015 proposal to reschedule OTC CACCs, pharmacists have been exposed to a constant stream of articles and education and supportive resources alerting them to problems with OTC CACCs:

- The pharmaceutical industry and pharmacy organisations have actively campaigned to oppose it
- There has been intense general media and pharmacy media debate about problems with OTC CACC misuse and the proposed rescheduling
- [redacted] introduced cautionary advisory labels "Can cause addiction. For 3 days use only" and provided patient information leaflets
- [redacted] launched a position paper about misuse and harm from inappropriate use of OTC analgesics and provided an extensive range of practice support resources
- Many products are now voluntarily labelled with a warning: "Can cause addiction".

With the best of intentions, pharmacists in community pharmacies are hampered by the circumstances in which they are required to assess the risks of misuse, and manage difficult conversations to refuse supply in public.

The true test of the effectiveness of *Pharmacists Only* scheduling is what happens in practice: a recent covert simulated patient study of 73 rural and metropolitan pharmacies in July 2015 reported that adequate counselling by pharmacists was received in only 25% of product purchases. (Attachment 10).

SUBMISSION ABOUT PROPOSED AMENDMENTS TO SCHEDULING OF S3 AND S2 CODEINE PRODUCTS FOR CONSIDERATION OF THE MARCH 2016 ACMS MEETING.

Interested parties were invited on 11 December 2015 to comment on some alternative responses to the proposal to reschedule codeine products.

Substance	Proposal
Codeine	**Schedule 2 (cough and cold medicine preparations):** a. Proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR b. Proposal to up-schedule the Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR c. Retain the interim decision to up-schedule to Schedule 4. **Schedule 3 (including, but not limited to codeine containing analgesics):** a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR b. Retain the interim decision to up-schedule to Schedule 4.

RESPONSE.

SCHEDULE 2 (COUGH AND COLD MEDICINE PREPARATIONS)

Efficacy.

Antitussive effects. There are not many products marketed in Australia claiming cough suppressant properties. The belief that codeine has cough suppressant activity is based on historical impressions, not objective evidence. Published research[1] and a recent Cochrane systematic review[2], has found no difference in efficacy between codeine 'cough suppressants' and placebo when randomised placebo controlled trials have evaluated the antitussive properties of codeine 'cough suppressants'.

See Attachment 1: Efficacy of codeine as an antitussive agent.

The Therapeutic Goods Administration's role is to protect the public from ineffective and potentially dangerous medications. The lack of efficacy means there is no justification to tolerate a real risk of severe side effects.

In the absence of evidence that a product is effective, no amount of toxicity or risk of abuse and addiction is acceptable.

[1] Freestone C et al. Sound Pressure Levels as a Means of Measuring Cough. Pulmonary Pharmacol 1996) 9, 365.
[2] Smith SM, SchroederK, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub5.

Treatment for cold and flu. While the purpose of adding codeine to 'cold and flu' preparations is not stated, presumably it is for its analgesic properties.

Schedule 2 entry confines the maximum amount of codeine to 10 mg or less per dosage unit, when compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance

.

- Firstly, 5-10% of Australians (0.95 to 1.95 million adults) do not metabolise codeine to morphine, so will not gain an analgesic benefit.
- Secondly, extensive metabolisers will metabolise codeine by a minor pathway, converting 5-10% of anhydrous codeine to morphine. So each dosing unit will contribute 0.5 – 1 mg of morphine to the analgesic effect of these preparations, which is not likely to contribute a clinically meaningful analgesic benefit.
- In the event that adults who are ultra-rapid metabolisers, or children who are less able to safely metabolise morphine, or are breast-feeding infants, their use of any codeine products provides a risk of toxicity, respiratory depression, and a rare but catastrophic risk of death.

Safety.

There are numerous cases of misuse, addiction or harm arising from the misuse of OTC cough, or cold and flu preparations containing codeine or other psychoactive 'antitussive' agents, in Australia[3] [4], and in other countries[5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19].

[3] Alam LY et al. Cough syrup psychosis: Is it under-recognised? Aust NZ J Psychiatry 2013;47:1209.
[4] Sim MG, Hulse GK, Khong E. Cough mixtures: not always for cough. Aust Family Physician, 2004; 33:327-31.
[5] O Reilly D, et al. Cough, codeine and confusion. BMJ Case Rep 2015. doi:10.1136/bcr-2015-212727
[6] Lo MY et al. Codeine consumption from over-the-counter anti-cough syrup in Taiwan: A useful indicator for opioid abuse. Acta Anaesthesiol Taiwan. 2015;53:135-8
[7] Au WY et al. Cough mixture abuse as a novel cause of folate deficiency: a prospective, community-based, controlled study. Haematologica. 2007 Apr;92:562-3
[8] Ford JA. Misuse of over-the-counter cough or cold medications among adolescents: prevalence and correlates in a national sample. J Adolesc Health. 2009;44:505-7.
[9] Miyatake R et al. Clinical study of BRON-L syrup (cough suppressant) abuse. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2002 Feb;37(1):67-74.
[10] Chasnoff IJ et al. Fetal alcohol effects and maternal cough syrup abuse. Am J Dis Child. 1981 Oct;135(10):968.
[11] Siu AS et al. Cough syrup addiction and rampant caries: a report of two cases. Prim Dent Care. 2002 Jan;9(1):27-30.
[12] Burns JM et al. Antitussives and substance abuse. Subst Abuse Rehabil. 2013 Nov 6;4:75-82
[13] Ahmed G et al. How many deaths before we put cough syrups behind the counter? Perspect Public Health. 2014 Nov;134(6):309.
[14] Tsang JS et al. Cough mixture abuse and rhabdomyolysis. Hong Kong Med J. 2012 Feb;18(1):68-9.
[15] Zheng D et al. Hypokalemia in patients with cough mixture abuse: a retrospective chart review. J Addict Med. 2014 May-Jun;8(3):211-5
[16] Kinoshita H et al. A fatal case due to cough syrup abuse. . Soud Lek. 2012 Oct;57(4):69-70.
[17] Jun I, Yoshiko Y, Mitsukuni M. Abuse of "BRON": A Japanese OTC cough suppressant solution containing methylephedrine, codeine, caffeine and chlorpheniramine. Prog Neuropsychopharmacol Biol Psychiatry 1991;15:513-21.
[18] Wong KM et al. Hypokalemic metabolic acidosis attributed to cough mixture abuse. Amer J Kidney Dis 2001;38:390-4.
[19] Qiu YW et al. Abnormal white matter integrity in chronic users of codeine-containing cough syrups: a tract-based spatial statistics study. Am J Neuroradiol. 2015 Jan;36(1):50-6.

Given that abuse of OTC combination analgesics containing codeine (OTC CACC) is so widespread, upscheduling them to *Prescription Only* is likely to lead to those several hundred thousand individuals currently misusing them to seek readily and widely available alternative sources such as codeine cold and flu preparations.

Addiction to codeine or other psychoactive components of cold and flu medications leads to escalation of dose, and high dose exposure to all the agents combined with them.

Various adverse effects of abuse of these combination medicines include hypokalaemia, folate deficiency, caries, foetal effects from abuse of cough medicines during pregnancy, psychosis and confusion.

In the United States of America misuse of codeine cough syrup has become a fad, with the street names 'lean', 'purple drank' or 'sizzurp' used to describe the practice of mixing codeine cough syrup with soft drink and confectionary, a practice that is propagated in public by rappers and other musicians [20] [21] [22] [23] [24].

Problems with misuse of OTC cough syups are endemic in South Asia[25]. In response to problems with the abuse of and trafficking in phensedyl (a codeine-based cough syrup), the Indian State of Bihar, which is close to India's border with Bangladesh, has placed restrictions on the sale of phensedyl within its territory[26]. Pharmacists have been instructed not to stock more than 1,000 bottles of phensedyl at any one time.

In Bangladesh in 2012, about 1.3 million bottles of codeine preparations were seized, compared with some 900,000 bottles in 2011, and about 2,500 loose litres of codeine-based solutions were seized, an amount that has decreased over the past two years, as about 4,000 litres were seized in 2010.

Codeine-based cough syrups are often abused in Bangladesh, in part owing to the taste of those products and to their easy availability. Drug abusers belonging to the educated upper class tend to abuse codeine-based cough syrups instead of heroin due to previous public awareness campaigns highlighting the health dangers of heroin abuse[27].

There is also now a problem of crime associated with the diversion and trafficking of large quantities of OTC cough syrup[28] [29].

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[20] Agnich LE et al. Purple drank prevalence and characteristics of misusers of codeine cough syrup mixtures. Addictive Behav 2013;38:2445-9.

[21] Elwood WN. Sticky business: patterns of procurement and misuse of prescription cough syrup in Houston. J Psychoactive Drugs.2001;33:121–133.

[22] Maxwell J. Substance Abuse Trends in Texas. Austin, Texas: Texas Commission on Alcohol and Drug Abuse; 1999.

[23] Hart M et al. 'Me and My Drank:' Exploring the Relationship Between Musical Preferences and Purple Drank Experimentation. American Journal of Criminal Justice 2014; 39:172-186.

[24] Peters RJ et al. Beliefs and Social Norms about Codeine and Promethazine Hydrochloride Cough Syrup (Cphcs) Onset and Perceived Addiction among Urban Houstonian Adolescents: An Addiction Trend in the City of Lean. J Drug Educ 2003;33:415-425

[25] Mattoo SK et al. Abuse of codeine-containing cough syrups: a report from India. Addiction 1997;92:1783-7.

[26] International Narcotics Control Board INCB Annual report 2014.

[27] Report of the International Narcotics Control Board for 2013 (E/INCB/2013/1)

[28] Chong, Elena. Woman jailed 21 months for forgery and supplying 20,300 litres of codeine. Straits Times. 11 November 2015.

[29] Jaffrey, Shumaila. Deadly risks run by Pakistan's cough syrup addicts. BBC Urdu, Lahore. 7 February 2013.

In the USA there is such demand for codeine cough syrup that a number of thefts and armed robberies from pharmacies have been reported[30]. In one case the local police described that "The codeine syrup seems to be the newest going thing and becoming the drug of choice, according to the DEA [Drug Enforcement Agency]."[31]

There is also a risk of unintentional poisoning of children if warning labels in English recommending avoidance of dosing of children are not able to be read by illiterate or non-English speaking Australians.

Should rescheduling or other restrictions be placed on OTC combination analgesics containing codeine, given that more than 200,000 Australians use them non-medically to obtain a drug effect, they are likely to replace OTC CACCs with OTC codeine or non-codeine cough, or cold and flu medicines with a psychoactive effect.

Conclusion. In the absence of evidence that these products provide any clinical benefit, no amount of toxicity or contribution to abuse or addiction is acceptable.

The first two options to limit pack size and add a warning label, or reschedule to *Pharmacist Only*, are unacceptable, given the current inability of non-prescription *Pharmacist Only* supply to control misuse of OTC CACC diversion and misuse.

SCHEDULE 3 (INCLUDING, BUT NOT LIMITED TO CODEINE CONTAINING ANALGESICS):

a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction.

This proposal is unlikely to make a substantial difference in preventing misuse and harm from misuse of OTC combination analgesics containing codeine (OTC CACC) because:

- a large proportion of packs currently supplied already contain 3 days' supply (24 tablets) and
- many brands have already been voluntarily labelled with a warning about the risk of addiction, and that they are for use for 3 days only. This is the case for market leaders Panadeine, Nurofen Plus, Panafen Plus, and many other brands.

[30] Day, Brian. Gunman robs Pico Rivera pharmacy of cough syrup commonly used to make 'purple drank'. San Gabriel Valley Tribune 9 April 2014.
[31] Tracey PJ. Local pharmacy robbed as part of theft ring. Arkansas News 29 July 2015.

In 2013 Reckitt Benckiser sent spools of 1000 adhesive labels to every Australian pharmacy with the same warning, and undertook to label all packs from 2014 onwards[32].

b. Retain the interim decision to up-schedule to Schedule 4.

This is supported for a number of reasons.

Firstly, the addiction of low, sub-therapeutic doses of codeine, a weak analgesic, to effective non-narcotic analgesics, provides little additional benefit.

What benefit does codeine add to OTC medicines?

Firstly, the 5-10% of the population who are non- or poor-metabolisers (1.2 to 2.4 million Australians) would not receive any analgesic benefit from codeine at any dose.

Secondly, OTC codeine combination analgesics contain sub-therapeutic doses of codeine.

Presently marketed OTC CACC tablet brands contain 8 to 15 mg codeine phosphate, equivalent to 5.9-11 mg anhydrous codeine (methylmorphine) respectively. Extensive metabolisers convert between 5-10% of codeine by demethylation to morphine, providing sub-therapeutic doses of morphine: 0.6-1.1 mg.

Anomaly in supply of codeine in *Pharmacist Only, Prescription Only* and *Controlled Drugs* products
It can be seen from the table below that it is possible for a codeine-seeking or addicted individual to obtain a similar amount of codeine phosphate (600 mg) from several *Pharmacist Only* packs of products (e.g. Panadeine Extra x 40 tablets) as from a prescription for a *Prescription Only* pack (e.g. Panadeine Forte x 20 tablets) or *Controlled Drugs* (e.g. Codeine x 20 tablets) product.

This is an example of irrational scheduling.

[32] Burton, Kirrilly, Brooker Chris. Profession judged on harm minimisation of codeine-based drugs. Pharmacy News. 4 December 2013.

Table: amount of codeine phosphate metabolised to morphine by extensive metabolisers.

Example			5% conversion	10% conversion	2 tabs	morphine
	codeine phosphate (mg)	Codeine (mg)	Morphine (mg)	Morphine (mg)	Morphine (mg)	in 40 tabs (mg)
Panadeine	8	5.9	0.3	0.6	1.2	23.6
Mersyndol D&N	9.6	7.1	0.4	0.7	1.4	28.3
Nurofen Plus	12.8	9.4	0.5	0.9	1.9	37.7
Panadeine Extra	15	11.0	0.6	1.1	2.2	44.0
Panadeine Forte (prescription)	30	22.1	1.1	2.2	4.4	20 tabs 44.0

A Cochrane systematic review of the analgesic efficacy of codeine 60 mg reports that "codeine 60mg provides good analgesia to few individuals", and 12 patients need to be treated for one to get a 50% or more pain relief benefit (NNT = 12)[33].

A Cochrane systematic review describes NNT for ibuprofen 400 mg/codeine 25.6-60 mg (high dose) compared to placebo: (2.2; 95% CI 1.8-2.6)[34]. 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.

Comparing paracetamol 800-1000 mg plus codeine 60 mg (high dose codeine) versus the same dose of paracetamol alone, the NNT for at least 50% pain relief over four to six hours was 6.1 (3.6 to 19)[35].

The figure below describes the results of a number of Cochrane systematic reviews describing the number of patients needed to be treated (NNT) for one to obtain a 50% or more analgesic benefit post-operatively. A number of different surgical procedures are used for these studies, including third molar surgery (extraction of wisdom teeth) and episiotomy.

Newly introduced non-opiate combination products of ibuprofen/paracetamol (Maxigesic, Nuromol) provide better analgesic efficacy measured in NNT than either the OTC codeine combinations of codeine with ibuprofen or paracetamol.

A Cochrane systematic review of the number needed to treat with an ibuprofen/paracetamol combination (NNT 1.5)[36] was lower than for either paracetamol/ codeine (NNT 2.2) or ibuprofen/codeine (2.2) combinations.

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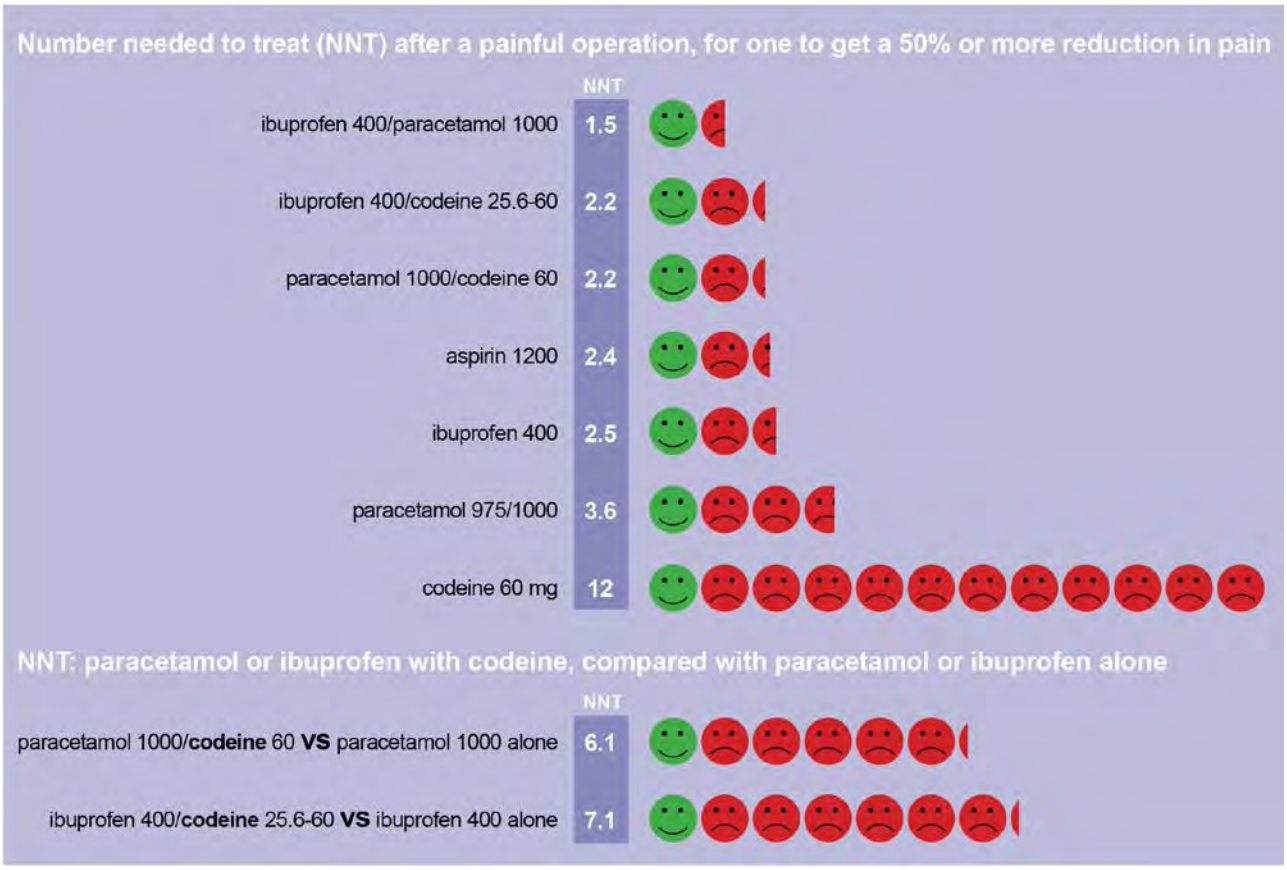
[33] Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2011; (9): CD008659

[34] 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

[35] Toms L et al. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev*. 2014; (1): CD001547. doi:10.1002/14651858.CD001547.pub2

[36] 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.

Figure: Number needed to treat (NNT) after a painful operation, for one to get a 50% or more reduction in pain.



Safety.

Codeine (methylmorphine), an opiate, is a prodrug of morphine, requiring metabolism by CYP2D6 to morphine to provide an analgesic effect. Morphine is a potent opioid with addiction potential. Codeine has a recognised abuse liability[37] [38].

Codeine (methylmorphine) is a natural opium alkaloid, but pharmaceutical codeine is manufactured from morphine by adding a methyl group to make methylmorphine. In 2012, 475 tonnes of morphine was manufactured globally, and 398 tonnes was converted into codeine, one of the commonest opioids globally[39].

Its psychoactive properties were recognised shortly after it was isolated from opium in 1832[40]. Its addictive properties led to it being included in international and national schedules for control, and descriptions of codeine addiction have been published in the medical literature over many years[41].

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[37] Sproule BA et al. Characteristics of dependent and nondependent regular users of codeine. J Clin Psychopharmacol 1999; 19: 367–372.

[38] Rossi S, ed. Australian Medicines Handbook 2012. Adelaide: Australian Medicines Handbook Pty Ltd, 2012.

[39] International Narcotics Control Board. Narcotic Drugs. Narcotic Drugs: Estimated World Requirements for 2015; Statistics for 2013 (E/INCB/2014/2). Vienna, Austria 2014. Table VI. Conversion of morphine, 2009-2013.

[40] Eddy NB, Friebel H, Hahn K, Halbach H. Codeine and its Alternates for Pain and Cough Relief. 1. Codeine, Exclusive of its Antitussive Action. Bull Wld Hlth Org 1968;38:673-741.

[41] Slight D. Codeine addiction. Can Med Assoc J. 1935 Jan; 32(1): 69–71.

What new information have we learnt about codeine?
Codeine is an old drug regarded as weak analgesic and cough suppressant, with a real but low risk of addiction, and a risk of rare but catastrophic harm in nursing infants or children[42]. Even though codeine is one of the most commonly used opioids, recent information suggests there are three main reasons to review its use.

Pharmacogenomics: There is a high degree of variability in CYP2D6 metabolism of codeine to morphine because of genetic differences between individuals, and racial and ethnic groups, making the benefits and risks of use unpredictable. Demethylation of codeine to morphine in extensive metabolisers (77-92% prevalence) occurs via a minor pathway accounting for 5-10% of clearance of codeine. Poor metabolisers (5-10%) do not metabolise codeine and experience no analgesic benefit. Ultra-rapid metabolisers (1-2%) are at the highest risk for morphine exposure and toxicity, including respiratory depression. Prevalence of ultra-rapid metabolisers varies considerably depending on ethnicity and race: Caucasian 1-10%; Arabs, Ethiopians and North Africans 16-28%[43]. In 2015 the Ethiopian government temporarily banned codeine[44].

Opioid toxicity and deaths of infants and children. Recent developments include the death of a nursing infant exposed to high levels of morphine in breast milk of an ultra-rapid metabolising mother taking codeine[45] and a number of fatal and life-threatening cases of respiratory depression in children treated with codeine at recommended doses for post-operative pain following adeno-tonsillectomy, some of whom were ultra-rapid metabolisers and/or suffering from obstructive sleep apnoea[46]. These reports describe rare but catastrophic events that would be avoided if codeine is not used, and other

These developments led to reviews by the European Medicines Agency, the US Food and Drug Administration, Health Canada, and the Australian Therapeutic Goods Administration recommending limiting prescribing to children and breast-feeding mothers, and ultra-rapid metabolisers.

A recent case report describes an acute confusional state in a 14-year-old girl taking OTC codeine cough suppressant syrup[47].

Harm from misuse of OTC combination analgesics containing codeine.
There are numerous published reports from several countries (Australia, New Zealand, Ireland, United Kingdom) of harm arising from prolonged high dose misuse of OTC codeine combination analgesics. Cases begin treatment for an approved indication, become addicted and escalate their dose to 40-80 tablets or more a day. Most cases involve OTC codeine-ibuprofen combinations causing characteristic NSAID toxic effects due to prolonged high dose ibuprofen exposure secondary to codeine addiction.

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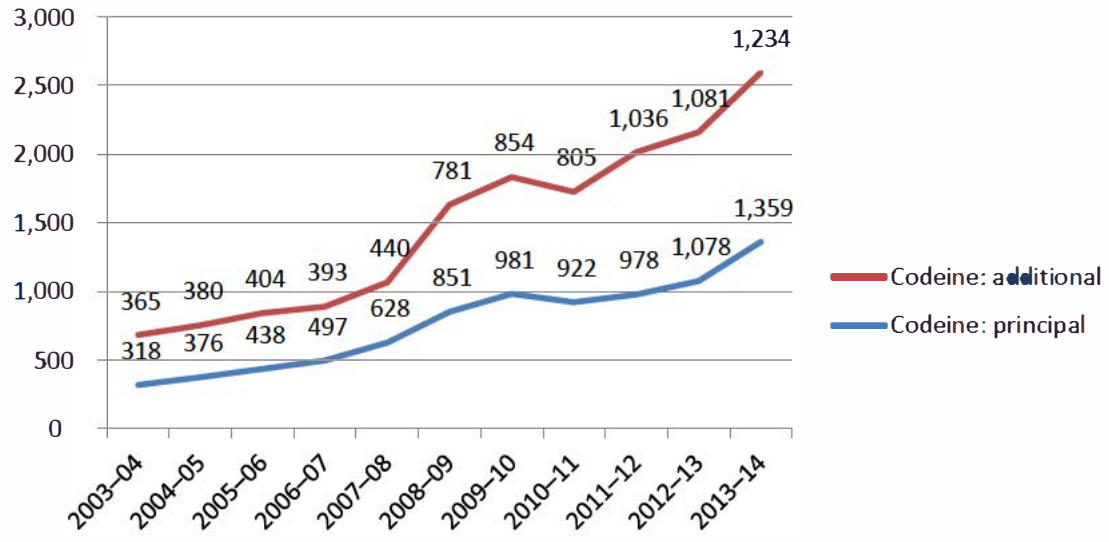
[42] Racoosin JA et al. New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy. N Engl J Med 2013;368:2155-7.
[43] United States Food and Drug Administration. FDA Briefing Document: Joint Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting December 10, 2015: The safety of codeine in children 18 years of age and younger. FDA 2015.
[44] Anberbir Y. Ethiopia: Authority Issues Red Alert On Codeine Drug. The Reporter (Addis Ababa). 21 November 2015. http://allafrica.com/stories/201511241318.html
[45] Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; 368(9536):704.
[46] Kelly LE, Rider M, van den Anker J, et al. More Codeine Fatalities after Tonsillectomy in North American Children. *Pediatrics* 2012; 129(5):e-1343-7.
[47] O Reilly D, et al. BMJ Case Rep. Cough, codeine and confusion 2015. doi:10.1136/bcr-2015-212727.

What evidence is there of misuse and harm from over the counter availability of codeine?
Codeine combination analgesics. It is difficult to obtain good data about covert activities such as misuse and harm from misuse of these analgesics. In Australia OTC CACCs are easily and widely available: in 2013 there were sales of 15.5 million packs[48].
Misuse. These analgesics have been misused by hundreds of thousands of Australians: in 2013 alone non-medical use of OTC codeine analgesics to induce or enhance a drug experience was reported by 209,000 (1.1%) of Australians adults[49].
Addiction. Codeine has long been recognised as subject to abuse and addiction[50]. Escalation of dose is one of the defining characteristics of addiction, and reports of harm describe patients taking 20-80 or more tablets a day for prolonged periods.
Treatment of codeine addiction. The funded Alcohol and other Drug sector reports a steady increase in the number of episodes of care for the treatment of codeine dependence[51]. The dip in numbers in 2010-2011 probably represent the effect of removing these OTC products from Schedule 2 where they could be promoted and available for self-selection in pharmacies, but the steady increase in numbers returned after that, and has increased substantially since then.

Table SD.9: Treatments for own drug use, by principal and additional drug of concern (codeine): 2003–04 to 2013–14.



Australian Institute of Health and Welfare 2015. Alcohol and other drug treatment services in Australia 2013–14. Drug treatment series no. 25. Cat. no. HSE 158. Canberra: AIHW.

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[52]. 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

[48] Degenhardt L et al. The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. Pharmacoepidemiol Drug Saf 2016. DOI: 10.1002/pds
[49] Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2013. Misuse of pharmaceuticals chapter. Online data tables. November 2014.
[50] Slight D. Codeine addiction. CMAJ 1935;32:69-71.
[51] Australian Institute of Health and Welfare 2015. Alcohol and other drug treatment services in Australia 2013–14. Drug treatment series no. 25. Cat. no. HSE 158. Canberra: AIHW.
[52] Australian Institute of Health and Welfare 2014. National opioid pharmacotherapy statistics 2013. Drug treatment series no. 23. Cat. no. HSE 147. Canberra: AIHW.

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, thouigh evidence suggests that they were mainly due to opioid dependence on OTC CACCs:

- Nielsen et al (2014) examined the characteristics of 145 clients presenting for treatment of opioid dependence on pharmaceutical opioids in 3 NSW local health districts[53]. 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.
- Personal communication from Warinilla Drug Clinic in South Australia indicates that pharmacotherapy treatment of codeine dependence almost always due to OTC CACC misuse.
- The trends in the figure above of treatment episodes at national AOD clinics shows an initial dip in 2010-2011 when shceduling changes restricted access to OTC CACCs

Harm. Apart from addiction hundreds of Australians have experienced serious adverse effects: there are published reports of more than 250 Australian and New Zealand cases in the medical literature alone[54]. Serious and often life-threatening harm arises from high dose exposure to supra-therapeutic doses of the ibuprofen or paracetamol in combination tablets secondary to codeine addiction.

High dose OTC codeine-ibuprofen misuse results in a number of characteristic NSAID adverse effects:

- gastric and duodenal ulcer with complications – haemorrhage and perforation, gastric outlet obstruction,
- NSAID enteropathy affecting the small bowel and colon, with diaphragm disease, strictures, bowel obstruction, and small bowel ulceration and perforation, chronic occult blood loss, hypoalbuminaemia, colon perforation,
- renal tubular acidosis,
- life-threatening hypokalaemia,
- rhabdomyolysis, and
- iron deficiency anaemia.

Many patients require intensive care admissions, and surgery such as partial gastrectomy, small bowel resection, colectomy, or dialysis. Managing these cases is complicated by the fact that patients either do not offer information about their misuse of OTC CACCs, assume that when asked about what drugs they are taking they respond with the prescription medicines they are using, or they deny use and misuse because of ambivalent feelings about their misuse.

A submission to the TGA in 2015 describes more than 250 cases of severe harm described in the medical literature. Many patients presenting with adverse effects do not offer information and even deny their high dose misuse, resulting in multiple admissions and unnecessary surgery without the underlying cause being identified[55]. Paracetamol hepatotoxicity occurs secondary to codeine

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[53] 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.

[54] Therapeutic Goods Administration. Public submission on scheduling matters to the Advisory Committee on Medicines Scheduling 15 August 2015. Number 03. Page 94-119 https://www.tga.gov.au/sites/default/files/scheduling-submissionpublic-submissions-scheduling-matters-referred-acms-15-august-2015-03.pdf (accessed 10 January 2016)

[55] Robertson CG, Kumar B, Bright T, Watson DI. Beware of NSAID abuse: think twice before operating! ANZ J Surg 2014; 84:495–497.

addiction to OTC codeine-paracetamol combination tablets. There have been a number of deaths associated with misuse[56].

Codeine cold and flu medications. There is currently no mechanism to collect information about misuse of these medications. There have been two Australian cases described in the literature – a case of psychosis from misuse of cough syrup[57], and addiction to cough mixture[58]. Reports from other countries indicate that abuse of cough syrup, including that involving codeine, is a major problem[59] [60] [61] [62].

Regulatory changes and countermeasures in response to misuse of OTC CACCs.
Concerns about misuse, abuse and harm, and concerns about patient safety have recently led to a number of countermeasures and tightening of controls in different countries:

Australia, New Zealand, Ireland and the United Kingdom. Patient safety issues with OTC CACCs have been identified in several Western countries, and this has led to countermeasures and regulatory responses to tighten control in Australia, New Zealand, Ireland and the United Kingdom[63].

South Africa. Because of widespread abuse of non-prescription codeine products[64], the South African Medicines Control Council indicated that in 2016 it will reschedule codeine to limit its availability, including by halving the maximum quantity of South African Schedule 2 codeine and dihydrocodeine per dosage unit from 20 mg to 10 mg and limiting the maximum daily dose to 80 mg and maximum treatment period to 5 days for oral solid preparations[65].

Canada. From February 2016, in response to concerns about misuse and dependence, codeine products currently available without a prescription will be required by the College of Pharmacists Manitoba, the regulatory authority, to be available only on prescription[66]. Other provinces are reconsidering the scheduling and controls of codeine taking into account the changes in Manitoba.

United States of America. Twenty-eight states and the District of Columbia permit the sale of codeine without a prescription, while 22 states and Puerto Rico prohibit the sale of codeine without

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[56] Pilgrim JL, Dobbin M, Drummer OH. Fatal misuse of codeine–ibuprofen analgesics in Victoria, Australia, Med J Aust 2013;199:329-30.
[57] Alam LY, Nelson A, Bastiampillai T. Cough syrup psychosis: is it under-recognised? ANZ J Psychiatr 2013;47:1209-10.
[58] Sim MG, Hulse GK, Khong E. Cough mixtures: not always for cough. Aust Family Physician, 2004; 33:327-31.
[59] International Narcotics Control Board Annual Report for 2013 (E/INCB/2013/1), Vienna 2014.
[60] Substance Abuse and Mental Health Services Administration, Results from the 2013 National Survey on Drug Use and Health: Detailed Tables. Center for Behavioral Health Statistics and Quality (CBHSQ), U.S. Department of Health and Human Services (HHS). Tables 7.25 A and 7.25B.
[61] Agnich LE, Stogner JM, Miller BL, Marcum CD. Purple drank prevalence and characteristics of misusers of codeine cough syrup mixtures. Addict Behav. 2013 Sep;38(9):2445-9.
[62] Chong E. Ex-pharma firm exec gets jail for illegal codeine sale. The Straits Times. Nov 12, 2015.
[63] 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.
[64] Mostoenena, Bontle. Codeine: SA's over-the-counter addiction. Health-e.org.za. 8 June 2015.
[65] Medicines Control Council. Scheduling Matters. Rescheduling of acetyldihydrocodeine, codeine, dihydrocodeine and norcodeine.
http://www.samed.org.za/Filemanager/userfiles/Scheduling_Codeine_Nov14_v2.pdf
[66] College of Pharmacists of Manitoba. Practice direction: exempted codeine preparations. 2015

a prescription[67]. Most if not all of the state laws allowing the OTC sale of codeine require the pharmacist to oversee or personally complete the transaction, and allow the pharmacist to choose not to sell the product OTC. For codeine that is sold OTC, all states require that the purchaser's identifying information and details of the sale be recorded. States differ on the maximum allowable quantity which can be purchased at one time (60 mL to 240 mL), the amount of time required before additional purchases are permitted (48 hours to 96 hours), and the minimum age of a purchaser (18 years to 21 years). The variations between states involve regulations and laws which are more restrictive than the federal requirements.

Changes have been made and an FDA review is underway to develop countermeasures to the risk of respiratory depression and deaths from the use of codeine to breast-feeding mothers, infants and children.

Ethiopia. Because of the high prevalence of ultra-rapid metabolism of codeine and the risk of respiratory depression and other opioid toxicity this entails in people of Ethiopian descent (16-28%)[68], in 2015 the Ethiopian government temporarily banned codeine[69].

Attitudes to codeine are changing, and its value increasingly questioned[70] [71] [72] [73] [74]. Codeine is being removed from hospital formularies[75]. Rather than being considered as a safer alternative to other opioids because it has a perceived lesser risk of addiction and abuse, the fact that it has no advantage over other opioids, has evident risks of rare but catastrophic harm to infants, children, and adult ultra-rapid metabolisers[76].

Proposal to reschedule all OTC codeine products to Schedule 4 (prescription only).

In February 2015 several senior clinicians requested that all codeine medicines currently available over the counter (OTC) without a prescription be rescheduled to require a prescription because they met criteria for Schedule 4 medicines, including that use at established therapeutic dosage levels may produce dependency, and because the seriousness, severity and frequency of adverse effects

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[67] FDA Briefing document. Joint Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting. December 10, 2015. The safety of codeine in children 18 years of age and younger. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM475975.pdf

[68] United States Food and Drug Administration. FDA Briefing Document: Joint Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting December 10, 2015: The safety of codeine in children 18 years of age and younger. FDA 2015.

[69] Anberbir Y. Ethiopia: Authority Issues Red Alert On Codeine Drug. The Reporter (Addis Ababa). 21 November 2015. http://allafrica.com/stories/201511241318.html

[70] Tremlett M, Anderson BJ, Wolf A. Pro-Con debate: is codeine a drug that still has a useful role in pediatric practice? Pediatr Anesth 2010; 20: 183–194.

[71] Racoosin JA et al. New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy. N Engl J Med 2013;368:2155-7.

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

[73] Drendel AL, Ali S. Efficacy and practicality of codeine. CMAJ 2011 2011;183:349.

[74] MacDonald N et al. Has the time come to phase out codeine? CMAJ 2010;182:1825.

[75] Jerome J et al. A Single Institution's Effort to Translate Codeine Knowledge into Specific Clinical Practice. J Pain Symptom Manage 2014;48:119-

[76] Gasche Y, Daali Y, Fathi M et al. Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism. N Engl J Med 2004; 351:2827-2831

are such that monitoring or intervention by a medical practitioner is required to minimise the risk of use.

This action was prompted by their experience that despite rescheduling in April 2010, they were still seeing a concerning number of patients admitted each year to their hospital with complications from, and significant issues associated with, codeine misuse and abuse of over-the-counter (OTC) (Schedule 3) codeine combination analgesics.

They were also prompted by a report from colleagues at Flinders Medical Centre describing that in the past year 5 young patients abusing OTC codeine-ibuprofen combination analgesics presented with upper gastrointestinal complications including perforation or gastric outlet obstruction caused by non-healing gastric ulcers, and complex issues during recovery from surgery. Four of them did not volunteer use of OTC codeine ibuprofen combination drugs until confronted with the results of their urine tests[77].

Scheduling is a national classification system that controls which particular healthcare professionals need to be involved in supply in order to promote safe and quality use, and depends on a risk/benefit analysis. Factors for supply without prescription as pharmacist only medicines (Schedule 3), include that the medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine, and the use of the medicine at established therapeutic doses is not expected to produce dependency.

Is pharmacy the best location to be supplying these opiate medications?

There is now good evidence that scheduling requiring involvement of a pharmacist in supply (*Pharmacist Only)* has not been successful in countering the misuse, abuse and serious harm arising from misuse.

This is an iatrogenic epidemic. Even with the best of intentions and professional practice, training, education and widespread public and pharmacy media attention, pharmacists' direct involvement in sales has been unable to prevent the serious problem of widespread abuse and consequent serious harm. This probably reflects the limitations of the circumstances of supply in community pharmacy.

Moving these products to Schedule 4 (Prescription only) adds an additional and more effective level of assessment and safety. For S4 medicines there are two levels of assessment of the appropriateness and safety of supply of potentially dangerous medicines such as OTC CACCs: by a medical practitioner in the privacy of a consulting room where assessment of risk for opioids when using standardised risk assessment tools such as the ORT or SOAPP-R (Attachments 2 and 3). These tools recommend questioning about personal or family history of substance abuse, mental health disorder or child abuse, intimate questions not suited to use in the public setting of community pharmacy. And a medical history may be accessed and the patient may be examined for diagnosis and assessment.

Attachment 4 compares the advantages and limitations of both *Prescription Only and Pharmacist Only* scheduling with respect to the supply of OTC CACC and cold and flu preparations.

[77] Robertson CG et al: NSAID abuse: think twice before operating: ANZ J Surg: 2014: 84(6): 495-6

Scheduling decisions about OTC CACCs.

Table: Factors appropriate for OTC CACC scheduling[78].

	Pharmacist Only (Schedule 3)	*Prescription Only* (Schedule 4
Harm, or assessment	**1. The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately** (Pharmacist-consumer dialogue is necessary to reinforce and/or expand on aspects of the safe use of the medicine)	**1. The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention**
Dependency	**2. The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist.**	**3. The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use.**
Risk profile	**3. The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are known, identifiable and manageable by a pharmacist**	
Seriousness of adverse effects.		**4. The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance.**

Seriousness of adverse effects.

The Australian Therapeutic Goods Administration (TGA) describes that serious adverse events include those that cause death, danger to life, admission to hospital, prolonged hospitalisation, absence from productive activity and increased investigational or treatment costs[79].

[78] Australian Health Ministers' Advisory Council. Scheduling Policy Framework for Medicines and Chemicals. February 2015. http://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals

[79] Therapeutic Goods Administration. Reporting medicine and vaccine adverse events. Serious adverse events. TGA Canberra. https://www.tga.gov.au/reporting-medicine-and-vaccine-adverse-events-0#events

The U.S. Food and Drug Administration (FDA) describes adverse events as any undesirable experience associated with the use of a medical product in a patient. They are considered serious if the outcome is: death, life-threatening, hospitalisation, disability or permanent damage, required intervention to prevent permanent impairment, or important medical events including the development of drug dependence or drug abuse[80].

OTC CACCs meet many of both these authorities' criteria for being serious: death, hospitalisation, danger to life (many cases require treatment in intensive care units, or require surgery, transfusion), experience prolonged hospitalisation, require absence from work or household responsibilities, experience permanent impairment, and misuse results in drug dependence and drug abuse.

Limitations of real time monitoring for *Pharmacist Only* medicines.
The proposal to establish a real-time monitoring system for OTC CACCs has limited potential to address the problem because:

- The expense, effort and administrative burden placed on pharmacists is not warranted by the insubstantial analgesic contribution of adding sub-therapeutic doses of codeine to effective non-narcotic analgesics, especially as there are now more effective combination analgesics (paracetamol/ibuprofen) available that would satisfy the needs of the vast majority of pharmacist customers
- OTC CACCs States/Territories will be using the ERRCD software supported by the Commonwealth, which is designed to initially only monitor Schedule 8 drugs
- Although all States/Territories will be using ERRCD, there is likely to be a long delay before they become nationally operative, with further delay to include Schedule 4 drugs, and then changed to include *Pharmacist Only* drugs should this occur at all.
- Codeine dependent people surveyed in two separate surveys report that they use others[81], including family members[82], to purchase packs of OTC CACCs for them.
- There are reservations about a real-time register by the Australian Self-Medication Industry (ASMI) because of concerns about the privacy of sensitive data, and the risk of stigmatising consumers, most of whom use the products responsibly[83].
- A system to capture information about *Pharmacist Only* medicines would not be integrated with dispensing software which automatically records information from prescription medicines dispensed, requiring additional effort by pharmacists for each OTC CACC pack sold.
- Real-time monitoring would impose a burden on pharmacists: an average of 10 packs per pharmacy of OTC CACCs are sold each day, and assuming that it would take 10 minutes per pack to establish a therapeutic need, assess the risk of addiction or misuse, check identity, manually enter personal and product details into the database, check the database for medication history, and counsel the customer about use and risks of addiction, would add 100 minutes a day to pharmacists' workload.

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[80] U.S. Food and Drug Administration. What is a serious Adverse Event? http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm

[81] Cooper R. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. Health Soc Care Community. (2013) 21(3), 254–262.

[82] Nielsen S, Cameron J, Pahoki S. Opportunities and challenges: over-the-counter codeine supply from the codeine consumer's perspective. *International Journal of Pharmacy Practice* 2013, 21, pp. 161–168.

[83] Browne R. Doctors and pharmacists call for tighter controls on codeine due to rise in addiction. Sydney Morning Herald September 14, 2014.

- In 2005 the average pharmacy dispensed 880 prescriptions a week [84].There were already concerns in 2011 that the 2010 rescheduling OTC CACCs requiring supply by a pharmacist imposed a burden on pharmacists and a negative effect on workflow, reducing the capacity of pharmacists to meet their professional obligations, and requiring customers to wait until a pharmacist was available to assess each request[85]. It was argued that greater demands on time might result in neglect of some aspects of their work, affecting public safety and/or quality of care.
- Responding to concerns revealed by RTPM would still require difficult conversations in public in community pharmacy, which has already proved problematic for pharmacists.

[84] Benrimoj SI, Roberts AS. Providing patient care in community pharmacies in Australia. Ann Pharmacother 2005 Nov 11;39(11):1911-7.

[85] Pharmacy Guild of Australia. Response to the discussion paper to support the development of the National Pharmaceutical Drug Misuse Strategy. June 2011.

Attachment 1. Efficacy of codeine as an antitussive agent.

Historically codeine has been regarded as having antitussive properties, and numerous scheduled products are registered with indications including suppression of cough. Despite this, there is a paucity of evidence to support that codeine has an antitussive action any greater than placebo. There are few good quality randomised, placebo controlled trials of the efficacy of antitussive preparations, including codeine, and those few trials, and reviews of trials, find that they are no more effective than placebo.

A 2007 citizen's petition to the U.S. FDA requesting measures to protect children from the risks associated with use of OTC antitussive agents estimated that in 1990 alone the American public spent $2 billion on cough and cold preparations and commented in their conclusion that OTC cough and cold preparations are neither safe nor effective in young children, and that FDA had never conducted an appropriate analysis to support their widespread use, and expert organisations agree that they are ineffective and pose a risk to health. Death and serious injury have been linked to misuse of these preparations.

Table: Trials and reviews of trials - antitussive efficacy of codeine cough and cold preparations.

Review (year)	**Finding.**
Smith MB, Feldman W. (1993)[86]	A review of clinical trials assessed over-the-counter cough and cold preparations. Only two studies had specifically targeted preschool children, neither of which had demonstrated that the medications were associated with symptom relief.
Freestone C et al. (1996)[87]	A study of a new method of screening antitussive agents in man that used a microphone attached to the subject's throat by means of a neck band connected to a digital sound level meter, and compared it with two well-established methods of evaluating cough severity: the subjective impression of symptom severity scored on a five point rating scale, and cough frequency recorded by microphone on the floor in front of the subject. It found that there were no significant differences between the codeine and placebo group.
Lopez LA (1997) [88]	An FDA Center for Drug Evaluation and Research Medical Officer conducted a literature search for an advisory committee and found only 11 clinical trials involving children treated with cough and cold medications over the preceding 50 years, of which some were so poorly designed they did compare active with placebo. They included reviews of codeine as an antitussive agent, and concluded that, "Based on the review of published clinical trials in children (1½ months to 18 years old) there is no convincing evidence of efficacy of cough and cold medications when used to treat symptoms of the common cold in this population".
American Academy of Pediatrics Committee on Drugs	No well-controlled scientific studies were found that support the efficacy and safety of narcotics (including codeine) or dextromethorphan as antitussives in children, indications for their use in children have not been

[86] Smith MB, Feldman W. Over-the-counter cold medications: a critical review of clinical trials between 1950 and 1991. J Amer Med Assoc 1993;269:2258-63

[87] Freestone C, Eccles R, Morris S, Jawad MSM. Assessment of the Antitussive Efficacy of Codeine Using Cough Sound Pressure Levels as a Means of Measuring Cough. Pulm Pharmacol 1996;9:365

[88] Lopez LA. Medical Officer's Review. Division of Nonprescription Clinical Evaluation, Center for Drug Evaluation and Research, July 24, 2007, p. 48. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf (p. 200).

(1997)[89]	established, and suppression of cough in many pulmonary airway diseases may be hazardous and contraindicated.
Schroeder K, Fahey T. (2002)[90]	Five trials tested antitussive drugs versus placebo. Two studies tested codeine and found it no more effective than placebo.
Carr BC (2006)[91]	This review concluded that codeine was not superior to placebo in the paediatric population.
Isbister GK et al. (2012)[92]	This review identified 72 studies or clinical reports, and concluded that there was little evidence for these medicines for coughs and colds in children, and that diphenhydramine and codeine appeared to be associated with a high frequency of severe adverse effects and toxicity
Smith SM et al. (2014)[93]	A 2014 Cochrane systematic review of studies examining the efficacy of over-the-counter (OTC) medications for acute cough could find only two trials of codeine in adults in which it appeared that codeine was no more effective than placebo.
Agarwal S, Grimstein C. (2015)[94]	In November 2015 the US FDA convened a meeting of two advisory committees to discuss the available safety data about codeine use in children for cough or analgesia. It included a review by a clinical pharmacologists who described that codeine is historically believed to possess antitussive properties, but the reviewer did not find any articles from literature indicating that codeine, morphine or any other codeine metabolites have antitussive properties

[89] Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children. Committee on Drugs. Pediatrics 1997; 99; 918-920.

[90] Schroeder K, Fahey T. Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. BMJ 2002;324:1–6.

[91] Carr BC. Efficacy, abuse, and toxicity of over-the-counter cough and cold medicines in the pediatric population. Curr Opin Pediatr 2006;18:184-8.

[92] Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. J Paediatr Child Health. 2012 Feb;48(2):91-8.

[93] Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub5

[94] Agarwal S, Grimstein C. FDA Office of Clinical Pharmacology. Clinical Pharmacology Review. Codeine. Office of Clinical Pharmacology. FDA, 2012. In: Food and Drug Administration. FDA briefing document for the Joint Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee meeting: The safety of codeine in children 18 years of age and younger. December 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM475975.pdf Page 67

Attachment 2: Opioid Risk Tool.

Date _____

Patient Name _____

OPIOID RISK TOOL

		Mark each box that applies	Item Score If Female	Item Score If Male
1. Family History of Substance Abuse	Alcohol	[ ]	1	3
	Illegal Drugs	[ ]	2	3
	Prescription Drugs	[ ]	4	4
2. Personal History of Substance Abuse	Alcohol	[ ]	3	3
	Illegal Drugs	[ ]	4	4
	Prescription Drugs	[ ]	5	5
3. Age (Mark box if 16 – 45)		[ ]	1	1
4. History of Preadolescent Sexual Abuse		[ ]	3	0
5. Psychological Disease	Attention Deficit Disorder, Obsessive Compulsive Disorder, Bipolar, Schizophrenia	[ ]	2	2
	Depression	[ ]	1	1
		TOTAL	———	———

Total Score Risk Category
Low Risk 0 – 3
Moderate Risk 4 – 7
High Risk ≥8

Reference: Webster LR. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. *Pain Medicine.* 2005;6(6):432-442. Used with permission.

Attachment 3: SOAPP-R tool.

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)

The following are some questions given to patients who are on or being considered for medication for their pain. Please answer each question as honestly as possible. There are no right or wrong answers.

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. How often do you have mood swings?	○	○	○	○	○
2. How often have you felt a need for higher doses of medication to treat your pain?	○	○	○	○	○
3. How often have you felt impatient with your doctors?	○	○	○	○	○
4. How often have you felt that things are just too overwhelming that you can't handle them?	○	○	○	○	○
5. How often is there tension in the home?	○	○	○	○	○
6. How often have you counted pain pills to see how many are remaining?	○	○	○	○	○
7. How often have you been concerned that people will judge you for taking pain medication?	○	○	○	○	○
8. How often do you feel bored?	○	○	○	○	○
9. How often have you taken more pain medication than you were supposed to?	○	○	○	○	○
10. How often have you worried about being left alone?	○	○	○	○	○
11. How often have you felt a craving for medication?	○	○	○	○	○
12. How often have others expressed concern over your use of medication?	○	○	○	○	○

PainEDU.org

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
13. How often have any of your close friends had a problem with alcohol or drugs?	○	○	○	○	○
14. How often have others told you that you had a bad temper?	○	○	○	○	○
15. How often have you felt consumed by the need to get pain medication?	○	○	○	○	○
16. How often have you run out of pain medication early?	○	○	○	○	○
17. How often have others kept you from getting what you deserve?	○	○	○	○	○
18. How often, in your lifetime, have you had legal problems or been arrested?	○	○	○	○	○
19. How often have you attended an AA or NA meeting?	○	○	○	○	○
20. How often have you been in an argument that was so out of control that someone got hurt?	○	○	○	○	○
21. How often have you been sexually abused?	○	○	○	○	○
22. How often have others suggested that you have a drug or alcohol problem?	○	○	○	○	○
23. How often have you had to borrow pain medications from your family or friends?	○	○	○	○	○
24. How often have you been treated for an alcohol or drug problem?	○	○	○	○	○

Please include any additional information you wish about the above answers.
Thank you.

Attachment 4: Differences between medical practice and community pharmacy for safe supply of opioids.

The current scheduling system provides different levels of regulatory control, and designates which professions need to be involved to ensure the effective and safe supply of potentially dangerous medicines.

In the case of prescription medicine subject to non-medical use, *Prescription Only Medicines* (Schedule 4) and *Controlled Drugs* (Schedule 8), there is an assessment additional to that of *Pharmacist Only* medicines.

There are two levels of assessment: the prescriber, and the pharmacist dispensing the prescription. In certain cases, there are three levels of assessment and control in circumstances where the permit system is required.

Non-prescription drugs, because of their easier availability, are perceived as safer, as should be the case, making it easier to rationalise self-dosing in excess of the safe dose regimen recommended. Consumers can request OTC CACCs by product name (direct product request (DPR)) and this may be perceived as a commercial transaction rather than a therapeutic alliance with a professional. They are less likely to receive professional advice than if they present with a symptom.

	Medical practitioner prescribing medicines	**Community pharmacy supply of non-prescription medicines**
How many levels of control in assessing patient need, optimising non-opioid treatment of pain, and ensuring the safety of supply?	• 2 levels of control -: the prescriber and the pharmacist dispensing the drug. In certain higher risk cases: • 3 levels of control: The prescriber, the pharmacist and the permit system	• 1 level of control – the pharmacist
Physical setting	Privacy of the consulting room with equipment to examine the patient	Over the counter in public space alongside other customers
Medical history available	Medical history and notes may be available if the patient is an established patient	Customer's prescription dispensing history may be available, but often not records of supply of non-prescription medicines. This history would not usually be available or arouse suspicion if the drug-seeking customer is visiting numerous pharmacies and calculating visits to avoid suspicion of drug-seeking.
Results of investigations available	Yes if an established patient	No
Ability to ask intimate and challenging questions.	Yes: Medical practitioners considering prescribing opioids are encouraged to assess risk of addiction using instruments such as the **Opioid Risk Tool** that includes questions about family or personal history of substance abuse, mental health disorder,	No. The public nature of over-the-counter settings in community pharmacy is a barrier to fully assessing the risk of addiction, particularly in the presence of other customers. Instead pharmacists assess this risk by the appearance, and

	and a history of child abuse.	presentation of the customer[95].
Ability to raise sensitive issues such as discussing whether the patient's use of opioids may constitute addiction.	This would be easier in the setting of a private consulting room using a patient-centred approach.	Difficult in the public setting of a community pharmacy.
Ability to examine the patient	Yes – full physical examination possible.	Only superficial assessment based on appearance and behaviour, and may be influenced by appearance, dress grooming and stereotypical perceptions of "drug addicts".
Ability for direct referral to other healthcare practitioners such as physiotherapists, psychologists with arrangements for reimbursement.	Yes. Can arrange psychologist treatment by developing a mental health plan to provide substantial reimbursement.	Can suggest referral.
Ability to prescribe non-opioid prescription medicines effective in addressing pain such as certain anti-depressants, anticonvulsants	Yes	No
Is there a potential conflict of interest in refusing a sale?	No	Because of the limiting circumstances of community pharmacy, assessment of risk is limited, and in the case of uncertainty about whether the Pharmacist Only Medicine is sought for abuse, pharmacists may find it difficult without good evidence to refuse supply. In the business environment of community pharmacy, some may be reluctant to lose a sale if they can't discuss with the customer robust evidence to justify this.
Does the current permit system operated by States and Territories for prescribing opioids provide an extra level of oversight and coordination of care?	Yes	No

[95] Nielsen S, Cameron J, Pahoki S. Over the counter codeine dependence. Final report. Turning Point Alcohol and Drug Centre, Melbourne. 2010.
Cooper R. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. Health Soc Care Community. (2013) 21(3), 254–262.

Attachment 5: Pharmacist interaction with customers in the supply of non-prescription medicines.

A journal article by Kelly FS, Williams KA, Benrimoj SI provides a good description of the nature of pharmacist interaction with customers in the supply of non-prescription medicines [96] and some of the themes appropriate to the supply of OTC codeine products is summarised with citation of the references in that article, with comments in some cases. Additional articles are also cited.

	Considerations and comments
When non-prescription medicine purchased in pharmacies are requested by name (Direct Product Requests [DPR]). • 60-85% of these medicines are requested by name[97] [98] [99].	Consumers may perceive the pharmacy as a source of supply rather than a source of advice. DPRs have been described as a transaction with no obligation for information exchange[100], implying that the customer has all information needed or is unreceptive to advice[101]. Pharmacy staff may assume that the patient is unreceptive to pharmacy advice. Pharmacists and support staff are more likely to abbreviate an interaction if there is a perception of customer disinterest[102]
Customers have an implicit trust in the safety of non-prescription medicines[103].	Consumers may have outdated or inaccurate information about safe use, or ignore recommended dosing regimens. (Comment: assumptions about safety are reasonable since the regulatory system is intended to determine an appropriate level of control, taking account of evidence supporting their safety, or identifying or anticipating an unacceptable level of risk requiring a higher level of control, as is the case with OTC CACCs and S2 codeine cold and flu medicines respectively.)
Inappropriate use can compromise patient safety.	Concerns by the FDA over paediatric use of cough medicines and changes to safety labelling[104].
Increasing patient autonomy	Increases the need for pharmacists to offer advice even if it is not sought, to bring consumers up-to-date with emerging information about risks to safety of use[105] [106] such as that provided by adverse event reporting[107]. (Comment: this is appropriate in the case of OTC codeine harm given its serious nature)

[96] Kelly FS, Williams KA, Benrimoj SI. Does advice from pharmacy staff vary according to the nonprescription medicine requested? Ann Pharmacotherapy 2009;43:1877-

[97] Chui WK, Li SC. Advice-giving on self-medication: perspectives of community pharmacists and consumers in Singapore. J Clin Pharm Ther 2005;30:225-31. DOI 10.1111/j.1365-2710.2005.00637.

[98] Krska J, John DN, Hansford D, Kennedy EJ. Drug utilization evaluation of non-prescription H2-receptor antagonists and alginate-containing preparations for dyspepsia. J Clin Pharmacol 2000;49:363-8.

[99] Emmerton L, Shaw J. Meditrends: current market purchasing trends for non-prescription medicines. N Z Pharm 2000;20:34-7.

[100] Stromme HK, Haugli A. Communication and interaction between customers and pharmacy personnel in two Norwegian pharmacies—an observational study. Int J Pharm Pract 1996;4:209-13.

[101] Hibbert D, Bissell P, Ward P. Consumerism and professional work in the community pharmacy. Sociol Health Illn 2002;24:46-65.

[102] Banks J, Shaw A, Weiss MC. Walking a line between health care and sales: the role of the medicines counter assistants. Pharm J 2005;274:586-9

[103] Hibbert D, Bissell P, Ward P. Consumerism and professional work in the community pharmacy. Sociol Health Illn 2002;24:46-65.

[104] Center for Drug Evaluation and Research/Office of the Center Director/Office of Drug Safety. Detailed view: safety labeling changes approved by FDA center for drug evaluation and research—November 2008. Washington: Food and Drug Administration, 2008. www.fda.gov/

[105] Hibbert D, Bissell P, Ward P. Consumerism and professional work in the community pharmacy. Sociol Health Illn 2002;24:46-65.

[106] Smith FJ, Salkind MR. Factors influencing the extent of the pharmacist's advisory role in greater London. Pharm J 1990;244:R4-6.

Mounting evidence of variability of pharmacy staff in their role in non-prescription medicine supply[108] [109].	Advice can be limited to non-clinical information (e.g. price) or can involve an exchange of clinical information[110]. Exchange of clinical information ranges from superficial to comprehensive and appears less likely for DPRs[111] [112].
The influence of request type on level of clinical information has long been recognised[113].	Clinical information exchange occurs in 90-100% of cases for a symptom-based request and 58-91% for DPRs. This implies that pharmacy staff may moderate exchange of clinical information according to the individual scenario.
Inappropriate supply has been attributed to inadequate assessment of consumer requests[114] [115].	
	Despite intensive efforts to ensure quality in the supply of non-prescription medicines, compliance with practice standards is variable[116].
Watson et al (2006) [117].	Conducted a staged observation of the supply of non-prescription medicines in community pharmacies to identify common problems with the consultation process, categorise problems, and evaluate performance. Most consultations (n = 75, 83%) were deemed deficient in information exchange, most commonly identified as violation of guidelines. Consultations involving product requests were less likely to be guideline compliant than symptom presentations. The large proportion of consultations classified as violations suggests that either pharmacy staff are unaware of professional guidelines and thus do not follow them (therefore these acts would not be violations),

[107] Center for Drug Evaluation and Research/Office of the Center Director/Safety Policy and Communication Staff. MEDWATCH—the FDA safety information and adverse event reporting program. Washington: Food and Drug Administration, 2009. www.fda.gov/Safety/MedWatch/default.htm

[108] de Almeida Neto AC, Benrimoj SI, Kavanagh DJ, Boakes RA. A novel educational training program for community pharmacists. Am J Pharm Educ 2000;64:302-7.

[109] Crampton M, Benrimoj SI, Gilbert A, Quintrell N. Standards of practice for the provision of pharmacist only and pharmacy medicines in community pharmacy: final report. Sydney: University of Sydney, University of South Australia, 1998.

[110] Bissell P, Ward PR, Noyce PR. Variation within community pharmacy. Part 1. Responding to requests for over-the-counter medicines. J Soc Admin Pharm 1997;14:1-15.

[111] Bissell P, Ward PR, Noyce PR. Variation within community pharmacy. Part 2. Responding to the presentation of symptoms. J Soc Admin Pharm 1997;14:105-15.

[112] Bissell P 1997 op cit.

[113] . Bissell P, Ward PR, Noyce PR. Variation within community pharmacy. Part 2. Responding to the presentation of symptoms. J Soc Admin Pharm 1997;14:105-15.

25. Emmerton L, Shaw J. The influence of pharmacy staff in non-prescription medicine sales. Int J Pharm Pract 2002;10:101-6.

[114] Norris PT. Purchasing restricted medicines in New Zealand pharmacies: results from a “mystery shopper” study. Pharm World Sci 2002;24:149-53.

[115] Anderson C, Alexander A. Response to dysmenorrhoea: an assessment of pharmacists’ knowledge and its application in practice. Int J Pharm Pract 1993;2:180-3.

[116] Watson MC(1), Hart J, Johnston M, Bond CM. Exploring the supply of non-prescription medicines from community pharmacies in Scotland. Pharm World Sci. 2008;30:526-35.

[117] Watson MC, Bond CM, Johnston M, Mearns K. Using human error theory to explore the supply of non-prescription medicines from community pharmacies. Qual Saf Health Care. 2006 Aug;15(4):244-50.

	or that they knowingly violate the guidelines due to reasons that need further research.
Watson et al (2009)[118].	conducted three covert visits from simulated patients at community pharmacies, and found that few SP consultations achieved the minimum standard of practice although most resulted in an appropriate outcome
Benrimoj et al (2007)[119].	examined a process for standards development and testing in community pharmacy in Australia by studying pharmacy staff behaviour during pseudo-patient visits, testing compliance with standards that had been developed, with immediate feedback to achieve change in practice. Overall compliance with the Standards increased from a rate of 47.4% to 70.0% following feedback.
Hattingh HL et al (2009)[120].	A study of integration of standards and guidelines into pharmacy practice in Queensland found that procedures followed concerning the supply of over-the-counter medicines varied. The majority of participants did not regard this as a pharmacist's immediate role, but rather relied on support staff to identify when the supply required a pharmacist's intervention. The study noted a lack of integration of practice standards.
Emmerton (2009)[121].	observed non-prescription medication sales in Queensland community pharmacies and interviewed all available patients following the transaction. Pharmacists consulted in only 54.7% of Pharmacist Only Medicine sales.
Spyrou P. (2015)[122].	Concern has also recently been expressed about the variability of pharmacists to provide clinical input to customers supplied with Schedule 3 medicines. It is described that the 'involvement' of the pharmacist can mean different things, depending on a pharmacy's structure and culture. Some pharmacists will say that overhearing the interaction between the patient and pharmacy assistant is adequate, and they will intervene if required. Other pharmacists prefer to speak with each client seeking a Schedule 3 medicine.

[118] Watson MC(1), Cleland JA, Bond CM. Simulated patient visits with immediate feedback to improve the supply of over-the-counter medicines: a feasibility study. Fam Pract. 2009 Dec;26(6):532-42.
[119] Benrimoj SC, Gilbert A, Quintrell N, Neto AC. Non-prescription medicines: a process for standards development and testing in community pharmacy. Pharm World Sci. 2007;29:386-94.
[120] Hattingh HL, King MA, Smith NA. An evaluation of the integration of standards and guidelines in community pharmacy practices. Pharm World Sci. 2009 Oct;31(5):542-9.
[121] Emmerton L. The 'third class' of medications: Sales and purchasing behavior are associated with pharmacist only and pharmacy medicine classifications in Australia.J Am Pharm Assoc 2009;49:31-7.
[122] Spyrou, Phil. Schedule 3: Use it or lose it. Australian Journal of Pharmacy. 8 September 2015.

Attachment 6: Pharmacists' management of requests for OTC combination analgesics containing codeine (OTC CACC)

Pharmacists' management of requests OTC combination analgesics containing codeine (OTC CACC)

Patient perspectives.

Nielsen et al (2013) interviewed 20 codeine dependent subjects using qualitative research methodology. Subjects described that they found it generally easy to access OTC codeine, describing 'standard' questioning, minimal intervention from pharmacists and only occasional refusal to supply. A better appearance and presentation was generally linked to easy codeine supply[123].

Very occasionally family members purchased packs for subjects.

Pharmacist responses fell into two categories: they either supplied the products with virtually no pharmacist interaction, or refused supply with limited discussion. Less commonly, refusal happened by the pharmacist stating they were out of stock, despite sometimes being clearly displayed on a shelf.

Some subjects purchased other items to allay suspicion.

No participant described an experience of a pharmacist who directly refusing supply raising concerns about abuse or dependence or suggesting they seek assistance with OTC codeine dependence.

Nielsen et al (2010) interviewed subjects dependent on OTC CACC, and included questions about their experience with pharmacies[124].

Common approaches were:

- Using multiple pharmacies
- Purchasing multiple days' supply at a time (often from multiple pharmacies in one "pharmacy run"
- Noting which pharmacies were easier, and even noting details about individual staff that did not ask questions
- Not going to the same place too often
- Purchasing lower quantities to avoid interaction with the pharmacist
- Internet was only identified as a source when it was becoming harder to source codeine, with one reason listed for this being wanting to avoid the record keeping that went with internet purchasing
- Opportunistic purchasing was common, for example when out of their usual area if a pharmacy was seen in passing this was identified as a good opportunity to stock up
- Going to a prescriber was considered expensive and a hassle

Interactions with pharmacy staff were described as "standard" questions and comments that included:

- Asking what the product was being used for
- Stating "don't take more than 8 a day"

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[123] Nielsen S, Cameron J, Pahoki S. Opportunities and challenges: over-the-counter codeine supply from the codeine consumer's perspective. *International Journal of Pharmacy Practice* 2013, 21, pp. 161–168.

[124] Nielsen S, Cameron J, Pahoki S. Over the counter codeine dependence. Final report. Turning Point Alcohol and Drug Centre, Melbourne. 2010

Little additional questioning was described by participants. No participant described an experience of a pharmacist directly raising concerns about abuse or dependence with the participants interviewed or referring them/suggesting they seek assistance with codeine dependence.

Subjects used different methods to avoid questioning by pharmacists, including:

- Going to 'easy' pharmacies where less questions were asked
- Speaking to staff they knew did not ask questions
- Buying smaller quantities from more pharmacies rather than asking for larger packs

Dressing well and looking respectable was associated with easier access to codeine. One subject perceived that the supply of codeine was based more on her appearance than therapeutic need.

Refusal was rarely reported, even by participants consuming or purchasing large quantities of codeine on a daily basis.

Refusals tended to result in going somewhere else to purchase the product. Refusals were not accompanied with referrals or discussion around codeine dependence or risks with prolonged or high dose use.

Cooper RJ (2013 (b)) conducted in-depth interviews with a sample of people misusing or addicted to OTC medicines[125].

- Codeine was the main medicine abused for nontherapeutic effects
- Current treatment may not be appropriate, based on hidden nature of OTC addiction and the subjects' perceived differences to other forms of addiction.
- A key feature was how unproblematic it was to obtain medicines,
- Policies to restrict supplies were perceived to be ineffective,
- some pharmacies were considered easier than others to obtain supplies
- Avoiding detection was a key concern for individuals who described intentionally varying the pharmacy used, using 'schedules, 'tables' or 'lists' of those visited
- Avoiding detection by lying and fabricating responses to questions from staff
- Most participants did recall isolated and uncomfortable instances of being challenged; in some cases, resulting in avoiding that pharmacy or visiting less frequently
- Critical incidents such as rare instances of being confronted in a pharmacy, medical problem such as a gastrointestinal bleed or illegal activity also appeared to represent moments when participants considered themselves to have a problem
- those describing codeine and ibuprofen (12.8 mg and 200 mg/tablet, respectively) compound tablet use reporting daily consumption between 32 and 64 tablets
- pharmacists were not referred to by participants at all in relation to treatment or support in the present study,
- the author described difficulties in implementing harm-reduction strategies in community pharmacy
- Those affected represent a hard to reach group, with little known about their experiences

[125] Cooper RJ. 'I can't be an addict. I am.' Over-the-counter medicine abuse: a qualitative study. BMJ Open 2013;3:e002913. doi:10.1136/bmjopen-2013-002913

Pharmacists' perspective and management.

Nielsen S et al (2010) describe that the interface between OTC codeine users and pharmacists was identified to have a number of challenges[126]. Pharmacists are currently in a difficult position to respond.

Themes that emerged from interviews with pharmacists:

- Codeine-seeking customers can become abusive if the pharmacist tries to intervene.
- Sometimes they will just go to another pharmacy instead.
- For pharmacists codeine dependence was associated with deviancy, and deteriorating general appearance.
- Another pharmacist based concerns solely on frequency of purchase
- Some were not confident of their ability to identify codeine dependence.
- Pharmacist do not know much about the codeine purchaser, making it difficult to know if a customer may be dependent
- Pharmacists are not comfortable explaining to customers that they suspect they may be using codeine inappropriately and have limited responses other than to try to avoid a sale in this situation.
- The challenge for pharmacists using frequency of purchase where sales are not uniformly recorded and records from other pharmacies are not available as an indicator, together with other pharmacy characteristics such as extended hours pharmacies, and shift changes in pharmacists, increases the difficulty in identifying frequent codeine purchases. The reluctance to identify a codeine user or refuse a sale in these circumstances can be clearly understood.

Hamer et al (2014) interviewed pharmacist following the upscheduling of OTC combination analgesics containing codeine (OTC CACC) to Pharmacist Only (Schedule 3) in 2010 that required pharmacists to be involved in all sales. They describe that pharmacists face a number of challenges to ensure safe supply and intervening in OTC CACC dependence [127].

Pharmacists were found to monitor the supply of OTC CACC by recording sales and to intervene when they felt that the medication was being used too frequently.

Pharmacists perceived a number of challenges surrounding the provision of OTC CACC including;

- Supply from other pharmacies,
- Establishing therapeutic need,
- Managing codeine dependent people,
- Lacking confidence in discussing misuse with people,
- Being unsure where to refer dependent people for help, and
- Purchaser resentment towards pharmacist involvement in all sales.

Pharmacists tended to stereotype people who request OTC CACC as either 'genuine' or 'misusers.'

[126] Nielsen S, Cameron J, Pahoki S. Over the counter codeine dependence. Final report. Turning Point Alcohol and Drug Centre, Melbourne. 2010.

[127] Hamer AM, Spark MJ, Wood PJ, Robes E. The upscheduling of combination analgesics containing codeine: The impact on the practice of pharmacists. Research Soc Admin Pharm 2014;10:669–678.

Cooper R (2013 (a)) interviewed pharmacists and medicine counter assistants in the United Kingdom about their response to perceived over the counter medicine abuse[128].

Frequency of purchase was central to assistants' and pharmacists' definition of those suspected of OTC medicine abuse to distinguish intentional from unintentional medicine misuse.

Barriers to pharmacists providing more support for those suspected of OTC medicine abuse were:

- There is uncertainty among pharmacists about how to manage over-the-counter abuse.
- The commercial environment of the community pharmacy may be a barrier to preventing abuse and providing support
- A lack of information about customers,
- Easy access to medicines,
- Poor communication between community pharmacies
- Many appeared uncertain of treatment options
- Uncertainty about how pharmacists could effectively stop the problem of abuse.
- Customer expectations
- Medicine advertising
- Easy access to different community pharmacies.
- Concerns about how to broach suspected abuse were considered harder in smaller, rural pharmacies,
- City pharmacies were associated with fewer regular customers and greater anonymity.
- Codeine-containing analgesics were the primary medicines referred to by assistants, but both they and pharmacists also referred to codeine-containing cough liquid products.
- A customers' negative reaction – and in some cases aggression – to a refused or referred sale was also suggestive of abuse
- Interventions to counter misuse were perceived as negative
- Interventions were associated with themes of uncertainty and incomplete customer information.
- Several also described how difficult it was to challenge customers, particularly in smaller, rural pharmacies
- There was a perception that customers abusing medicines used deception and lied to obtain supplies,
- Some used others to purchase medicines for them, and
- Several pharmacists noted their concerns that some customers had rehearsed their responses to enable successfully purchasing medicines subject to misuse.

Van Hout MC et al (2016) reviewed recommendations for misuse of non-prescription codeine containing products[129].

They noted that:

- Pharmacy tactics currently include removal of codeine containing products displayed at point of sale,
- Refusal of sale or restriction of quantity sold in the event of suspect requests,
- The on-site recording of incidences of suspected misuse,
- Medicines information provision by medicines counter assistants and pharmacists,

[128] Cooper R. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. Health Soc Care Community. (2013) 21(3), 254–262.

[129] Van Hout MC, Norman I. Misuse of non-prescription codeine containing products: Recommendations for detection and reduction of risk in community pharmacies. Int J Drug Pol 2016;27:17-22

- Direct pharmacist intervention by additional customer questioning and customer referral to primary care professionals

They note some inherent difficulties in the incorporation of these additional roles and responsibilities:

- The business models and the public environment of most pharmacies.
- Many requirements for the detection of codeine misuse are not widely achievable in the community pharmacy environment because lack of privacy prevents the assessment of intimate details of the customer, and the management of challenging questions and provision of advice.

Byrne GA et al (2015) study of the practices of pharmacists responding to requests for OTC CACCs. This study investigated practice behaviour of community pharmacists using a covert simulated patient (SP) methodology to observe the response of pharmacy staff to a standardised OTC-CACC request[130]. The field work was done in July 2015.

SPs were trained for two scenarios involving a direct request for Nurofen Plus. Each SP provided identical information for the reason for use, symptoms, and medical history; Scenario One (Sc1) SPs described no previous history of OTC-CACC use and Scenario Two (Sc2) SP described using OTC-CACC regularly for the past month. SPs visited 38 metropolitan and 37 non-metropolitan pharmacies.

An OTC-CACC was purchased in 71% (75%, n=55 Sc1; 67%, n=48 Sc2) of pharmacy visits; an alternative treatment was recommended five times. Adequate counselling was received for 25% of product purchases for both scenarios. The SP for Sc2 was referred to a health professional in 19% (n=14) of visits. In 18% (n=19) of product purchases the SP was not provided with medication counselling.

A positive outcome (Sc1-product with counselling, Sc2-referral, product, counselling) was reported in 19% of Sc1 visits and 5.6% of Sc2 visits.

A negative outcome for the requester was more likely for repeat purchase primarily because the need to refer was not identified. Overall, minimal product advice was received.

[130] Byrne GA, Pene J, Spark MY. Over-the-counter supply of combination analgesics containing codeine in community pharmacy: A simulated patient study. APSA-ASCEPT Joint scientific meeting 2015. Abstract no. 122.

Attachment 7: Pharmacist exposure to information about misuse of OTC CACCs prior to the Latrobe University simulated patient field work in July 2015[131].

There is a background of ongoing training and quality use of medicines activities by pharmacy organisations, journals and pharmacy news media. The Pharmacy Guild of Australia's Quality Care Pharmacy Program (QCPP) is a quality assurance program for community pharmacy that has operated for 15 years, with over 90% of pharmacies accredited across Australia and externally audit every two years by QCPP Licensed Assessors. It provides a range of resources to guide professional services. QCPP was recognised in 2011 as Australian Standard 85000:2011 - quality management system for pharmacies in Australia. The Guild is accredited by Standards Australia as a Standards Development Organisation, and QCPP is accredited by JAS-ANZ (Joint Accreditation System of Australia and New Zealand) as a conformity assessment body.

There have been major changes and events surrounding the supply and misuse of OTC CACCs for many years in Australia and other countries where these medicines are available, that could be expected to heighten awareness and enhance the care with which they are supplied by pharmacists.

- In June 2005 the National Drugs and Poisons Schedule Committee (NDPSC) first considered the issue of codeine abuse from bilayer tablets of an OTC codeine-ibuprofen analgesic. This had been in response to information from the custodian of a website that among the more than 500 people contacting the site that they were the leading cause of concern. The committee considered that since they did not meet the definition of 'compounded' they should be rescheduled to Schedule 8. They were quickly replaced by a compounded product.
- Pharmacists have a sense of non-medical use of OTC medicines. Surveys since 2000 consistently describe that the opiate OTC codeine analgesics are the leading OTC products of concern about abuse[132] [133] and a recent survey reported that codeine-containing products were perceived as the leading OTC medicine misused [134].
- At the June 2007 NDPSC meeting a jurisdictional representative informed the committee that pharmacists had raised concerns about abuse of an OTC codeine-ibuprofen product, and that codeine could easily be separated from ibuprofen by simply dissolving in water. The NDPSC had received other communications expressing concern about misuse of this product, and undertook a lengthy review of the situation leading up to the notice of rescheduling of all OTC CACCs to *Pharmacist Only* to be implemented in May 2010.
- During this lengthy consideration (2007-2009) and around the time of rescheduling there were numerous public and media articles describing misuse, and the opposition from the pharmaceutical company trade association and Pharmacy Guild of Australia.
- In 2009 and 2010 Reckitt Benckiser (Nurofen Plus) employed Edelman, a global public relations company, to execute their codeine issues management[135]. It included an extensive pharmacist and patient education program. Edelman conducted an issues management

[131] Byrne GA, Pene J, Spark MY. Over-the-counter supply of combination analgesics containing codeine in community pharmacy: A simulated patient study. APSA-ASCEPT Joint scientific meeting 2015. Abstract no. 122.
[132] Pates R, McBride A, Li S, et al. Misuse of over-the-counter medicines: a survey of community pharmacies in a South Wales health authority, The Pharmaceutical Journal 2002;268:179-182.
[133] Matheson C, Bond C, Pitcairn J, Misuse of over-the-counter medicines from community pharmacies: a population survey of Scottish pharmacies, The Pharmaceutical Journal 2002;269:66-68
[134] Wright J, Bond C, Robertson HD, Matheson C. Changes in over-the-counter drug misuse over 20 years: perceptions from Scottish pharmacists. J Public Health 2015 Nov 27. pii: fdv169. [Epub ahead of print]
[135] Public Relations Institute of Australia. Edelman: Codeine Issues Management Program Golden Target Award Entry. 2012. http://www.pria.com.au/documents/item/4284 (accessed 19 January 2016)

campaign that included an education campaign *Manage Pain – effectively, safely and responsibly* targeting pharmacists and pharmacy assistants, and consumers. The educational materials were endorsed by the Pharmacy Guild of Australia and the Pharmaceutical Society of Australia. The *Manage Pain* materials were distributed via the Pharmacy Guild of Australia to pharmacies nationally in August 2009. The education program comprised the following materials: **Sticky notes:** to be placed on a pack of codeine containing analgesic for the customer to read the three things to remember when taking these medications. **Pharmacy Information card:** A reference tool for the pharmacist and pharmacy assistants when consulting with customers purchasing or requesting analgesics with codeine. **Magnet:** Contains a series of contact numbers for Alcohol and Drug Information Services in each state and territory for pharmacy staff to access quickly. **Website** as an information hub to be used by pharmacy staff and consumers to find out more about OTC codeine combined analgesics. Two pharmacy media campaigns were executed. Following the implementation of the *Manage Pain – effectively, safely, responsibly* program in August 2009, Edelman worked with RB to generate a second wave in March 2010. Prior to this, Edelman disseminated a survey to pharmacists through the Pharmacy Guild seeking feedback about the program. Changes were made based on the feedback and the second wave was disseminated in April 2010. There was also a comprehensive and prolonged media campaign.

- Rescheduling, particularly the removal of products from a lower schedule (Schedule 2), and increasing limitations of products, is unusual. In May 2010 OTC CACCs were rescheduled, and this was the subject of intense pharmacy media activity, and should have raised awareness of pharmacists to the unique challenges of providing these products over-the-counter.
- In 2014 Reckitt Benckiser sent spools of 1000 adhesive warning labels “For 3 days use only. Can Cause addiction.” to every pharmacy in Australia, together with patient information leaflets describing the risk of addiction and adverse effects of misuse.
- Reckitt Benckiser and GSK subsequently labelled their packs of Nurofen Plus, Panafen Plus, Panadeine and Panadeine Extra with this warning label, followed by many other companies marketing OTC CACCs.
- Since the TGA announced the proposal to reschedule OTC CACCs to *Prescription Only* in April 2015 there has been intense public and pharmacy media about the proposal.
- On 27 March 2015 the Pharmaceutical Society of Australia issued a media release noting that it strongly promotes QUM and responsible self-medication, supported by continuing professional development and practice support resources to inform pharmacists’ skills in pain management and addiction care. PSA concurrently released a position paper *Minimising harm from the inappropriate use of over the counter analgesics*, together with practice support materials including pads of *Using codeine pain relievers safely* consumer information leaflets. A one-hour training session on codeine containing analgesics was made available online, approved the QCPP, available from March 2015 to February 2017.The position statement notes that PSA was committed to supporting pharmacists to provide solutions to consumers seeking to manage pain and addiction issues, and supports consumers continuing to have reasonable access to OTC analgesics with the advice of a pharmacist, as pharmacists are well equipped to assist consumers with appropriate pain management options in accordance with QUM principles.

Given this extensive public and pharmacy media coverage, and numerous educational and supportive activities, pharmacists should be well equipped to manage the safe supply of OTC CACCs, provided they are unrestrained by the limitations of *Pharmacist Only* circumstances. From

widespread targeted media, and pharmacists' own observations[136] of 'codeine road trips' to visit multiple pharmacies to obtain OTC CACCs, and difficulties in managing requests and descriptions of 'codeine tantrums' when refused[137] [138] it is unlikely that any Australian pharmacist would be unaware of problems of drug seeking for OTC CACCs, and the harm that misuse can cause.

The table below describes some activities and a small selection of the many media articles prior to Latrobe University's field work in July 2015 observing pharmacists' response to requests for OTC CACCs.

14 September 2014 Browne, Rachel. Doctors and pharmacists call for tighter controls on codeine due to rise in addiction. Sydney Morning Herald September 14, 2014.	Doctors and pharmacists call for tighter controls on medicines containing codeine due to increasing concern about addiction, with users being referred to drug programs – including methadone – for treatment. With pharmacists reporting addicts can be difficult to detect because they tend to be well presented, middle-class professionals, PSA, PGA RACP support recording of over the counter codeine product sales to deter "pharmacy shoppers". The owner of Stanmore Station Pharmacy, said the addiction does not discriminate. "In terms of the demographics of people misusing it, it seems to be younger people but from stable, professional backgrounds," he said. The Pharmaceutical Society of Australia's Dr Shane Jackson believes up to 10 per cent of people who buy over the counter codeine products may be misusing them. "Typically, these people are functional professionals with jobs and families who start using the combination analgesic quite legitimately for chronic pain ," Dr Jackson said
Haggan, Megan. Pharmacists worried by OTC codeine. Pharmacy News 16 March 2015	A survey of 1022 Australian pharmacists reported that: • 72% of respondents said they were either somewhat or very concerned about the potential for adverse consequences resulting from the ordinary use of codeine-based analgesics; • 99% said they were either somewhat concerned, or very concerned, about the potential for adverse consequences resulting from the misuse of codeine-based analgesics; and • 92% either somewhat agreed, or strongly agreed, when asked whether they thought codeine combinations are used too often by consumers and patients in Australia.
March 2015 Cautionary Advisory Labels (CALs)	Cautionary Advisory Labels. (CALs) CALs are an effective way of supplementing verbal counselling and assisting pharmacists to fulfil their legal and professional obligations.

[136] O'Donoghue N. Codeine road-trips demand Project STOP. Pharmacy News 11 January 2012 http://www.pharmacynews.com.au/news/latest-news/codeine-road-trips-demand-project-stop

[137] 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

[138] Pharmacy Guild of Australia. 'Codeine tantrums' sparks Facebook frenzy. Forefront 30 April 2014

Australian Pharmaceutical Formulary and Handbook.	The 2015 edition of the Australian Pharmaceutical Formulary and Handbook (APF)[139] introduced a number of significant changes to the CAL recommendations, and introduced a new set of CALs including label 24 for use on non-prescription analgesic medicines containing codeine or non-prescription dihydrocodeine products[140]. 
27 March 2015 Booker, Chris. PSA calls for real-time codeine monitoring. Pharmacy News. 27 March 2015	In its new position paper, *Minimising harm from the inappropriate use of over the counter analgesics*, PSA explains it remains committed to supporting pharmacists to provide solutions to consumers seeking to manage pain and addiction issues. PSA has developed an extensive range of practice support resources including: • Existing Pain Management Pharmacy Support Resource on PSA's website • Professional guidelines for the supply of codeine-containing analgesics (revised for APF23) • The March edition InPHARMation, available to Self Care subscribers • A Webinar on pain being held in March • A pain article in April's *Australian Pharmacist* • Resources for pharmacists to use with consumers In addition, a leaflet alerting consumers to the dangers of inappropriate use of combination codeine pain relievers titled *Using codeine pain relievers safely*, was made available
2 April 2015 TGA announcement of rescheduling proposal with an invitation to comment	The TGA is seeking comments from interested parties on the following proposed amendments to the Poisons Standard referred by the delegate for scheduling advice. 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
7 April 2015 Haggen, Megan. Codeine to go script-only? Aust J Pharmacy 7 April 2015.	It is proposed that the current Schedule 3 codeine entry be rescheduled 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

[139] Sansom L, ed. Australian Pharmaceutical Formulary and Handbook. 23rd edn. Canberra: Pharmaceutical Society of Australia; 2015.
[140] Cautionary Advisory Labels in practice. Australian Pharmacist. March 2015.pages 12-13.

	products containing codeine. Consideration may be given as to whether the Schedule 2 entry for codeine should also be amended.
24 April 2015 Dow, Aisha. Over-the-counter sale of codeine pain killers such as Nurofen Plus and Panadeine may end. Sydney Morning Herald 26 April 2015	Codeine addicts swallowing up to 100 tablets a day have been known to visit multiple pharmacies to get around rules introduced in 2010 that restrict purchases of more than five days' supply of the drug at one time. Recent government agency data shows the number of Australians being treated for codeine addiction more than tripled over the decade to 2012-13, from 318 to more than 1000 a year. But Matthew Frei, addiction medicine specialist and clinical director of Turning Point Alcohol & Drug Centre, said this figure probably vastly underestimated the number of problem users as many patients who abused drugs were not detected. Pharmacy Guild Victorian president Anthony Tassone said pharmacists were qualified to determine who could purchase codeine products over the counter and who should be referred to a doctor for further discussion. "For pharmacists to supply schedule 3 medication including codeine they need to establish a genuine therapeutic need," he said.
30 April 2015 Haggan, Megan. Consumers need codeine access. Aust J Pharmacy 30 April 2015	**The Pharmaceutical Society of Australia has welcomed comments made by the Federal Minister for Health, Sussan Ley, acknowledging and supporting the skills of pharmacists to effectively and safely manage the supply of medicines containing codeine.** The Minister said: "Pharmacists are well qualified to advise, to assess, and to determine what somebody's requests for medicines are, and how appropriate those requests may be." "Pharmacists are the recognised medicines experts and as the Minister said, have the qualifications and knowledge to determine the appropriateness of supply of these medicines," Dr Emerson says. Dr Emerson says pharmacists are aware of and share concerns over the rising levels of harm associated with the inappropriate use of over-the-counter analgesics containing codeine. "PSA has suggested a number of strategies in our recent position statement, *Minimising harm from the inappropriate use of over the counter analgesics*, and have developed resources for use by pharmacists and consumers to strengthen the appropriate use of these medicines," he said. "We strongly promote quality use of medicines and responsible self-care, and are committed to supporting pharmacists to provide solutions to consumers seeking to manage pain and addiction issues.
30 April 2015 Why making codeine products prescription-only is a good idea The Conversation.	What's more, some pharmacists are unsure how to assess if a person is seeking drugs beyond their therapeutic need, or how to manage "codeine tantrums" when sale is refused. Some Australians take "codeine road trips" – travelling long distances to visit multiple pharmacies and purchase large quantities of these drugs.
30 April 2015 Vagg, Michael. Four reasons why codeine should not be sold without prescription. The Conversation. 30 April 2015.	OTC doses of codeine aren't really more effective than the drugs they are added to There are better alternatives to codeine-containing OTC formulations Unsupervised dose escalation can have serious risks with no prospect of benefit This is an opportunity to improve the care of acute pain in the community
6 May 2015 Haggan, Megan. ASMI welcomes Vic real-time monitoring.	ASMI welcomes announcement by Victorian Government commitment of $300,000 for planning of real time prescription monitoring because it could be used to monitor the use of OTC codeine combination analgesics

Australian J Pharmacy 6 May 2015	and help pharmacists manage the risk of these medicines..
4 May 2015 Pigrim, Meg. Pharmacy leaders reject bid to restrict codeine. Pharmacy News. 4 May 2015	The PSA and the Pharmacy Guild of Australia have rejected calls to make 150 codeine-based analgesics prescription only medication. They say pharmacists play an important role in assisting consumers to appropriately manage their pain through the provision of over the counter (OTC) analgesics in accordance with Quality Use of Medicines (QUM) principles. The PSA says it is concerned about the rising levels of harm associated with inappropriate use. However, it believes there are other ways of controlling the medications. "The Guild recognises there are safety concerns associated with OTC codeine products. But the majority of people who use them under advice are using them appropriately."
7 June 2015 Sinnerton, Jackie. Stressed mums are becoming accidental drug addicts. Courier Mail 7 June 2015.	MORE Queensland mothers are becoming accidental addicts as they turn to over-the-counter painkillers to ease the stresses of life. Addiction specialists see more women under the age of 45 swallowing 60 to 100 codeine-ibuprofen tablets each day. They say over-the-counter drugs are perceived as "respectable" and not addictive, but users can end up hooked and, in the worst cases, lining up for methadone to kick the habit. Matthew Frei, who researches the misuse of codeine-ibuprofen analgesics, said the move to behind-the-counter, rather than over-the-counter, had made little difference to the number of people abusing the drugs. Dr Rowan said people had no problem accessing 100 tablets a day from pharmacies.
23 June 2015 Schoombie, Deon. Codeine crackdown could leave us all worse off. Aust J Pharmacy 23 June 2015	ASMI, which represents the non-prescription medicines industry, acknowledges that addiction is a serious problem that warrants specialist attention. What the committee is considering has the potential to effectively inconvenience a very large number of people in order to safeguard a relatively small number who misuse these medicines. Australia already has in place several measures to curb misuse, such as limiting pack sizes and requiring them to be available only after consultation with a pharmacist. Recent research by the Macuarie University Centre for the Health Economy found that re-scheduling of current S3 analgesics to S4 would result in an additional $93 million in costs for GP visits and a further $162 million in lost productivity
June 2015 Australian Journal of Pharmacy. June 2015 CPD questions:	4 questions were about OTC CACCs, and the efficacy of OTC paracetamol/ibuprofen products.
2 July 2015 Huxhagen, Karalyn. Clinical tips:	Like all community pharmacists, I kick myself when I fall for the story that causes an avalanche of codeine-seeking patients to think I am an easy hit

Counselling the codeine-seeking patient. Aust J Pharmacy. 2 July 2015	for their medication fix. Today I had a gentleman drive an unregistered, unroadworthy car at least 30km to the pharmacy to ask for Panadeine Extra. He passed over a licence that was not his and gave me three different addresses. He could not turn his car off so left it running at the front door! He gave an award winning performance of a sore back walk and groaned a lot. There are many performances like these every day in every pharmacy in Australia, as codeine seekers are a large problem that we work with. Describes a number of strategies and referral opportunities to help patients with pain.

ASMI: Australian Self Medication Industry
PSA: Pharmaceutical Society of Australia
PGA: Pharmacy Guild of Australia
RACP: Royal Australasian College of Physicians

In July 2015, after this intensive general and pharmacy media attention, and educational efforts of pharmacy organisations, Latrobe University conducted a study using simulated patients[141] that reported that adequate counselling was received for only 25% of product purchases, and concluded that overall minimal product advice was received and needs to be increased to ensure appropriate and safe use of these products. (see below).

[141] Byrne GA, Pene J, Spark MY. Over-the-counter supply of combination analgesics containing codeine in community pharmacy: A simulated patient study. APSA-ASCEPT Joint scientific meeting 2015. Abstract no. 122.

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Over-the-counter supply of combination analgesics containing codeine in community pharmacy: A simulated patient study

Georgia A. Byrne[1], Pene J. Wood[1], M. Joy Spark[1]. School of Pharmacy and Applied Science, LaTrobe University[1], Bendigo, VIC.

Introduction. Over-the-counter combination analgesics containing codeine (OTC-CACC) are Pharmacist Only Medicines used for short term treatment of pain; misuse of OTC-CACC has become a significant health issue in Australia. Pharmacists are required to establish a therapeutic need for every sale. However current quantitative evidence on the practice behaviour of community pharmacists during OTC-CACC product requests is limited.

Aims. To investigate the current management of OTC-CACC requests in Australian community pharmacies.

Methods. A covert simulated patient (SP) methodology was used to observe the responses of pharmacy staff during an OTC-CACC request. SPs were trained for two scenarios involving a direct product request for Nurofen Plus® (OTC-CACCI, 200mg ibuprofen, 12.8mg codeine). Each SP provided identical information relating to reason for use, symptoms, and medical history; Scenario One (Sc1) SPs had no previous history of OTC-CACC use and Scenario Two (Sc2) SP had used OTC-CACCI regularly for the past month. Data were recorded immediately post-visit on a data collection form.

Results. SPs visited 38 metropolitan and 37 non-metropolitan pharmacies (73 Sc1 and 72 Sc2). An OTC-CACCI was purchased in 71% (75%, n=55 Sc1; 67%, n=48 Sc2) of pharmacy visits; an alternative treatment was recommended five times. Adequate counselling was received for 25% of product purchases for both scenarios. The SP for Sc2 was referred to a health professional in 19% (n=14) of visits. In 18% (n=19) of product purchases the SP was not provided with medication counselling. A positive outcome (Sc1-product with counselling, Sc2-referral, product, counselling) was reported in 19% of Sc1 visits and 5.6% of Sc2 visits. There was a significant association between scenario and outcome ($\chi^2(2, n=145) = 47.5$, $p < 0.005$, Cramer's $V = 0.57$) with a large effect size.

Discussion. Outcomes varied depending on whether the requester was initiating or continuing treatment; a negative outcome for the requester was more likely for repeat purchase primarily because the need to refer was not identified. Overall minimal product advice was received and needs to be increased to ensure appropriate and safe use of these products.

Attachment 8: The Hoopla article: Codeine addiction destroyed my family. 2014[142]

CODEINE ADDICTION DESTROYED MY FAMILY

BY ANONYMOUS SEPTEMBER 10, 2014 95 6 14

My seven year old spent his first football presentation night with one eye on the car park saying, "My dad is coming, my dad is coming". It was as though saying it enough times might somehow make it real. His father never came.

The story of how my children become the ones with a deadbeat dad is shocking because at its centre is a chain of professionals who claim their life work is to help and heal, not hinder and harm.

When I returned to work, after having three babies in two-and-a-half years, my husband, Tom (not his real name), chose to become a stay-at-home dad.

Coming home, the children would tell me about the parks they had visited that day; some were hundreds of kilometres away from our home in a sleepy fishing village in rural Victoria.

I objected to the seeming waste of petrol these daily grand tours cost. Tom would say, "The boys fell asleep in the car so I just kept driving," or "it was just a special treat," or "I let them choose today so I had to."
It was years before I discovered that visiting parks was just a short break in between the real activity – chemist hopping for codeine.

[142] Codeine addiction destroyed my family. The Hoopla. http://thehoopla.com.au/counter-addiction/

Tom was driving with my children in the car, on roads he shared with you and people you love, under the heavy influence of this mind-numbing drug.

In Australia, codeine is a "Pharmacy Only" medication. It is available in high doses and large packets. Codeine is a narcotic, like heroin. Breaking the addiction is hard, with methadone considered "best practice" treatment.

Before making the sale, pharmacists go through a procedure where they record the purchaser's driver's licence details. The procedure is a farce.

Codeine is not a Schedule 8 drug and therefore the information they collect is never shared with chemists in the next street, shopping centre, suburb or town. Addicts know this. They simply make a mental note to avoid that particular chemist for a week.

Last year pharmacists dispensed 16 million packets of codeine worth $145 million across Australia. 'Dispensed' makes the transaction sound more dignified than the seedy reality. With a highly tuned route, addicts can purchase 50 packets in an afternoon.

There are two main groups of codeine addicts. The first are those like Tom. They are otherwise decent, middle class people who once had a basic medical procedure or minor injury (in Tom's case it was his neck) and were discharged from hospital with a box of Panadeine Forte.

After just a week taking codeine, the patient's body is already dependent on it so when they run out of tablets they cannot sleep and begin feeling anxious, agitated and achy all over.

The addiction detox magnifies any residual pain from the initial injury, making it seem unbearable. A local chemist then cements the addiction by dispensing powerful codeine packed pills to treat a pain that, in truth, barely exists.

Such addicts are people who would never wake up one morning and decide to go to a drug dealer for narcotics. If pharmacists asked more questions, gave better advice and kept better records, they would not be drug addicts.

The other codeine addicts are from Generation Y – those who have a strong preference for 'clean drugs' over 'street drugs'. They like their recreational drugs to come in labelled blister packs so they can be sure of exactly what and how much they are taking.

Addicts behave in despicable ways you probably will not believe unless you have been there or witnessed it yourself. Their every move and word is laced with deceit.

Most Sundays Tom would wake me with newspapers and a cooked breakfast— smoked salmon and scrambled egg on croissants with fresh hollandaise and herbs from the garden. One Saturday evening, when I returned home from grocery shopping, I reset the odometer in the car. After breakfast, I discovered that the car had travelled 300km— the shop for the newspapers is less than 5km away.

I thought he was having an affair, and in a way he was. His only love is codeine.
A year after the initial round of drug rehab and counselling Tom was admitted to hospital for an elective hernia repair. Despite my pleas to doctors, he was fed a cocktail of codeine-laden medications. They discharged him with a little goodie bag— he swallowed the lot that afternoon.

Over the years things went missing— the TV from our bedroom, jewellery I rarely wore, video cameras, the Kindle he gave me for my birthday. Tom would shrug or say it had broken.

Despite me working in an executive role there was never any money in our bank account. He would say things like, "I paid a year's worth of ballet fees this week to get the discount."

When I started looking into our finances it turned out that the ballet fees had never been paid, school fees were a year in arrears, we had a massive account at the local supermarket, his car was unregistered…

My despair and disgust reached a new low when the strong pain medication recommended for my daughter by her ENT specialist disappeared. I had a child writhing in pain from ear infection in the middle of the night and my husband casually said, "The bottle was knocked off the bench yesterday and it broke."

"Pharmacy Only" drugs are supposed to be dispensed at the discretion of a qualified pharmacist. Pharmacists are supposed to be discerning in deciding who really needs those addictive drugs, who they sell them to and in what quantity.

They have utterly failed in this responsibility— my broken family is proof.

A system was implemented to stop individuals buying too many cold-and-flu tablets containing pseudoephedrine, because it can be made into speed. It seems doing the same for a drug more addictive than heroin is not worth the trouble.

The word codeine does not cause enough community outrage to warrant action like speed does; plenty of nice people take it after all, and perhaps they do not want to be questioned too closely at the chemist or fear being branded "drug addicts".

Federal and state governments do that crazy cartoonish cross-pointing game whenever this issue is raised; each insists the responsibility and cost of implementing better controls lies with the other.

The Pharmacy Guild of Australia have no incentive for things to change. I have cried at their counters and have been told, rather coldly, they are "not breaking the law by selling Tom codeine."

I would like to see codeine made a prescription only drug.

Yes, that would mean having to go to the doctor to get it, but doesn't that seem common sense if you are legitimately in severe pain and honestly need access to highly addictive drugs?

***UPDATE 3/9/14:** The Pharmacy Guild of Victoria has responded to this article with the deepest sympathy to Anonymous and her family. They would like to point out that while there is currently no legal requirement for pharmacists to record the supply of over-the-counter sales of codeine-based products, some pharmacies have a policy of keeping such records with the consent of the customer.

Anthony Tassone, President of the Victorian Branch of the Pharmacy Guild, said that the Guild believes there needs to be real-time monitoring involving patient consent, keeping purchase records on a central data base that can be accessed by other pharmacies.

He said it was the Guild's hope that changes can be made to allow the profession to better monitor the supply of over the counter codeine and in doing so, minimise the risk of misuse or abuse."
To see the full statement from the Pharmacy Guild of Victoria go here.

Watch Gabrielle Jackson discuss the issue the Studio 10 panel:
info@wemagazines.com.au
** We welcome stories from Hoopla readers. Please go here to learn more about Your Stories.*
14 COMMENTS

- REPLY SEPTEMBER 2, 2014

JUDITH

I felt sad for you and your family after reading your article, but I think you are being unfair on pharmacists especially. As you say, your husband was buying a legal product and the poor pharmacist can't be expected to assess whether anyone is an addict or not in a two minute pharmacy consultation. Addicts will say what they

think the supplier wants to hear in order to get their drugs. I don't know what the solution is, keep a close eye on any relative who is taking strong pain killers and don't be afraid to seek help if you are concerned.
2

0 REPLY SEPTEMBER 15, 2014

ANOTHER FAMILY VICTIM

She's not anti – pharmacist in this article. She's saying the system doesnt support proper cross-checks and accountability. The whole system needs an overhaul.
LikeBtn.com [**?**]

- REPLY SEPTEMBER 2, 2014

CATHERINE

As a person who suffers chronic pain, I would like others to understand that people in severe and/or chronic pain need access to good pain relief.
I am sorry that people abuse medications. However, prohibition has not stopped addicts from accessing their drug of choice – it has only prevented people in serious, horrible pain from accessing good pain relief.
Can we please stop make life even harder for people who genuinely need access to pain relief in order to make ourselves feel better about addicts? Prohibition does not work. It never has. It never will. We need to look at better support services for addicts – but please, do not forget the people who genuinely need pain relief in the rush to protect society from those who do not.
LikeBtn.com [**?**]

0 REPLY SEPTEMBER 15, 2014

ANOTHER FAMILY VICTIM

If you have chronic pain, you need appropriate pain management by a doctor and a care plan. Not over the counter drugs.
LikeBtn.com [**?**]

- REPLY SEPTEMBER 2, 2014

LESLEY

I agree with Catherine. My regular Go To Chemist for all my medication only ever asked me once "Have you used this medication before?" The other chemist, which I rarely go to anymore because they are like robots tut tutting about my pain medication before proceeding to give me a lecture about it and making me feel like a criminal. Every single time. With the exception of the owner of that pharmacy, there is not one of them over the age of twenty-something. I try to avoid them like the plague and only go there in an emergency. On the other hand, my regular chemist knows me and trusts my judgment and that is as it should be. I noticed the author of this piece mentioned methadone. Now there's a problem program the government should be looking at seriously.
LikeBtn.com [**?**]

- REPLY SEPTEMBER 2, 2014

EDITH

Judith: pharmacists ARE expected to make that determination. That's the whole point of it being available only from chemists & not the supermarket.
Legislative requirements for a 'pharmacy only' drug is that the pharmacist must take all reasonable steps to ensure a therapeutic need exists for the supply of the medication.
Clearly, that isn't happening. Buying 50 packets a day is not anyone's 'therapeutic need'.
LikeBtn.com [**?**]

- REPLY SEPTEMBER 4, 2014

S U E

It seems to me that Tom may have felt disempowered by being a “stay-at-home” Dad with an executive wife. Instead of being “disgusted” by his behaviour and spending habits his wife should have perhaps been aware of this.

- REPLYSEPTEMBER 4, 2014

L E S L E Y

Actually, with regard to the update … it must be the case in Victoria that there is no legal requirement for pharmacists to keep these records. It certainly is the case in NSW and Qld and they certainly do not ask your consent either … all pharmacists in both states will tell you that they are required by law to take your details. The policy should not vary from state to state and there definitely should be a central monitoring system.

- REPLYSEPTEMBER 15, 2014

J O D I E

The answer is not to treat the problem the same way as Pseudoephedrine sales and requiring ID for sale. Pseudo is being used by organised crime to make ILLEGAL drugs.
Codeine is being abused by every day people usually starting from a very genuine health problem. Creating a central database of users does nothing to address why it is being abused in the first place.

Pharmacists need to take more ownership of the fact this is a ‘Pharmacist Only Medicine’ and stop routinely selling it and intervene as necessary especially educating around the risks of high doses of paracetamol and ibuprofen.

If Pharmacists continue to shrug responsibility of these types of issues, then perhaps one day there will be no need of pharmacies and people will one day only have the choice of open sellers such as supermarkets or prescription. It’s time for Pharmacists to step-up I say.
Codeine is a very effective pain reliver and to make it prescription only would be a shame.

- REPLYSEPTEMBER 15, 2014

D A I N A

While it is very sad for this family – living with an addict of any sort is especially stressful – making pharmacists try to decide who is an addict and who isn’t is completely crazy. I understand this woman feels like she needs someone to blame, but there isn’t anyone to blame when it comes to addicts. Would she blame the man behind the counter at Dan Murphy’s if her husband was an alcoholic? You cannot FORCE someone to not be an addict, or in fact anything else, even if you’re convinced it’s what they should do.

- REPLYSEPTEMBER 15, 2014

K A T E

Anything containing codeine that can be sold in a pharmacy without a prescription is not ‘pharmacy only’ it is ‘pharmacist only’ which is the next level of scheduling – meaning a transaction where the pharmacist is not involved in some way, shape or form is an illegal sale of the medication. The problem with over the counter codeine is the dosage being such a sub-theraputic amount, it is basically useless even selling it in the pharmacy. The effect from most OTC codeine products is basically ‘placebo’ – the recommended therapeutic dose is about 3x that of what is contained in one of these tablets, but despite the lack of pain relief even achieved from these small doses, addiction is still highly possible. Making codeine something that is available as a prescription only medication would make a lot of sense.

- REPLYSEPTEMBER 15, 2014

N A N C Y

It's not just happening in Victoria it's all over Australia. These drugs destroy families and lead to other drug addictions. People who have not had their families ripped apart due to this drug will NEVER understand! My ex was not a stay home dad, He was executive and well respected in our community. He had everything someone could ever want, yet this drug is so powerful he tossed it all away for his addiction. These addicts will only get help when they themselves are ready not when their family is begging them because it is falling apart.
LikeBtn.com [**?**] xxx

- REPLY NOVEMBER 27, 2014

K R I S T I E

Hi,
I have a sister in-law who has this very addiction. I would like ton know what you would suggest to get her help. I am very worried especially as she has young children in her care and my brother has just been in an accident and can't help her as much.
Thank you
LikeBtn.com [**?**] xxx

- REPLY MARCH 6, 2015

S H A R O N

My ex husband was addicted to nurofen plus for 11 years and nearly died twice. It was only after nearly losing him the second time and him refusing to do rehab that I left with our 4 kids. To be honest I think he is still alive today because I left.
LikeBtn.com [**?**] xxx

Attachment 9: Marie Claire article: Why addiction has never been so easy. January 2015

- **IT'S STOCKED EVERYWHERE**
- **NO PRESCRIPTION NEEDED**
- **IT COSTS LESS THAN $10**

WHY ADDICTION HAS NEVER BEEN SO EASY

It can start with a few *pills* for a headache and quickly escalates into a *dangerous* dependence. Megan Lehmann investigates Australia's *hidden epidemic* of codeine abuse

Sweat was pooling on the hospital sheets and her whole body felt on fire. One minute she was curled up in a ball, shaking and sobbing in agony. The next, she was on her knees, gripping the bedrail and screaming at the nurses for a blanket. "Oh my God," Natalia recalls thinking, "I'm just like one of those junkies you see in withdrawal."

That's when Natalia, a 31-year-old fashion retailer from Perth, made a startling realisation: she was a junkie. She'd hit bottom and wound up in rehab, but the drug that had her in its torturous grip wasn't heroin or ice – it was a popular over-the-counter (OTC) painkiller. Natalia – articulate, well-dressed and gainfully employed – was addicted to codeine, shovelling in 96 Nurofen Plus tablets a day to feed her habit. "I'd put 15 in my hand and swallow them in one gulp," she says. "I had cuts around the cuticles on my thumb from popping pills out of the blister packets all the time."

Natalia is part of what Jason Bowman, program manager at ▷

Melbourne drug and alcohol rehabilitation clinic Arrow Health, labels a "hidden epidemic" in Australia of codeine addicts, many of whom are taking up to 100 pills a day. Hidden – but potentially deadly. Recent revelations of a spate of deaths linked to long-term misuse of pills containing codeine – a potentially addictive opiate that is a chemical cousin to heroin – have doctors and pharmacists so concerned, they're calling for tighter controls on the drug.

"The impact of these medications is every bit as traumatic for the individual and their loved ones as heroin or ice," says Bowman. "I have seen many people who've nearly destroyed their lives and all of their organs from the impact of codeine. And there are many more who are silently struggling with addiction in their homes out of the public eye."

Walk into any pharmacy in Australia and you'll see a number of painkillers on the shelves containing codeine mixed with either ibuprofen or paracetamol. These include Nurofen Plus, Panadeine, Panafen Plus and Mersyndol. It's the ready availability of these drugs, on top of society's love of a medical quick fix, which has led to an increase in what Brisbane addiction medicine specialist Dr Christian Rowan calls "accidental addicts".

"There are more time pressures on people today and more expectations as to what people have to get done, so we're often looking for quick and easy solutions to chronic, complex problems," says Dr Rowan.

It's far easier to reach for a pill than to seek out pain management like physiotherapy, counselling or proper exercise, he says. "Just saying, 'I don't have time to deal with pain,' and taking more and more painkillers to make it go away can lead to dependency."

Dr Rowan says the majority of codeine-addicted patients he treats at his private clinic at Brisbane's Wesley Hospital are women younger than 45. "I find women in that demographic are often dealing with gynaecological problems, like menstrual pain or endometriosis, or with chronic migraines, postnatal depression or general anxiety, and those are the people having problems with codeine-containing drugs."

The fact that codeine addicts don't fit the profile of a stereotypical junkie means they can be difficult to detect as they travel from chemist to chemist to fuel their habits. Dr Matthew Frei, clinical director at Turning Point Alcohol & Drug Centre in Melbourne, says the typical codeine addict is a young, socially stable professional. "They're usually people who started taking medication for recurring headaches or back pain and then it escalates," he says.

Natalia knows all about that slippery slope. The bubbly brunette's problems with codeine began in 2005, aged 22. She was struggling through work at a shoe store with a hammering headache when a co-worker came to the rescue with painkillers. Natalia took three. "It gave me a buzz and I just loved the feeling," she says. The next day, she bought a packet of Nurofen Plus. "I kept thinking, 'I have to have this feeling again,' and each time it took more and more pills to get to that level. That escalated over a four- or five-year period to me getting up to 96 tablets a day."

Natalia had always been up-beat and sociable, but says she became moody and snappy. Before long she was spending hundreds of dollars a week on OTC pills, lying to pharmacists, friends and family as she fed her habit. "I became sneaky junkie Natalia. Codeine was my best friend and I didn't want anyone to know because they'd take it away from me."

ASKED FOR HELP

Like Natalia, Kerry van der Helm, a 34-year-old publicist from Brisbane, doesn't look like a stereotypical drug addict. She's happily married, with her own business and a busy social life. She began taking

FATAL ADDICTIONS

64 TABLETS A DAY

Linda Docherty, 2007

The 49 year old died of kidney failure resulting from her Nurofen Plus addiction.

FOUR-YEAR ADDICTION

Nikola Bradford, 2013

The 36 year old died after taking a cocktail of illegal drugs following a battle with codeine addiction.

Nurofen Plus, which contains 12.8mg of codeine, for period pain. "I struggle with depression and I noticed that the codeine also made me feel good," she says. "Soon, I was taking it for everything – headache, back pain, even when I felt a cold coming on. If I was feeling a bit down, I'd take some codeine and it made me feel better."

Before long, Kerry was popping 30 pills a day and planning her schedule around pharmacy shopping. "I'd tell lies, use different names," she says. "You do whatever you can to get it because you can't survive without it. I'd had a stressful two or three years – for example, our home flooded in the [2011] Brisbane floods – and codeine blocked out all sensation, so I didn't have to deal with any of the emotional stuff."

After several failed attempts to kick the habit, Kerry knew she needed help. "Every time I stopped I'd suffer terrible withdrawal symptoms like vomiting, body aches, fever – you just can't believe how sick you feel," she says. "You feel like you're dying; you'd actually rather die." She began outpatient detoxification at a public rehabilitation clinic in June.

"I'm a professional with a university degree and I own my own business, and there I am sitting in the clinic with all the junkies who inject," says Kerry. "It's a very confronting thing – I've never touched a recreational drug in my life. I've never even smoked a cigarette."

Many of us have painkillers in the bathroom cabinet and it's the first place we turn when pain hits. Typically, we take two, the pain goes away – end of story. But those who have addictive natures or underlying issues, such as depression or anxiety, can get hooked on the euphoria that accompanies the pain relief.

"People find if they take more than the recommended dose, they get even more relief, then they feel a bit of a buzz, then they build up a tolerance and they keep needing more and more," says Dr Frei.

OTC painkillers combine the narcotic codeine with simple analgesics, which work on the central nervous system to block pain. "Codeine is what causes the dependency, but it's the other component in high doses – whether that's paracetamol or ibuprofen – that can cause problems with organ function," says Dr Rowan. Excessive ibuprofen can damage the stomach, heart and kidneys, while too much paracetamol is toxic to the liver.

Kerry and Natalia are among the lucky ones: their organs are still intact. "Because these drugs are available over the counter without a prescription, many people think they're harmless," says Monash University researcher Dr Jennifer Pilgrim. "But they can have serious adverse effects, including gastrointestinal bleeding, perforated stomach ulcers, kidney failure and liver damage."

They can also be fatal. In 2013, Dr Pilgrim co-authored a study that found nine Victorians in the decade from 2001 whose deaths were directly linked to internal damage caused by long-time misuse of drugs such as Nurofen Plus and Panadeine Extra.

One of these, a 48-year-old woman, died after abusing Panafen Plus even though she had been identified as a doctor-shopper and had restricted access to prescription medicines. It was still easy for her to visit different chemists and amass large quantities of OTC codeine.

The problem isn't confined to Australia. In the UK in 2007, a coroner's inquest was told that 49-year-old mother-of-two Linda Docherty died of kidney failure resulting from her Nurofen Plus addiction, which saw her taking up to 64 tablets a day. And on December 1, 2013, 36-year-old English police communications officer Nikola Bradford died after taking a cocktail of illegal drugs following a long battle with codeine addiction. She'd started taking Nurofen Plus for back pain in 2010, but soon became addicted.

Melbourne pharmacist Adam Spiteri says because there's no way of spotting a codeine addict, his dispensary has installed software to record codeine sales in an effort to monitor users. Spiteri is one of a number of pharmacists ▷

BY THE NUMBERS

Amount of codeine in over-the-counter medications

Panadeine	Mersyndol	Nurofen Plus	Panadeine Extra
8 mg	9.75 mg	12.8 mg	15 mg
+ PARACETAMOL	+ PARACETAMOL + THE ANTIHISTAMINE DOXYLAMINE	+ IBUPROFEN	+ PARACETAMOL

reporting a rise in what have been dubbed "codeine tantrums" – customers abusing staff after they're refused OTC codeine pills. "Some people get very defensive, very quickly," he says, adding that he sees up to four codeine tantrums a day. "They swear and threaten staff and even throw things at them."

New controls on codeine sale were introduced in 2010: pack sizes have been reduced from 96 tablets to 30 and pharmacists must be involved in all sales. But many say this doesn't go far enough.

"In theory, you can only be sold five days' supply at a time," says Dr Frei. "But there's nothing to stop you going to 20 other chemists. It's not difficult to do."

He estimates that 10 per cent of people who buy OTC codeine products are misusing them, and says only a national database with the names and addresses of those who purchase codeine will curb pharmacy-shopping.

While there are calls for codeine sales to be prescription-only, as they are in many other countries, the more popular measure is the implementation of a real-time drug monitoring system similar to Project STOP, which tracks the sales of products containing pseudoephedrine.

"Codeine is a wonderful servant, but a terrible master," says Australian Medical Association vice-president Dr Stephen Parnis. "There's a legitimate and necessary place for good pain relief, but it's got to be under medical supervision because these medications have got risks. People are aware they can access good pain relief easily, but they're less likely to focus on the risks of it. So we need education, awareness and appropriate controls to minimise the harm from misuse."

"NON MEDICAL USE OF PAINKILLERS IS AT ITS HIGHEST LEVEL SINCE 1998"

Nearly a decade after Natalia was seduced by this readily available drug, she's still struggling. She's on a drug register and must visit a pharmacy every day to pick up her Suboxone, the modern-day replacement drug similar to methadone. It stems the cravings and keeps her in a "safe place", she says, while she works with a psychiatrist to rebuild her life.

"I never in a million years thought this would happen to me," she says. "I'm still not clean; I'm just on medically supervised opiates. This codeine addiction has taken up a big chunk of my life. It's nasty stuff."

If you believe that you or someone you know might be addicted to codeine, talk to your GP or call Lifeline on 13 11 14.

David* watched helplessly as his wife Lisa's* codeine addiction destroyed their marriage ...

"IT STARTED OUT HARMLESSLY, BUT SOON [MY WIFE] WAS TAKING 72 TABLETS A DAY"

"My soon-to-be ex-wife, Lisa, started taking Nurofen Plus in 2000 after she gave birth to a stillborn baby at nine months. She found the painkillers not only addressed the physical pain, but had the very welcome side effect of numbing her emotionally.

"You should try not to judge people who slide down this slippery slope. Lisa attended a self-help group of women who had also lost their babies and for them it was like having a coffee together: one would say, 'I've got a couple of Nurofen Plus, do you want some too?' It started out harmlessly, but soon she was taking 72 tablets a day.

"I tried everything to get her to quit. Once I found her hitchhiking at midnight to get codeine. I sent her to rehab on four occasions, but she would just discharge herself early and head straight to the pharmacy. I went to all the local pharmacies, provided them with a photo of her and said, 'If she comes in, please don't sell them to her.'

"But addicts are incredibly good at hiding stuff; she became so cunning. The stress of keeping up with all her lies got to her and she would take it out on me. I would say, 'Tell me what is going on, we can fix it together.' But it was too embarrassing for her – she couldn't declare her absolute uselessness when it came to stopping and so she would be in denial.

"My wife never openly acknowledged she had a problem. But she had stomach ulcers and acid reflux. I lived in fear she would end up in the intensive care ward. She finally stopped when she fell pregnant with our daughter, who she's still breastfeeding. But I have just had to say to her, 'I went through eight years of this together with you, I can't do it anymore.' I'm not able to trust her and she knows that." ☐

Attachment 10: Covert simulated patient study, July 2015[143]

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Over-the-counter supply of combination analgesics containing codeine in community pharmacy: A simulated patient study

Georgia A. Byrne[1], Pene J. Wood[1], M. Joy Spark[1]. School of Pharmacy and Applied Science, LaTrobe University[1], Bendigo, VIC.

Introduction. Over-the-counter combination analgesics containing codeine (OTC-CACC) are Pharmacist Only Medicines used for short term treatment of pain; misuse of OTC-CACC has become a significant health issue in Australia. Pharmacists are required to establish a therapeutic need for every sale. However current quantitative evidence on the practice behaviour of community pharmacists during OTC-CACC product requests is limited.

Aims. To investigate the current management of OTC-CACC requests in Australian community pharmacies.

Methods. A covert simulated patient (SP) methodology was used to observe the responses of pharmacy staff during an OTC-CACC request. SPs were trained for two scenarios involving a direct product request for Nurofen Plus® (OTC-CACCI, 200mg ibuprofen, 12.8mg codeine). Each SP provided identical information relating to reason for use, symptoms, and medical history; Scenario One (Sc1) SPs had no previous history of OTC-CACC use and Scenario Two (Sc2) SP had used OTC-CACCI regularly for the past month. Data were recorded immediately post-visit on a data collection form.

Results. SPs visited 38 metropolitan and 37 non-metropolitan pharmacies (73 Sc1 and 72 Sc2). An OTC-CACCI was purchased in 71% (75%, n=55 Sc1; 67%, n=48 Sc2) of pharmacy visits; an alternative treatment was recommended five times. Adequate counselling was received for 25% of product purchases for both scenarios. The SP for Sc2 was referred to a health professional in 19% (n=14) of visits. In 18% (n=19) of product purchases the SP was not provided with medication counselling. A positive outcome (Sc1-product with counselling, Sc2-referral, product, counselling) was reported in 19% of Sc1 visits and 5.6% of Sc2 visits. There was a significant association between scenario and outcome ($\chi^2(2, n=145) = 47.5$, $p < 0.005$, Cramer's $V = 0.57$) with a large effect size.

Discussion. Outcomes varied depending on whether the requester was initiating or continuing treatment; a negative outcome for the requester was more likely for repeat purchase primarily because the need to refer was not identified. Overall minimal product advice was received and needs to be increased to ensure appropriate and safe use of these products.

[143] Byrne GA, Pene J, Spark MY. Over-the-counter supply of combination analgesics containing codeine in community pharmacy: A simulated patient study. APSA-ASCEPT Joint scientific meeting 2015. Abstract no. 122 http://www.asceptasm.com/wp-content/uploads/2015/03/APSA-ASCEPT-Book-of-oral-abstracts.pdf

28th January 2016

Re: Consultation - Proposed amendments to the Poisons Standard (Codeine)

Thank you for the opportunity to comment once more on this important topic.

Prior to gaining registration on the Australian market, all new medicines are subject to 'rigorous and detailed' assessment[1]. The burden to provide proof of safety and efficacy lies with the manufacturer. Only products with data to support a favourable risk-to-benefit ratio are approved for registration. All medications currently on the markets need to fulfill the same requirements - available evidence must demonstrate that the benefits to the Australian public outweigh the risks.

Low-dose codeine containing products do not meet these basic requirements. Quality evidence of efficacy for low-dose codeine containing products is lacking completely, while evidence for substantial harm has been clearly documented[2-7]. Thus, **I strongly support the Therapeutic Goods Administration's (TGA's) interim decision to reschedule low-dose codeine containing products to Schedule 4**. Below I outline my rebuttal to the arguments put forward in support of retaining low-dose codeine products in Schedule 3. Note my background is in pain management, thus my comments primarily relate to low-dose codeine containing analgesics, however I am not aware of any convincing evidence of a low-dose codeine providing clinically meaningful benefit when added to cold and flu preparations either.

In response to the TGA's interim decision, others have argued that low-dose codeine combination analgesics represent the only option for patients who have not achieved adequate pain relief with single-ingredient paracetamol and ibuprofen products. However, current evidence gives little reason to expect any increase in pain relief following the addition of low-dose codeine to simple analgesics[8-10]. Thus, any benefits of low-dose codeine reported by consumers in a clinical setting seems likely to represent a placebo response brought about through expectation, as they perceive these products to be 'stronger painkillers'. While I accept that the placebo response can in fact provide meaningful analgesia, a product proven to cause harm should not remain on the market purely for its use as a placebo.

The pharmacy profession and other groups have produced many cost estimates relating to the rescheduling of low-dose codeine products. First, responses regarding the financial impacts of rescheduling put forward by the pharmacy profession must be reviewed with caution, in light of the obvious conflict of interest present. Secondly, I would like to reiterate that the regulation of customer access to medicines in Australia is based upon assessment of safety, quality and efficacy, rather than the cost of healthcare alone. Finally, *number needed to treat* data calculated across multiple Cochrane reviews, show combinations of paracetamol and ibuprofen provide superior analgesia, compared to codeine containing combination analgesics, even when the dose of codeine is increased to 60mg[11]. Thus, much of the projected cost associated with GP appointments to obtain low-dose codeine containing analgesics could be off-set through the supply of over-the-counter ibuprofen/paracetamol combination products. If such products are not suitable for an individual patient, it is an entirely appropriate for that patient to visit their GP. It may be that proper assessment and development of a pain management plan

could not only reduce the use of ineffective medications (and eliminate the risks they bring), but may reduce future health care costs if a proactive management approach is adopted.

Real-time recording has also been proposed as an alternate solution to rescheduling. I feel this tool alone will not be sufficient to manage Australia's codeine misuse. Codeine-addiction is particularly difficult to treat, thus prevent is key, and by the time a patient raises a flag on a real-time recording system, they may well be dependent already. The risk of a patient gaining sufficient access to become dependent is sizeable, given only 1 in 4 patient transactions are likely to involve appropriate counseling, as demonstrated in a recent study that found just 25% of patients received adequate counseling when purchasing codeine-containing analgesics[12]. Notably, this study was conducted after the TGA's interim decision, when codeine had been a major topic in the pharmacy media.

The additional time that would be required to process requests for low-dose codeine containing products using a real-time recording system is also associated with an opportunity cost. Most pharmacists working in community practice already work under substantial time pressure, and the added time burden of recording would likely reduce the time available to provide counseling and advice on other more suitable strategies for managing pain. Real-time recording also raises a number of unanswered questions - how often is too often to purchase codeine-containing products? Is it okay for the patient to have such access an ineffective product with known risks, so long as they use it once or twice a year? Or once or twice a month? Real-time recording does nothing to address the lack of efficacy of these products, thus whether the product sale is recorded or not seems largely irrelevant.

The pharmacy profession have also suggested rescheduling to S4 will be of no benefit as prescription opioids are also abused. While it is of course true that prescription opioids are also abused, this does not justify over-the-counter access to other products, which are known to be abused. While rescheduling codeine to S4 does not guarantee that abuse will be reduced, it most certainly will not increase abuse. In a study of patients dependent upon low-dose codeine containing products, a common theme emerged - many patients were initiated on prescription opioids during an acute episode of pain, and when their doctor refused to provide prescriptions for ongoing supply of prescription opioids these patients switched to over-the-counter low-dose codeine containing products[2] (anecdotally this pattern is also reflected in my personal clinical practice). This group of patients could have had more favourable trajectory if low-dose codeine products were not so easily accessible as Schedule 3 products.

Another argument put forward in support of retaining Schedule 3 low-dose codeine products is that they are misused by only a small fraction of patients. While quality data regarding the use scale of misuse of over-the-counter low-dose codeine products in Australia are scarce, a poll conducted recently by *AusPharm e-news,* ascertained that 24% of pharmacist respondents stated suspected off-label over-the-counter codeine use was "rampant" (results published Nov 27 2015). This is in line with a survey that recruited any patients who had recently used codeine products via advertisement to the public, which found 17% of codeine users were likely to meet the criteria for substance dependence[2]. To me 17% is not a small fraction of patients, and it would seem from the *AusPharm e-news* poll results that many other pharmacists see misuse to affect a significant proportion of patients as well.

To summarise, **I strongly support the TGA in upholding the interim decision to reschedule low dose codeine containing products to Schedule 4**. No new data has been presented to in relation to the unacceptable risk to benefit ratio of these products. Given the paucity of efficacy data and well-documented harms, the initial decision must stand.

[redacted]

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28th January 2016

[redacted]

To Whom It May Concern

My name is [redacted] and I am a wife of a codeine addict and a mother of [redacted] girls. My submission is purely emotive driven and up until [redacted] months ago was a world so foreign to me. I don't know how powerful or even if my voice will be heard but all I do know is that I am not alone, the epidemic that is codeine abuse is high and is rife.

The day my [redacted] daughter was born was supposed to be so happy, but yet my husband was not quite with it. I could never put my finger on it as that was just him but behind his eyes I knew there was something wrong. [redacted] weeks later my husband had pneumonia, stomach ulcers, sweating and was grey he looked so unwell [redacted]. I would lay in bed listening to his laboured breathing and would dread coming home as I was so scared I was going to find him dead on the floor. It was then my world fell apart before me. My husband eventually told me about what he was doing and [redacted] booked him into rehab. I was left feeling numb, scared, shocked, bewildered, helpless and constantly questioning myself – how? Why? I should have known? I was alone with a [redacted] baby and my [redacted] but me being me would soldier on and do only what a mother and wife would do – keep the family together and ticking along.

At this time my husband was using 120 OTC Ibuprofen/ Codeine products a day. He had been using for [redacted] years unbeknown to me. This dosage was a gradual build up over the years as I remember very early on even going out and buying his Panafen Plus tablets (for back ache), although back then the pack sizes were 96. Then a few years later the TGA reduced the pack size to 30. All this meant was instead of going to 1 or 2 pharmacies it now meant 3 or 4, this doesn't mean anything to an addict. His daily ritual astounded me as I listened in rehab how he would acquire his fix. He would drive around to 4 Pharmacy's a day, they all asking the same screening questions and handing over his tablets. One pharmacist would joke and when he came in would say [redacted] in [redacted] years of using only ever has there been 1 pharmacist whom refused to serve him and actually said 'I cannot serve you, if you have a problem with these you can come and talk to me'. He said he went out and was screaming for help even cried in his car, nearly went back in but instead said [redacted] drove off to the next pharmacy. He would sit in his car for 15 minutes swallowing his tablets gagging and wanting to vomit but would keep pushing them down. The memory loss, the ups and downs, the sweating, the stomach ulcers, Welcome to Codeine Addiction……..

His addiction is not expensive, generic codeine brands are $7.95 a pack. For $30 a day he would be happy, entering into his own [redacted] which was not real but he believed was real, because his real world was now slowly falling apart. In rehab they talk about recovery and how as an addict you distance yourself from your dealers and known associates. My husband's addiction in not like other drug choices, I don't mean that flippantly as he is still a drug addict, much to his disgust, but when there is a pharmacy every couple of kilometres the mental torture of recovery makes its very hard to drive pass and avoid.

[redacted] His addiction has cost him his job, he has no job security, no self-esteem, has depression and I am powerless to help prevent or stop. In the past 20 months I have learnt so much about addiction so much about myself and so much about my husband. His addiction has sucked the life out of me, his disconnect from the real world is alarming, his emotions and feelings are so supressed from the years of abuse, not to mention the physical abuse his body has endured. He relapse not even [redacted] weeks after coming out of rehab and since then has got himself clean [redacted] but it doesn't last long. Any excuse and off he goes again. His addiction is real. His mental torment is real, he hates himself as he now admits he's an addict but thinks he's soft as his drug of choice is OTC codeine. He has come a long way in the past [redacted] months from his 120 a day drug habit and health issues to now using between 30 and 60 a day. We are both in counselling now as I want to keep my family together but I honestly don't know if I will succeed. The road to recovery is long.

Codeine addiction affects millions of people, it does not discriminate. Everyday people whom may start off needing it for medical reasons but soon after rely on it for so much more. Most countries around the world do not allow codeine OTC sales they are prescription only, Australia and the UK are definitely in the minority and when you research Codeine you only have to look at the articles, all screaming out for help and change. Reducing the pack size will simply just mean it will take longer to acquire an addicts ceiling – they will have to call on that extra pharmacy.

Knowing, seeing and going through what I am doing now my preference would be to have codeine put on script. Retain the interim decision to up-schedule to Schedule 4. It is a highly addictive pain relief and thus like all pain medication should be constantly reviewed by a GP meaning patients should see a Gp if they require ANY pain relief. Patients whom DR shop will always Dr shop, removing codeine from OTC will not change that fact.

My other suggestion would be similar to pseudoephedrine whereby when customers come into the pharmacy to purchase codeine based products they present their driver's license and its recorded, whether it be live or not. This can be in conjunction with a reduced pack size also. Knowing that your name is recorded with all your personal details on it will definitely hinder some abusers. It will also allow for the young Pharmacy assistants who dispense the drug to be more familiar with the effects of codeine and also take note of whom and how many times they are coming into the store. (I know it's not their fault addicts are liars, deceitful and masters of manipulation).

I don't think the proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; OR the Proposal to up-schedule the Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction; is merely enough.

I could go on and on as the emotional pain I feel is still so raw, there is nothing new you haven't heard or even seen in practice. I know there is so much backlash from Health care professionals but Codeine addiction is a real problem, it destroys lives and it's not going away it's only going to get worse if something significant is not done.

I beg please help, please change the laws whereby all codeine products become prescription.

Kind Regards

[redacted]

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28 January 2016

I write to support the re-scheduling of codeine to Schedule 4. This is further to my submission with others dated May 7, 2015.

Codeine is an opium-based drug. It is sold as a Schedule 3 combined with pharmaceuticals that themselves cause toxicity if used in excessive doses or over lengthy periods of time. It is rare for people to unintentionally overdose on straight paracetamol or non-steroidal anti-inflammatory drugs. However, when people develop compulsive use of opium-based substances, as may regularly be seen amongst laboratory mammals so exposed, they may suffer toxicities from these compounded substances. For this reason, it is risky policy to sell opium-based drugs compounded in this way.

Codeine is a potential precursor to morphine, however its metabolic activation is variable releasing an unpredictable level of morphine. Because 5-10% of the population may have either ultrarapid or non-existent rates of activity of the required CYP2D6 enzyme, they may risk respiratory depression, or alternatively, have no analgesia from the same dose of codeine. It has been said that consuming any specific dose of codeine may equate to taking an unknown dose of morphine (1). Other pharmaceuticals may inhibit CYP2D6 and make it ineffective. Cessation of these may indirectly elevate morphine levels and, potentially, cause respiratory depression. To describe codeine as a “weak opioid” is false and dangerous advertising because codeine can cause all the problems seen with other full opioid agonists. It may be that the TGA is of the opinion that our community should have easy access to opium-based drugs. If so, it would be safer to return to the practices of the early 19th or 20th century and sell bottles of morphine or heroin elixir respectively, rather than sell codeine compounds (2).

Personally I think all of these options are equally unwise. Our society does not currently support unrestricted access to drugs of dependency.

Pharmacists have a conflict of interest here regarding selling opioids. They are selling a drug of addiction with little or no regulatory supervision or control with volume of sales directly relating to pharmacy profitability. There are many non-opioid pharmaceuticals potentially efficacious for analgesia and I have no objections to their liberal sale (with the usual safeguards). In the first round of submissions over this issue, there were insinuations that doctors were fighting this issue for their vested interests. It would be unfair to say doctors are hoping to wrest control of pharmaceutical opioids from pharmacists for financial reasons. In a study of 645 general practice registrars across four Australian states, for those clinical problems where an opioid analgesic was prescribed, consultations were longer with an increased likelihood of the registrar seeking assistance, advice or information. This indicates the extra degree of time and effort involved in the management of pain and opioids (3).

Education for pain management is also problematic. The majority of this is funded by commercial interests, ironically even that of the Risk Evaluation and Mitigation Strategies (REMS) programme in the USA (4). Pharmaceutical industry marketing strategies rely heavily on physician education to boost drug sales (4). There is expert consensus that essential aspects of pain medicine to be covered include psychiatric aspects of pain and its management (5). Additionally addiction medicine should be covered, including drug testing and the management of pain in those with drug use disorders (5). Given concerns about the level and provenance of pain management training for doctors, are pharmacists going to do better?

To reduce opioid harms, we need to decrease opioid availability outside end-of-life care or short-term use associated with surgery or acute trauma (6, 7). The volume of consumption is critical related to both individual and public harms. The most frequently sold pack of opium-based product in Australia is codeine which accounts for two thirds of all pack sales (8). Overall, 37% of total pack sales involve OTC codeine (8). While volume does relate to diversion and misuse, problems may occur amongst the majority of consumers where the medications are taken as prescribed by a doctor or advised by

a chemist. Few regular OTC opioid users resemble heroin users; they are characterised by higher levels of education and employment (9). The majority, even of the dependent users, source their codeine from a single pharmacy (9). The majority of opioid overdoses occur amongst those using lower doses of opioids (presumably because the vast majority of consumption is of low dose) (10). According to US NSDHUH data, an estimated 2.1 million Americans are addicted to opioid analgesics, whilst an estimated 467,000 are addicted to heroin (11). Increasing codeine related deaths in Australia have been primarily driven by an increase in accidental deaths (12). They have now reached around half the number of deaths attributed to heroin and Schedule 8 opioids (12). Attempts to reduce overdoses from pharmaceutical opioids have said to be have been "stymied… (by) the misattribution of the crisis to nonmedical use or abuse rather than to addiction" (11). A clear example of this is the disingenuous proposal by the Guild to have real-time OTC codeine monitoring ("MedsASSIST" - https://www.guild.org.au/news-events/forefront/forefront-article/2016/01/26/pilot-begins-on-codeine-real-time-recording-and-monitoring-system). There is a seamlessness between opium-based substances making people feel better (i.e. more therapeutic use) and their making people feeling good or great (i.e. more euphorigenic use). Many of those presenting for help with codeine dependence have initiated them, or continued using them, for symptom relief (13, 14). Liberal access to opioids rapidly can actually make pain worse by processes such as tolerance, withdrawal and opioid-induced hyperalgesia, changes which may commence from the first day of usage.

Opioids are deemed "essential medicines" by the World Health Organisation. They may even be life-saving when provided as opioid substitution therapy (OST) for dependency care. However, not every pharmacy is prepared to provide opium-based medicines prescribed as OST. If so many pharmacists feel uncomfortable dispensing methadone or buprenorphine due to the conversations this would entail, how can they affirm they would be able to negotiate about addictive behaviours from OTC codeine? Doctors feel unwilling to prescribe OST in dependency due to stigma, time-pressures and apprehension, with these barriers reported by the majority of GPs (15). The ability to have these difficult conversations is daunting for doctors where patients have an allocated appointment, a private consultation and the health care provider has OST

training. How much more problematic would it be to assess and manage the various styles of usages of OTC opium-based drugs. Surely this is the classic case where the discussions and discussions about a medication are best made with separation of physician and pharmacist. On the other side of the coin, is it hypocritical for pharmacists to call for continuing OTC codeine rights if so many refuse to dispense OST when it is prescribed?

Deprescribing opioids is rarely reported by doctors, even when dealing with behaviours suspicious of addiction (16), it must almost impossible for pharmacists. Qualitative studies indicate that consumers may feel attempts to wean or cease opioids show a lack of empathy by the provider. Patients may interpret this as an attempt to delegitimize their pain. They may feel criminalized and become angry due to the perception that their relationship has become conflictual or paternalistic in nature (17).

[redacted] regularly use an anti-inflammatory for a chronic rotator cuff injury but still have trouble sleeping with the pain. [redacted] the pharmacist advised to use the paracetamol together with the anti-inflammatory and added if sleep was still a problem, to return for some paracetamol/codeine. It was reminiscent of the suggestive selling seen in a fast food chain. Yesterday I saw a lady who had swept cobwebs and dust into her eyes. Within an hour, they became extremely inflamed with profuse debris. The went immediately to the pharmacist who sold her chloramphenicol drops: a clear example of poor diagnosis and over-prescribing. The next day she consulted me and I assessed her, ceased the antibiotics and recommended symptomatic therapy only. It seems to me some pharmacist lobbyists would like them provide most outpatient care for acute and chronic conditions by the sale of devices, equipment or pharmaceuticals. The only comment I wish to make on this model of care is that doctors have special health training and skills not directly leading to saleable items. These clinical arts are essential when considering addictive substances.

In my general practice I do not enquire about OTC codeine use in chronic pain patients every consultation. However, when I do, its use seems to be ubiquitous, even if the patients are on prescribed opioids. This has exactly the same impact on medication

safety as doctor shopping does, as I may have no idea how long someone may have been using OTC opioids or how many are being added to the prescribed opioids. It also does make a mockery of prescription monitoring programmes or drug trafficking laws. In NSW it is illegal to get S8s from more than one prescriber but it is OK to get OTC pre-morphine with impunity.

I wish to conclude with the description of a few cases.

[redacted]. A female of about [redacted], with no previous illicit drug history, had multiple admissions to our local hospital over the last [redacted] years. I was asked by the surgical team to be involved as she was describing refractory post-operative pain despite the use of a fentanyl drip. She had just had a laparotomy and over-sewing of a bleeding peptic ulcer. She also had an acute hepatic and renal injury. Prior to the admission after an overdose of OTC codeine-compound tablets, which caused her presentation, she had been increasing her consumption of these tablets till she was swallowing up to 3 packs per day. Her consulting surgeon told me he sees complications of OTC codeine-containing compounds frequently. I rotated her opioids to OST and she was able to leave hospital and has done well over the first month of this dependency management. She is still dosed at the public dosing point as we always have difficulty finding pharmacists willing to take OST clients. About half of them refuse to do it and all the others are at capacity.

A [redacted]-year-old overweight lady with an anxiety disorder had high levels of distress from an obsession about her figure. She could only find relief with OTC codeine compounds, of which she was taking up to 60 per day. She did well on a small dose of methadone for a few months until she left medical care. She re-presented once a few years later about the same problem with OTC codeine but refused the restrictions of a treatment programme and was lost to follow-up.

Another case involved a patient of in her [redacted], with no previous illicit drug history, who was taking 560 mg daily of Codeine in the form of OTC Rikodeine Linctus. She found that it gave her the help she needed to cope with unresolved grief.

[redacted] who, apart from tobacco, had no previous substance use history. She commenced of OTC codeine-compound tablets after a complicated [redacted]. She was left with chronic pain and regularly consumed a packet of 24 at one time. She presented to me after a car accident which she blamed on the codeine. She was unable to return to [redacted] due to pain and anxiety. She has remained on an OST programme now with me over a year and we are working hard on her mental health, her return to [redacted], and attempting to wean her off opioids and nicotine.

None of these patients injected their codeine.

The temperance movement of the early twentieth century restricted therapeutic access to opioids. It was motivated by a previous opioid epidemic. Around 1880, the majority of those addicted were middle-class middle-aged women whose narcotic use was for a painful disorder, often of a chronic nature (2, 11) similar to the cases as described above. The prohibition movement also was responding to the perceived abuse of opium in Imperial China. Many historians indicate, however, that opium in China was a popular, multi-purpose drug used socially, with only a minority used in the context of compulsion and degradation (2). The Qing dynasty had originally prohibited opium importation. Commercial pressures, backed by Western government-backed cartels, saw gunships sailing up the Yangtze River demanding liberal access to the sales of opioids. Thus profiteering triumphed over attempted regulatory restrictions by the weakening Chinese imperial power.

The deliberations of the TGA now see such a contest between commercial forces and those supporting public interests and public health, with the first round of submissions including 14 submissions supportive and 113 opposing the re-scheduling. The personal submissions by consumers and pharmacists canvassed the same territory as qualitative studies of paired narratives of patients with chronic pain and their physicians (17). Each patient described their pain narrative involving the experience of isolation and suffering. Both parties emphasised how opioid analgesics were intrinsically linked to the genuineness of the pain. Patients stated that their validated pain provided them a right to opioid analgesics. Both parties had strong negative attitudes toward drug seekers or

drug addicts. Few patients thought they were at risk of addiction as they did not abuse their medications and took them as directed (17).

For these reasons I support the proposed regulatory restrictions on access to OTC opioids especially when compounded to non-opioid analgesics of potential toxicity. Pharmacists should stick to selling OTC non-opioid analgesics due to the ineffectiveness, the individual toxicities (including addiction or worsening pain) and the public health dangers of easily accessible opium-based products. To save lives and to minimise the harms from opioid addiction, pharmacists, so eager to sell codeine, should be encouraged to dispense OST.

[redacted]

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The Therapeutic Goods Administration,

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I would like to reiterate my response to the rescheduling of Codeine to S4 from all S2 and S3 preparations.

I will not re-emphasise the evidence that has been restated and re-emphasized by colleagues, including those with whom I wrote a prior joint submission.

[redacted]

I have an interest in treating Patients with any dependency.

I also have an interest in [redacted]. I have worked tirelessly to educate doctors, adopt standards, reduce prejudice in treating people with any addiction. I advocate for the patient population. [redacted]

I will restrict my comments to my dependent Opiate population.

[redacted] years ago, the few Patients that I treated with Codeine dependency were often Iatrogenic creations. As opposed to the group of Heroin Dependent people, I noted very early in the piece that these people were often reclusive, and appeared to have a much higher mortality than the Heroin user. As I analysed my group, I realised that the reason was that they found it very easy to drop out of treatment and resume their old ways. Patients not infrequently required Liver transplant if they survived because of their Paracetamol load from OTC Paracetamol/Codeine products. I would see some of these patients in Pharmacies myself, stalking the shelves, and waiting for the opportune moment to reach the counter.

Later the Codeine containing compounds were placed behind the counter (a move that I believe failed). The Pharmacist is unfortunately compromised by conflicts of interest; their employer demands efficiency and sales, the patient in front of them demands service now and can be quite intrusive. There are hindrances to practising a good level of practice and it takes time. In an electronic age, the systems between pharmacies and medical practitioners are not linked, so they are prone to not be aware of these Patients who “fall between the cracks”.

Over the past 10+ years, the number of Codeine misusing Patients has swelled considerably. I attribute this to the aggressive marketing of Nurofen Plus by Pharmaceutical companies direct to consumer. For any opiate containing compound, this should be banned and policed, with significant penalties to Pharma in my opinion.

It has been reflected in the Patient population adopting an additional era of complication. The closet becomes clogged; The 40 something year old male who became addicted after his work accident. The 60 something year old female who found relief after a significant person in their life died, and she had a post infective cough treated with codeine linctus. A 20 something year old female who adopted Nurofen plus for menstrual pain, and found that she just felt better. All of these

examples are real and took in excess of 50 tablets daily. The 20s female had a Hb of < 5 when she eventually reached hospital. Her Gastroenterologist thought that the changes in her stomach were attributable to Coeliac disease! These Patients are hidden because they are not recorded nor monitored until they seek help. This happens infrequently as we know that they are ashamed, and can too easily disguise their dependency. The 40s year old male who dose escalates and binges out because he cannot deal with his Borderline Personality Disorder is unable to work, and thus his marriage will implode soon. The 30s female who has found that the pain associated with SLE has caused her to find solace in x 40 Nurofen plus daily. She also has untreated Psychiatry of major proportions.

I have not mentioned the Renal Complications…

Emergency departments don't have the time or the opportunity to deal with these patients as they move out of crisis back to home in hours.

My cases go on and on and are all real, and substantially greater than listed above.

In my field, I see these Patients and I see the bigger problem of the ignorance that occurs in Dispensing; some innocent due to system failures, some complex motivated by profit.

I see colleagues ignoring and creating many other issues (ie: prescription drug misuse), which are not the subject of this discussion.

My point is that we have an escalating problem in our community that is not being dealt with adequately under the current S2/S3 Codeine legislation. It is uncontrolled, unregulated, and unmeasured. Patients unfortunately receive a low standard of responsible care for a multitude of Medical and Pharmacy reasons and are not given the opportunity of care that they shy away from. They are different to the Heroin Users and have a significant Morbidity and Mortality.

The victims, being the Patients that I treat, are begging me to 'please make this drug restricted' and essentially 'protect me from myself'. They are often unable to write their story.

It is time for the TGA to be bold and act in the interest of the health of the Australian population, so that Patients problems are addressed and disease burden is decreased.

From where I sit, S4 Codeine is the start of this journey.

Yours etc.,

[redacted]

Dear Sir/Madam,

Proposed amendments to the Poisons Standard for Codeine

With regard to the proposed amendments referred by the Scheduling Delegate for consideration by the ACMS at their March 2016 meeting, we wish to register our support for the interim decision to up-schedule codeine-containing analgesics and cough/cold preparations to Schedule 4.

The key support from medical experts and medical groups is unchanged. However we raise the concern that there has been a concerted campaign driven by vested interest groups to delay or reverse the interim decision which was made following significant input from medical groups.

The alternative proposal to reduce pack sizes to not more than 3 days' supply and apply label warnings will not address the issues of misuse and dependence that was at the heart of the original submissions and the subsequent interim scheduling decision.

In 2010 when codeine-containing analgesics were up-scheduled to Schedule 3 the pack size was limited to not more than 5 days' supply, but that has done nothing to address the increasing incidence of codeine misuse, abuse, harm and dependence that has been well documented since that time.

OTC analgesics containing codeine are specifically intended for the treatment of acute self-limiting pain, but it is clear that many Australians are using them inappropriately for long-term chronic pain. A simple Google search uncovered one online forum where a number of people openly discussed their misuse and dependence on codeine (http://patient.info/forums/discuss/codeine-addiction-nurofen-plus--425842), and submissions made by members of the public affected by OTC codeine abuse and misuse also indicate the likelihood that the issues with codeine are more widespread than is publicly reported.

Reducing the pack sizes and applying warning statements will have little or no impact on current misusers of codeine-based analgesics. It will further encourage the behaviour of 'pharmacy hopping' that is already seen under the current scheduling. For those people who are dependent on codeine it is likely to amplify this behaviour and put increased pressure on pharmacy staff to deal with it.

From reading many of the consumer submissions that opposed the interim decision it is apparent that there is a prevailing public perception that codeine-containing analgesics are safe and represent the strongest and most effective form of OTC pain relief available in Australian pharmacies, while at the same time there is a lack of awareness about alternative pain medications that could also address their needs. Codeine users too often confuse the euphoric effect they get from using the drug with an analgesic effect and this potentially feeds an ongoing dependence on these products, particularly when alternatives are not known or promoted to them. In amongst the often emotive responses to the interim decision one key piece of information seems to have been overlooked – the evidence that there are alternative analgesics that are more effective in providing pain relief than codeine-containing OTC

analgesics. This has been demonstrated in a number of clinical studies, and is reinforced in a recent Cochrane review that we have attached for reference.

Ultimately codeine-containing analgesics are ineffective, but still potentially harmful, in up to the 10% of the population (poor metabolisers), and 4-10% of the population are ultra-rapid metabolisers for whom codeine poses a potentially life-threatening risk. For the remainder of the population, OTC codeine-based analgesics still pose the risk of abuse, misuse, dependence and harm without providing any significantly greater analgesic effect than the accompanying drug in combination. New combination analgesics are now available in Australia that provide greater efficacy than codeine combinations without the same risks of harm, in addition to established single drug and combination analgesics that are also equally effective to codeine combinations and suitable for treating acute pain.

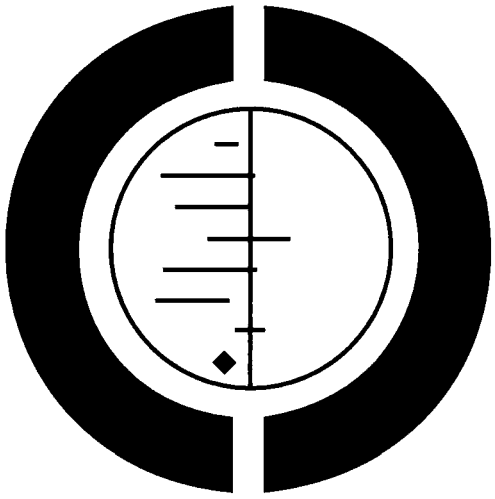
The up-scheduling of OTC codeine products will help protect consumers from the harm that these drugs can and have caused over many years, enable safer and more effective analgesic treatments for acute pain to be promoted to consumers in their place, and ensure that the need for any form of treatment with codeine-based products is appropriately assessed by a medical practitioner on an individual basis.

We endorse the interim decision to up-schedule OTC codeine products that has been supported and advocated by medical experts, and encourage the ACMS to ratify their original recommendation, which was based upon a sound risk-benefit analysis, at their March 2016 meeting.

Yours sincerely,

Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews (Review)

Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L



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[Overview of Reviews]

Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews

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ABSTRACT

Background

Non-prescription (over-the-counter, or OTC) analgesics (painkillers) are used frequently. They are available in various brands, package sizes, formulations, and dose. They can be used for a range of different types of pain, but this overview reports on how well they work for acute pain (pain of short duration, usually with rapid onset). Thirty-nine Cochrane reviews of randomised trials have examined the analgesic efficacy of individual drug interventions in acute postoperative pain.

Objectives

To examine published Cochrane reviews for information about the efficacy of pain medicines available without prescription using data from acute postoperative pain.

Methods

We identified OTC analgesics available in the UK, Australia, Canada, and the USA by examining online pharmacy websites. We also included some analgesics (diclofenac potassium, dexketoprofen, dipyrone) of importance in parts of the world, but not currently available in these jurisdictions.

We identified systematic reviews by searching the Cochrane Database of Systematic Reviews (CDSR) on *The Cochrane Library* through a simple search strategy. All reviews were overseen by a single review group, had a standard title, and had as their primary outcome numbers of participants with at least 50% pain relief over four to six hours compared with placebo. From individual reviews we extracted the number needed to treat for an additional beneficial outcome (NNT) for this outcome for each drug/dose combination, and also calculated the success rate to achieve at least 50% of maximum pain relief. We also examined the number of participants experiencing any adverse event, and whether the incidence was different from placebo.

Main results

We found information on 21 different OTC analgesic drugs, doses, and formulations, using information from 10 Cochrane reviews, supplemented by information from one non-Cochrane review with additional information on ibuprofen formulations (high quality

evidence). The lowest (best) NNT values were for combinations of ibuprofen plus paracetamol, with NNT values below 2. Analgesics with values close to 2 included fast acting formulations of ibuprofen 200 mg and 400 mg, ibuprofen 200 mg plus caffeine 100 mg, and diclofenac potassium 50 mg. Combinations of ibuprofen plus paracetamol had success rates of almost 70%, with dipyrone 500 mg, fast acting ibuprofen formulations 200 mg and 400 mg, ibuprofen 200 mg plus caffeine 100 mg, and diclofenac potassium 50 mg having success rates above 50%. Paracetamol and aspirin at various doses had NNT values of 3 or above, and success rates of 11% to 43%. We found no information on many of the commonly available low dose codeine combinations.

The proportion of participants experiencing an adverse event were generally not different from placebo, except for aspirin 1000 mg and (barely) ibuprofen 200 mg plus caffeine 100 mg. For ibuprofen plus paracetamol, adverse event rates were lower than with placebo.

Authors' conclusions

There is a body of reliable evidence about the efficacy of some of the most commonly available drugs and doses widely available without prescription. The postoperative pain model is predominantly pain after third molar extraction, which is used as the industry model for everyday pain. The proportion of people with acute pain who get good pain relief with any of them ranges from around 70% at best to less than 20% at worst; low doses of some drugs in fast acting formulations were among the best. Adverse events were generally no different from placebo. Consumers can make an informed choice based on this knowledge, together with availability and price. Headache and migraine were not included in this overview.

PLAIN LANGUAGE SUMMARY

Oral painkillers available without prescription for acute pain

Acute pain is often felt soon after injury, and is of short duration. Most people who have surgery have moderate or severe pain afterwards. Painkillers (analgesics) are tested in people with pain, often following the removal of wisdom teeth. Study participants have to have at least moderate pain levels and the pain is usually treated with painkillers taken by mouth. This overview is useful mainly for acute pain lasting only a few days or weeks, and not for chronic pain lasting for many months. For this overview we have not included information from reviews on migraine, tension headache, or period pain.

In May 2015 we looked on pharmacy websites for the range of painkillers available in the UK that could be taken by mouth, and available without a doctor's prescription. We also looked at websites in Australia, Canada, and the USA. We then looked for Cochrane reviews reporting about how well these painkillers worked, and any side effects. We used high quality evidence from 10 Cochrane reviews supplemented with information from one non-Cochrane analysis.

The outcome we used for successful treatment was that of people with moderate or severe pain having at least 50% of the maximum possible pain relief, over a period of about six hours. This is an outcome that people with acute and chronic pain, and headache, think is useful to them.

Combinations of ibuprofen plus paracetamol worked in 7 out of 10 (70%) people, and fast acting ibuprofen formulations 200 mg and 400 mg, ibuprofen 200 mg plus caffeine 100 mg, and diclofenac potassium 50 mg worked in over 5 out of 10 (50%) people. Dipyrone 500 mg, which is available OTC in many parts of the world, also worked in about 5 out of 10 people. Paracetamol plus aspirin at various doses worked in 1 out of 10 (11%) to 4 out of 10 (43%) people. An important finding was that low doses of some medicines in fast acting formulations were among the best. We could find no information on many of the commonly available combinations containing low doses of codeine. Taking painkillers with food may reduce how well they work.

There were fewer side effects for people taking ibuprofen plus paracetamol than those taking placebo (a pretend treatment). The results for side effects may be different if the painkillers are taken for more than a few days.

BACKGROUND

Description of the condition

Acute pain is experienced from time to time by almost everyone and is usually defined as short-term pain of less than 12 weeks' duration. It may be due to tissue damage or nerve injury, or both, as a result of injury (eg sprains and strains, falls), surgery, or temporary or intermittent 'malfunction' of a body system (eg dysmenorrhoea (period pain), constipation), or to some form of headache (eg tension headache). It is frequently a manifestation of inflammation and sometimes swelling, especially in joints and muscles. By definition, it is not expected to continue indefinitely, even if not treated, but it can have a significant impact on ability to function normally.

Studies to determine the efficacy of analgesics in acute painful conditions are most commonly carried out in people who are experiencing postoperative pain. The methods have been standardised over many years and the study design has proved to be robust (McQuay 2012). Trials have to be randomised and double-blind. Typically, in the first few hours or days after an operation, people develop pain that is moderate to severe in intensity, and will then be given the test analgesic (the intervention) or a placebo. Pain is measured using standard pain intensity scales immediately before the intervention and then afterwards using pain intensity and pain relief scales, usually over the following six hours. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) has become the standard outcome to measure successful treatment. For people given rescue medication it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention.

Non-prescription analgesics for migraine headache will be covered in a different Cochrane overview.

Description of the interventions

The aim is to try to assess the relative efficacy of drugs such as aspirin, paracetamol (acetaminophen), ibuprofen, diclofenac, naproxen, and other drugs both alone, and in combinations with each other, with weak opioids such as codeine, or with caffeine.

There is a bewildering variety of analgesics available without prescription in various parts of the world. They include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) (such as aspirin and ibuprofen), and opioids (usually codeine), as well as numerous 'complementary therapies' and 'herbal' products. They may be available in different formulations, such as standard tablets, fast acting tablets, effervescent powders, or liquids, and are frequently combined with each other, or with other products such as caffeine. Packaging and branding can make it difficult to identify similar products or to compare them.

Many of these analgesics can be bought from open shelves in pharmacies, supermarkets, and convenience stores, without any consultation with a doctor or checking by a pharmacist, while some are not displayed on open shelves and require some form of authorisation from a pharmacist before they can be sold. Regulations regarding the availability of these products vary between countries. There are a number of websites that provide information on analgesics available without prescription. In the UK, this is the Proprietary Association of Great Britain (www.pagb.co.uk). For Europe, a searchable database is available from the European Self-Medication Industry (www.aesgp.be), and for countries outside Europe there is the website of the World Self-Medication Industry (www.wsmi.org).

How the intervention might work

NSAIDs reversibly inhibit the enzyme cyclo-oxygenase (prostaglandin endoperoxide synthase or COX), now recognised to consist of two isoforms, COX-1 and COX-2, mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive (pain) processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their abiliry to inhibit cyclo-oxygenase-dependent prostanoid formation (Hawkey 1999). Aspirin is a special case, in that it irreversibly blocks COX-1. It also has good antipyretic (fever reducing) properties.

Despite similarities to NSAIDs, the mode of action of paracetamol has been uncertain, but it is now generally accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes (Graham 2013). Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but has subsequently been considered as a selective COX-2 inhibitor (Hinz 2008). Paracetamol metabolism is considerably influenced by genetic make-up, with large inter-subject and ethnic differences in susceptibility to toxicity and efficacy (Zhao 2011).

Codeine is an opioid that is metabolised in the liver to the active compounds morphine and morphine-6-glucuronide, but is subject to significant genetic influence (Crews 2014). Opioids bind to specific receptors in the central nervous system (CNS), causing reduced pain perception and reaction to pain, and increased pain tolerance. Binding to receptors elsewhere in the body (primarily the gastrointestinal tract) may cause nausea, vomiting, and constipation, and binding to receptors in the CNS may cause adverse events such as drowsiness and respiratory depression. In an effort to reduce the amount of opioid required for pain relief, and so

reduce problematic adverse events, opioids are commonly combined with non-opioid analgesics, such as paracetamol.

While there may be other components in some non-prescription analgesics, these are usually present infrequently, and at doses too low to have any major impact. An exception is caffeine, which adds to analgesic effects in acute pain, in conjunction with conventional analgesics, and at caffeine doses of 100 mg or above (Derry 2012).

Why it is important to do this overview

This review is intended to provide information to consumers about non-prescription oral analgesics for treating acute (of short duration, usually with rapid onset) pain conditions such as toothache or strains and sprains. Many products are available, but there is little information about their relative efficacy.

Scanning the pharmacy online databases demonstrates how many drugs, formulations, and combinations are available to treat mild headache, joint and muscle pain, dental, back, and period pain. The amount of high quality information about the efficacy of these analgesics is limited. Although Cochrane reviews are intended for use by consumers as well as healthcare providers and commissioners, there is to date no overview that directly addresses consumer issues relating to acute pain treatments that can be obtained without a prescription, and their effectiveness. The consumer is faced with a variety of different pain relieving medicines, at different amounts per tablet, sometimes alone, and sometimes with other ingredients; this makes choosing a product rather difficult for the consumer.

A broad range of analgesics is available without prescription in many parts of the world. This review is intended to cover most of the less costly analgesics available almost anywhere in the world. Licensing of analgesics available without prescription in the UK is broadly similar to that in the USA, Australia, and much of Europe. It was also our aim to provide sufficient information for individuals to work out for themselves what the efficacy may be for specific over-the-counter (OTC) products not included by name in this review.

Use of non-prescription analgesics

OTC analgesics are used frequently, though the reasons for their use are not often described. For example, in Norway, one large population survey found that the prevalence of using OTC analgesics at least once per week in the last month was 47% (Dale 2015). Prevalence of paracetamol use was almost 40%, compared to 19% for NSAIDs and 8% for aspirin; more women used OTC analgesics. A lower figure of 25% over three months was found in Germany (Freytag 2014), with paracetamol and aspirin predominating. There was a much higher prevalence of 76% over one month in the USA (Paulose-Ram 2003), again with use higher in women.

A systematic review found the prevalence of non-prescription analgesic use in individual studies examining older people varied between 4% and 87%, with most reporting between 20% and 60% (Jerez-Roig 2014). Studies report that 5% to 94% of adolescents use OTC analgesics (Shehnaz 2014).

OBJECTIVES

To examine published Cochrane reviews for information about the efficacy of pain medicines available without prescription using data from acute postoperative pain.

METHODS

Criteria for considering reviews for inclusion

All Cochrane reviews of randomised controlled trials (RCTs) of single dose oral analgesics for acute postoperative pain in adults (aged 15 years or over).

We included reviews providing information on any drug, dose, or formulation matching the content of analgesic products available without prescription in the UK, where the usual recommended dose involves taking two tablets of most products. A list of available medication was drawn up from the Internet sites of Boots (www.boots.com/en/Pharmacy-Health/Health-shop/Pain-relief/) and Lloyds Pharmacy (www.lloydspharmacy.com/en/medicines-treatments/pain-relief/) on 21 May 2015 (Appendix 1). We limited the overview to medication available in the UK because it is almost impossible to know with certainty what is available in other parts of the world. However, for completeness, we examined online pharmacy websites in the USA (Walgreens, CVS), Canada (Shoppers Drug Mart), and Australia (Guardian, Terry White Chemists) to check on any major drugs or combinations not available in the UK, and for alternatively named products sold in those countries. We planned specifically to include dipyrone (metamizole), which, while not available in any of the countries listed, is available without prescription in many parts of the world.

Medicines covered in the review are applicable to all parts of the world, and will include the most commonly used, although there are likely to be many other products, doses, and combinations available in different countries. Four examples highlight the difficulties in trying to produce an overview for OTC analgesics. Diclofenac potassium was available as an OTC product in the UK until early 2015, when market authorisation was withdrawn because of concerns about potential cardiovascular events. But it is still available in a number of other countries (though not Australia, Canada, or the USA), and so we have included it in the overview for completeness. Dipyrone is similarly available in many parts of

the world, but not in Australia, Canada, the UK, or USA. Again, combinations of ibuprofen plus caffeine are available in some parts of South America, and we have included it here because caffeine is known to increase analgesic efficacy (Derry 2014a), and the amount required to provide greater efficacy can be derived from a cup of coffee or other drinks, or as tablets, and so is available for possible use by consumers. We also became aware that dexketoprofen is available as an OTC analgesic in Estonia, Italy, Lithuania, and Spain.

We have included Cochrane reviews of randomised controlled trials (RCTs) carried out to high methodological standards, using validated methods and outcomes of interest to patients. Each medicine was compared with placebo to allow indirect comparison. We anticipated that included reviews would be of medication used in acute postoperative pain, where study participants have established pain of moderate to severe intensity before treatment. In most circumstances it is considered appropriate to extrapolate these results to acute pain generally. The outcome had to be of direct relevance to patients, namely no worse than mild pain, or at least 50% of maximum pain relief (McQuay 2012; Moore 2013a). We expected that the bulk of studies contributing information would have been performed in pain following third molar extractions, as demonstrated in a Cochrane overview (Moore 2015a). For this review, we have not included information on reviews on migraine, tension headache, or period pain.

Search methods for identification of reviews

We searched the *Cochrane Database of Systematic Reviews* Issue 4 on *The Cochrane Library* for relevant reviews. See Appendix 2 for the search strategy. A series of Cochrane reviews have been conducted by the same team, covering analgesics identified in the *British National Formulary*.

Data collection and analysis

Two review authors (RAM, SD) independently carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. We resolved any disagreements by discussion, involving a third review author if necessary.

Selection of reviews

Included reviews assessed RCTs evaluating the effects of a single oral dose of analgesic given for relief of moderate to severe postoperative pain in adults, compared to placebo, and included:

- a clearly defined clinical question;
- details of inclusion and exclusion criteria;
- details of databases searched and relevant search strategies;
- patient-reported pain relief; and
- summary results for at least one desired outcome.

Data extraction and management

We extracted data from the included reviews using a standard data extraction form. We used original study reports only if specific data were missing.

We collected information on the following.

- Number of included studies and participants.
- Drug, dose, and formulation (if formulation was an issue).
- 50% or greater maximum pain relief over four to six hours (participant-reported): this outcome encapsulates both degree of pain relief and duration of the effect, and is a dichotomous (yes/no) measure of success over a defined period following drug ingestion.
- Success and failure rates, where success (as a percentage of the maximum possible) was calculated from the drug-specific effect and maximum possible effect (Moore 2013b).
- Participants experiencing one or more adverse events.

Assessment of methodological quality of included reviews

All included reviews were carried out according to a standard protocol that satisfied the criteria specified in the 'assessment of multiple systematic reviews' (AMSTAR) measurement tool for rigorous methodological quality (Shea 2007).

Each review was required to:

- provide an *a priori* design;
- carry out duplicate study selection and data extraction;
- carry out a comprehensive literature search;
- include published and unpublished studies irrespective of language of publication;
- provide a list of studies (included and excluded);
- assess and document the scientific quality of the included studies;
- use the scientific quality of the included studies appropriately in formulating conclusions;
- use appropriate methods to combine the findings of studies; and
- state conflicts of interests.

Data synthesis

We used information on the selected efficacy outcomes to draw up comparisons of analgesic efficacy, using indirect comparison of different drugs from almost identical clinical trial conditions, with placebo as a common comparator (Glenny 2005; Song 2003). We required a minimum of 200 participants in any comparison of an intervention with placebo (Moore 1998).

We have expressed comparative results at recommended doses as:

- participants achieving at least 50% maximum pain relief, as a percentage, and as number needed to treat for an additional

beneficial outcome (NNT) for at least 50% maximum pain relief over four to six hours, compared with placebo;

- success and failure rates;
- participants experiencing at least one adverse event.

We planned to list marketed products for which no good quality evidence is available from Cochrane reviews, and to attempt to produce estimates of their efficacy based on a model that predicts the analgesic efficacy of combination products (Moore 2012).

RESULTS

A similar range of OTC analgesics was available in the UK, Australia, Canada, and the USA (Appendix 1). We added diclofenac, dipyrone, and ibuprofen plus caffeine to the list of reviews to look for.

We examined 39 separate Cochrane reviews investigating 41 analgesics or analgesic combinations given as single oral doses in acute postoperative pain conditions (Aceclofenac 2009; Acemetacin 2009; Aspirin 2012; Celecoxib 2013; Codeine 2010; Dexibuprofen 2009; Diclofenac 2015; Diflunisal 2010; Dihydrocodeine 2000; Dipyrone 2010; Etodolac 2009; Etoricoxib 2014; Fenbufen 2009; Fenoprofen 2011; Flurbiprofen 2009; Gabapentin 2010; Ibuprofen 2009; Ibuprofen + caffeine 2015; Ibuprofen + codeine 2015; Ibuprofen + oxycodone 2013; Ibuprofen + paracetamol 2013; Indometacin 2004; Ketoprofen and dexketoprofen 2009; Lornoxicam 2009; Lumiracoxib 2010; Mefenamic acid 2011; Meloxicam 2009; Nabumetone 2009; Naproxen 2009; Nefopam 2009; Paracetamol 2008; Paracetamol ± dextropropoxyphene 1999; Paracetamol + codeine 2009; Paracetamol ± oxycodone 2009; Piroxicam 2000; Rofecoxib 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009). Results for ibuprofen formulations were supplemented with data from a non-Cochrane review but based on Cochrane reviews (Moore 2014a).

We checked the contents of these reviews against the list of available OTC analgesics in Appendix 1, and included in this review only the relevant reviews (Aspirin 2012; Diclofenac 2015; Dipyrone 2010; Ibuprofen 2009; Ibuprofen + caffeine 2015; Ibuprofen + codeine 2015; Ibuprofen + paracetamol 2013; Ketoprofen and dexketoprofen 2009; Naproxen 2009; Paracetamol 2008).

We found information on 21 different OTC analgesic drugs, doses, and formulations, using information from 10 Cochrane reviews, supplemented by information from one non-Cochrane review with additional information on ibuprofen formulations (Moore 2014a, high quality evidence). The included reviews provided information on several doses of aspirin, dexketoprofen (as the trometamol salt), diclofenac potassium, dipyrone, ibuprofen in various formulations, naproxen, and paracetamol, and the combinations of ibuprofen plus caffeine and ibuprofen plus paracetamol. No or insufficient information was available on combinations of analgesics with low doses of codeine, or a range of the other combinations identified in Appendix 1.

The amount of information available for included interventions varied greatly, from a minimum of two studies with about 200 participants to over 50 studies and about 5000 participants (Appendix 3).

Description of included reviews

Included reviews each had the same structure and organisation, and used identical methods based on criteria established by extensive analysis and validation, using individual participant data. They all used the same criteria and typically these were as follows.

- Adults with established pain of at least moderate intensity (Collins 1997).
- Single dose oral administration of analgesic or placebo (with additional analgesia available, typically after 60 to 120 minutes).
- Randomised, double-blind studies.
- Pain assessed by participants using standard pain intensity and pain relief scales.
- Study duration of four hours or more.
- Searching included electronic searches, plus databases created by hand searching the older literature, now part of the Cochrane Central Register of Controlled Trials (CENTRAL). Searching also included different retail names for drugs.
- No language restriction on included papers.
- Assessment of study quality according to established criteria and minimum criteria for inclusion.

Methodological quality of included reviews

All the reviews:

- had an *a priori* design;
- performed duplicate study selection and data extraction;
- had a comprehensive literature search;
- used published and any unpublished studies included irrespective of language of publication, though not all reviews contacted companies or researchers for unpublished trial data;
- provided a list of included and excluded studies;
- provided characteristics of included studies;
- assessed and documented the scientific quality of the included studies;
- used the scientific quality of the included studies appropriately in formulating conclusions, because only studies with minimal risk of bias were included (a particular issue was trial size, but conclusions were not drawn from inadequate data sets, based on previously established criteria (Moore 1998));
- used appropriate methods to combine findings of studies and importantly provided analyses according to drug dose; and
- had universal conflict of interest statements.

The reviews all used validated methods for conversion of mean to dichotomous data (Moore 1996; Moore 1997a; Moore 1997b), providing the number and proportion of participants with the clinically relevant outcome of at least 50% maximum pain relief. Remedication is common within a few hours with placebo, therefore the method of imputing data after withdrawal is potentially of importance to the measurement of treatment effect. In the case of the primary outcome of the reviews, that of NNT for at least 50% maximum pain relief compared with placebo over four to six hours, the imputation method had been shown not to make any appreciable difference (Moore 2005), although use of last observation carried forward tended to overestimate treatment effect compared with baseline observation carried forward over longer periods (Moore 2005).

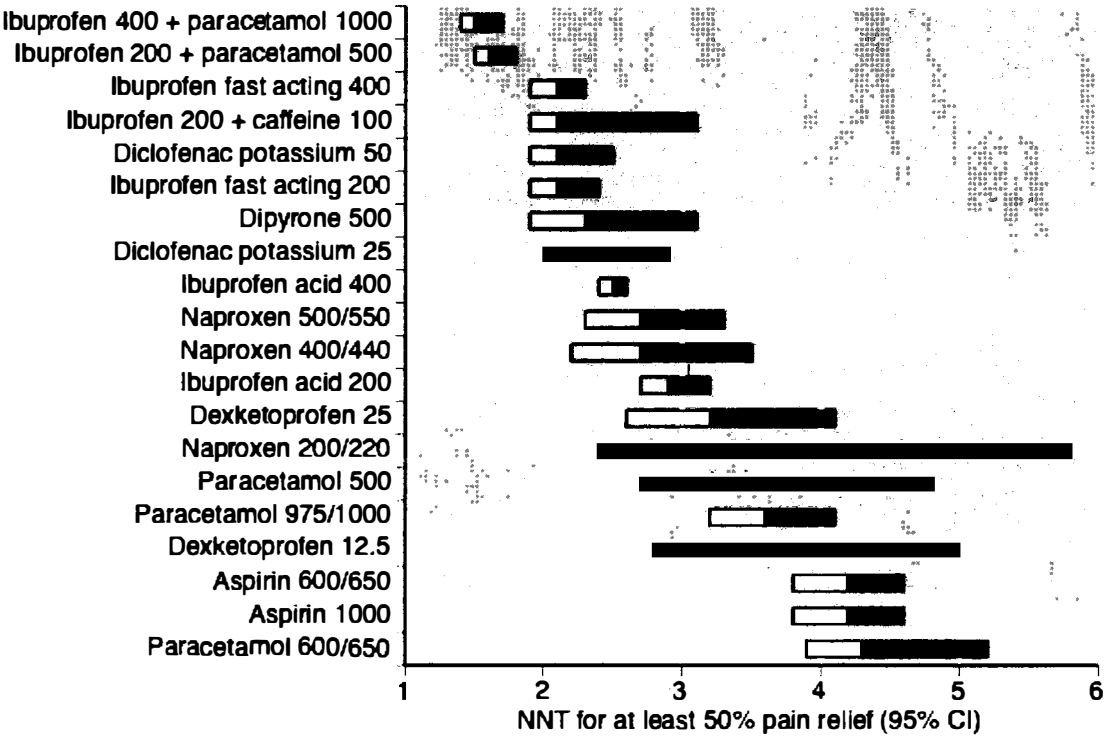
Effect of interventions

The effects of the analgesics are reported according to dose in milligrams, not as the number of tablets required to obtain that dose. This is because the dose per tablet can be quite variable (Appendix 1).

1 Number needed to treat for an additional beneficial outcome (NNT)

NNT is used widely in medicine to report the magnitude of the effect of an intervention. In this case it describes the number of participants in studies who need to be treated with an analgesic for one more person to have good pain relief than if the same number had been treated with placebo. Lower numbers are clearly better, and the ideal number is an NNT of 1, which would occur if every participant had good pain relief with an analgesic and none with placebo. Summary of results A and Figure 1 shows the NNTs for OTC drugs where a minimum of two studies with 200 participants was available. Full details are in Appendix 3.

Figure 1. Number needed to treat for an additional beneficial outcome (NNT for at least 50% maximum pain relief over four to six hours compared with placebo. The bars show the 95% confidence interval (CI), and the colour change is the point estimate.



The lowest (best) NNT values were for combinations of ibuprofen plus paracetamol, with NNT values below 2. Analgesics with values close to 2 included fast acting formulations of ibuprofen 200 mg and 400 mg, ibuprofen 200 mg plus caffeine 100 mg, and diclofenac potassium 50 mg. By contrast, paracetamol plus aspirin at various doses had NNT values of 3 or above.

Summary of results A

Drug	Dose (mg)	NNT (95% confidence interval)
Aspirin	500	Not better than placebo
Aspirin	600/650	4.2 (3.8 to 4.6)
Aspirin	1000	4.2 (3.8 to 4.6)
Dexketoprofen	12.5	3.6 (2.8 to 5.0)
Dexketoprofen	25	3.2 (2.6 to 4.1)
Diclofenac potassium	25	2.4 (2.0 to 2.9)
Diclofenac potassium	50	2.1 (1.9 to 2.5)
Dipyrone	500	2.3 (1.9 to 3.1)
Ibuprofen acid	200	2.9 (2.7 to 3.2)
Ibuprofen acid	400	2.5 (2.4 to 2.6)
Ibuprofen fast acting	200	2.1 (1.9 to 2.4)
Ibuprofen fast acting	400	2.1 (1.9 to 2.3)
Ibuprofen + caffeine	200+100	2.1 (1.9 to 3.1)
Ibuprofen + paracetamol	200+500	1.6 (1.5 to 1.8)
Ibuprofen + paracetamol	400+1000	1.5 (1.4 to 1.7)
Naproxen	200/220	3.4 (2.4 to 5.8)
Naproxen	400/440	2.7 (2.2 to 3.5)
Naproxen	500/550	2.7 (2.3 to 3.3)
Paracetamol	500	3.5 (2.7 to 4.8)

(*Continued*)

Paracetamol	600/650	4.6 (3.9 to 5.5)
Paracetamol	975/1000	3.6 (3.2 to 4.1)

2 Success rate

Success rate is a different way of describing different degrees of effectiveness between drugs. It is calculated by taking the proportion of participants who get good pain relief with analgesic minus the proportion who get good pain relief with placebo, and expressing this as a percentage of the maximum possible success rate for the analgesic, namely 100 minus the response rate with placebo. It has been used to explore high failure rates with analgesics, especially in more complex chronic conditions (Moore 2013b).

Summary of results B and Figure 2 show the success rates for OTC drugs where a minimum of two studies with 200 participants was available. Full details are in Appendix 4. Results expressed in this way show the same general order as with NNT. Again combinations of ibuprofen plus paracetamol have the highest success rates, at almost 70%, with dipyrone 500 mg, fast acting ibuprofen formulations 200 mg and 400 mg, ibuprofen 200 mg plus caffeine 100 mg, and diclofenac potassium 50 mg having success rates above 50%. Again, doses of aspirin plus paracetamol tended to have the lowest success rates.

Figure 2. Success rate - percentage achieving at least 50% maximum pain relief.

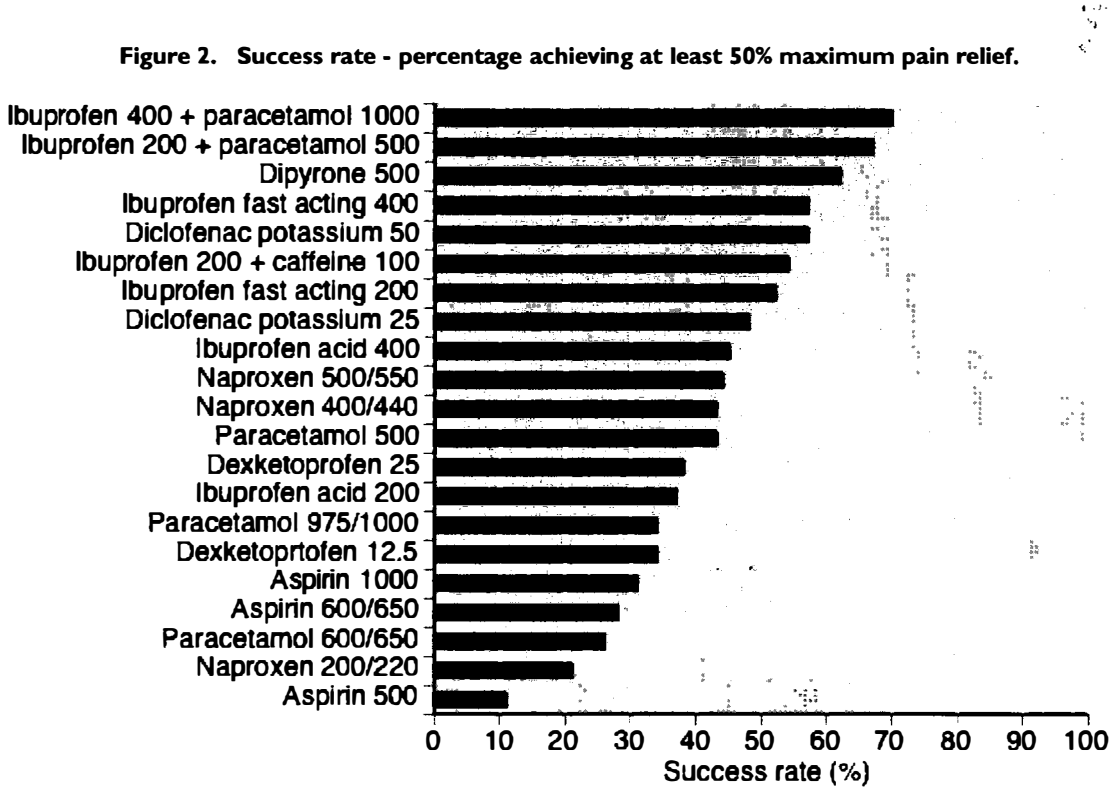
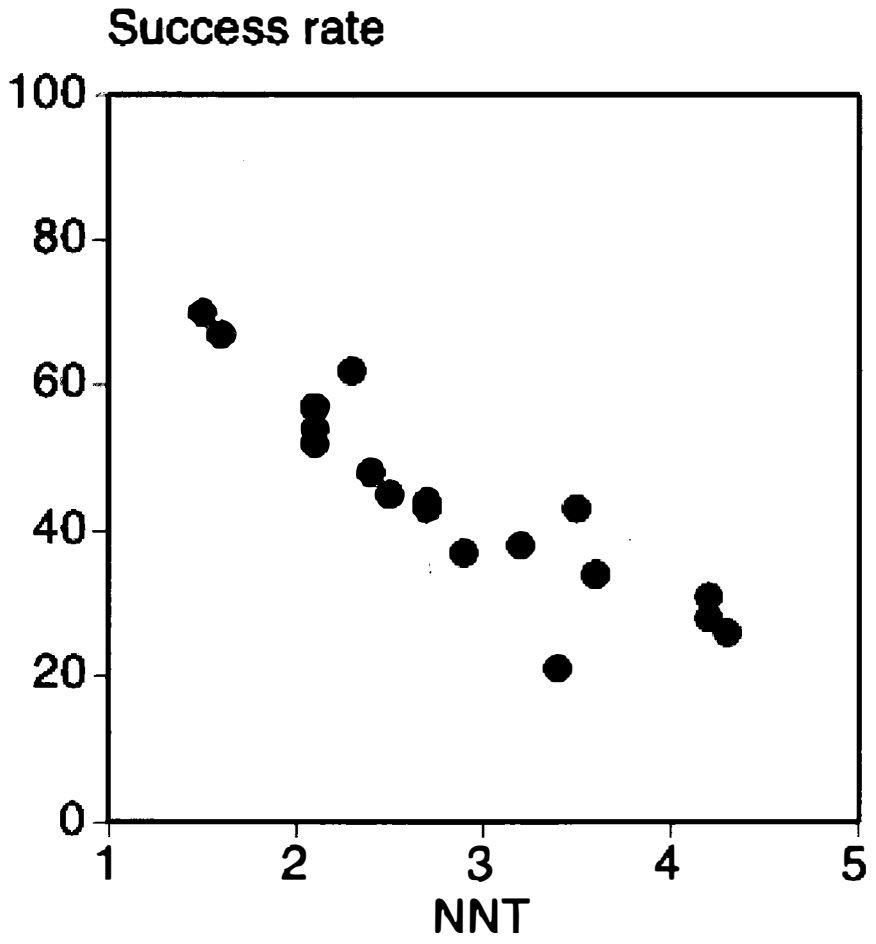


Figure 3 shows the relationship between success rate and NNT for these drugs.

Figure 3. Relationship between success rate and number needed to treat for an additional beneficial outcome (NNT



Summary of results B

Drug	Dose (mg)	Success rate (%)
Aspirin	500	11
Aspirin	600/650	28
Aspirin	1000	31
Dexketoprofen	12.5	34
Dexketoprofen	25	38

(*Continued*)

Diclofenac potassium	25	48
Diclofenac potassium	50	57
Dipyrone	500	62
Ibuprofen acid	200	37
Ibuprofen acid	400	45
Ibuprofen fast acting	200	52
Ibuprofen fast acting	400	57
Ibuprofen + caffeine	200+100	54
Ibuprofen + paracetamol	200+500	67
Ibuprofen + paracetamol	400+1000	70
Naproxen	200/220	21
Naproxen	400/440	43
Naproxen	500/550	44
Paracetamol	500	43
Paracetamol	600/650	26
Paracetamol	975/1000	34

3 Adverse events

The reviews reported the number of participants who experienced at least one adverse event during the course of the studies. This could be any adverse event, such as headache, nausea, or dizziness. Full details are in Appendix 5. For the most part there was no difference in adverse event rates between analgesics and placebo in these studies involving single doses.

For two analgesics, aspirin 1000 mg and ibuprofen 200 mg plus caffeine 100 mg, adverse event rates were statistically significantly higher with analgesic than placebo, although barely so for ibuprofen and caffeine. For aspirin 1000 mg the number needed for one participant to be harmed more than with placebo was 7.5.

For both doses of ibuprofen plus paracetamol in combination, the adverse event rate was lower with analgesic than placebo, with a number needed to treat to prevent one more adverse event happening with analgesic than with placebo of about 5.

Serious adverse events were rare. In total there were four reported for ibuprofen, four for placebo, and one for naproxen.

4 Non-prescription analgesics with no or insufficient data

We found no data for a range of OTC analgesics, particularly those combining a low dose of codeine plus aspirin or paraceta-

mol, and combinations that included caffeine. We conducted some searches of PubMed to find any other non-Cochrane review or randomised trials with low dose codeine combinations, but found none. Within a review of ibuprofen plus codeine, we found information on one trial of an OTC combination product (Ibuprofen + codeine 2015), but concluded that the amount of information was too small to make the estimate of efficacy reliable.

5 Predicting analgesic efficacy where there were no direct data

It became clear after looking at the range of combination products available, principally those with low doses of codeine, that this part of the review could not be completed as there were no reliable data to use.

DISCUSSION

This overview of non-prescription (OTC) oral analgesics for acute pain builds on evidence from a large number of clinical studies of oral analgesics for acute postoperative pain, a common test of analgesic efficacy that has been in use since the 1950s (McQuay 2012). It has proved a reliable indicator of whether drugs can act as analgesics, and in systematic review, how well they work. Two other overviews have looked in detail at all available data on efficacy (Moore 2015a) and adverse events (Moore 2015b).

New information continues to inform on analgesic effectiveness. For example, in the recent past we have learned much about the importance of drug formulation on efficacy, and recognise that speedy absorption into the body not only provides more rapid pain relief, but better overall pain relief and longer lasting pain relief (Moore 2014a; Moore 2015c). Taking analgesics with food can delay absorption and is likely to reduce the effectiveness of drugs for acute pain (Moore 2015d); the studies in the included reviews were probably all conducted in fasting participants, reducing the relevance of food for this overview. However, the advice is often given to take analgesics with food, with the ostensible aim of reducing adverse effects in the gastrointestinal tract, and this advice needs urgent re-evaluation. Finally, relative analgesic efficacy determined in this acute postoperative pain model generally holds up in other circumstances (Moore 2015e).

This overview is directed specifically at acute painful conditions, and not at migraine, tension headache, dysmenorrhoea, chronic musculoskeletal conditions, or other chronic painful conditions such as neuropathic pain or fibromyalgia. For those conditions different drugs might be used, or the same drugs at different doses, or using different formulations. Increasingly, overviews are being produced for some of these, such as antiepileptic drugs for neuropathic pain and fibromyalgia (Wiffen 2013), or sumatriptan (all routes of administration) for migraine Derry 2014b).

Summary of main results

A wide range of analgesic efficacy exists for OTC products for acute pain, whether expressed as NNT or success rate. Taking success rate as the more easily understood method of reporting results, success ranged from below 20% to about 70%. Better-performing analgesics included combinations of ibuprofen plus paracetamol, dipyrone 500 mg, fast acting ibuprofen formulations 200 mg and 400 mg, ibuprofen 200 mg plus caffeine 100 mg, and diclofenac potassium 50 mg. Aspirin and paracetamol at various doses had the lowest success rates.

It was clear that combination products and fast acting formulations performed particularly well, and that it might easily be possible to obtain greater analgesic effects with lower doses by varying formulation and combination. For example, the ibuprofen plus paracetamol combination that performed best used a formulation designed for rapid dissolution, and resulted in very good analgesia with only ibuprofen 200 mg with paracetamol 500 mg. This also produced long lasting analgesia (Ibuprofen + paracetamol 2013), so that fewer doses need to be taken, resulting in a lower exposure to the drugs. This is also the case with fast acting formulations (Moore 2014a), and the combination of ibuprofen plus caffeine. The combination of ibuprofen plus caffeine need not be in a single tablet, and it might well be that individuals could achieve very good analgesic results by taking a fast acting 200 mg tablet of ibuprofen with a drink containing caffeine, like a mug of strong coffee or a caffeinated beverage.

Some formulations sold without prescription are described as being slow release (Appendix 1). There is no reason to expect that these will be of any value for acute pain where rapid pain relief is needed.

For the most part, the OTC analgesics in single dose studies resulted in no more participants experiencing an adverse event than with placebo. Serious adverse events were rare, and not necessarily related to the drug taken.

The available data do not cover every available dose or combination product available in four large Western countries, and there will be many other products available worldwide. Even so, there is a reasonable amount of evidence to help consumers choose therapies that can help them. Some are available from open shelves, while some have to be asked for at a pharmacy counter; regulations vary. We did not consider the cost of analgesics to consumers.

Overall completeness and applicability of evidence

For many of the analgesic doses and combinations available OTC, there was simply no evidence. Combination products with low doses of codeine represent the major gap in the evidence, but probably represent a large part of OTC analgesic sales.

Moreover, the evidence we have is rather general, and there is no way of knowing whether a product with ibuprofen 200 mg in it is