Public Submissions on the Proposed Amendments to the Poisons Standard

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 submission on the proposed amendments to the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* - SUSMP). These submissions were considered by the Advisory Committee on Medicines Scheduling (ACMS) #15 (August 2015 meeting).

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

Material claimed to be commercial-in-confidence was 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.

Discrete submissions have been grouped by substance. Those submitters who provided submissions that related to multiple substances have been separately grouped. A number of submissions provided for codeine and naloxone have not been published due to confidential information.

List of Submissions

Substance	Total number of public submissions
CODEINE	60 submissions
ESOMEPRAZOLE	7 submissions
HYDROCORTISONE/HYDROCORTISONE ACETATE	5 submissions
LEVOCETIRIZINE	3 submissions
NALOXONE	96 submissions
ORLISTAT	5 submissions
PROTON PUMP INHIBITORS	3 submissions

From: [redacted]
To: Medicines Scheduling
Subject: submission -over the counter codeine combination analgesics-re-scheduling submission.
Date: Wednesday, 22 April 2015 11:51:13 AM
Attachments: consultation-invitation-public-comment-acms-meeting-july-2015-coversheet.docx
2010 apsad Alan Fisher poster 2 GW 201110.ppt

Dear Sir/ Madam,

Please find attached a case study abstract relating to Over The Counter (OTC) -Combination Analgesics Containing Codeine (CACC) dependence, and major medical problems.

It was published in 2010, however the picture remains similar in that;

Point of sale changes provided a reduction of those trying to procure the CACC, with limited transport to access multiple pharmacies in a regional setting.

The presentations continue in a similar manner for those that can travel distances, and our clients articulate that it is still relatively easy to aquifer large amounts, with a plausible story.
It is my belief that:

There is a significant body of contemporary evidence does not support the efficacy of these analgesic agents.

Rescheduling has the potential to reduce harm through diminished acquisition.

The potential for harm with CACC agents, in their current schedule outweighs the benefits with the above efficacy doubts.

Please contact me if need be,

[redacted]

Albury Wodonga Health

Over The Counter and into the Grave: Morbidity and mortality related to NSAIDs & codeine dependence

Lisa Ferguson, Robert Batey, Charles Clarke, Gail Legg, Alan Fisher
Greater Southern Area Health Service (GSAHS) Albury, Wagga, Goulburn and Batemans Bay Hospitals, New South Wales (NSW), Australia.

Background & Aim

Misuse of Over-The-Counter (OTC) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) containing codeine has been associated with serious medical consequences including nephrotoxicity, hypokalemia[1], gastric perforation and haemorrhage.[2]

A number of patients have been referred to Drug & Alcohol (D&A) Consultation/Liaison Nurses (CLNs) in GSAHS. Most had not sought assistance for dependence on these drugs. All met criteria for substance use disorder (SUD).

Regulatory point-of-sale changes occurred in NSW in mid 2010, with OTC combination analgesics containing codeine (CACC) requiring pharmacist approval and restriction on the quantity of tablets able to be purchased.

Aim: To present a case series highlighting complications from misuse of these drugs.

Method

A retrospective audit of patients referred to the D&A CLN Service for management of NSAID-codeine dependence from 2008 to June 2010.

- Examination of the disease process and psycho-social factors of patients referred to D&A CLN nurses in GSAHS.
- Discussion of trends relating to pre and post point-of-sale regulatory changes for OTC CACCs.

A total of 5 cases were identified. Three patients are presented in more detail as they were more complex and in one case fatal.

Case1

A 27 year old female with past history of sexual abuse and unplanned pregnancy commenced NSAIDs (Nurofen Plus) to relieve right sided abdominal pain following a termination. Use escalated to over 50 tablets per day. She presented with anaemia Hb 79, confusion, malnutrition, Alb 16 and BMI of 16. She had a history of admissions for blood and iron transfusions, with previous gastroscopy revealing a duodenal ulcer. The patient had been treated, after each of these admissions with pharmacotherapy for codeine dependence, and had been well and abstinent from NSAIDs for 8 months. About one month prior to the last admission she lapsed into Nurofen Plus use of unknown quantities. The patient underwent a laparotomy. However she suffered hypoxic brain injury from cardiac arrest due to lactic acidosis, sepsis, malnutrition and gastrointestinal bleeding. She died several days after the surgery.

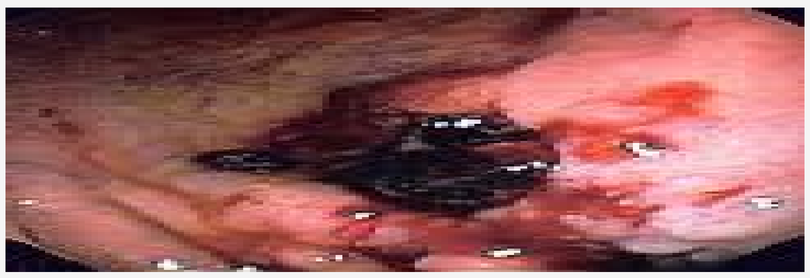

Figure 1. Bleeding gastric ulcer

Case 2

A 31 year old female presenting with severe muscle weakness, taking >50 Nurofen Plus per day, stating neck pain as the indication. She had been dependent for several months. The patient had a history of sexual assault and had been diagnosed with depression and anxiety. She was treated in ICU and biochemistry included: serum potassium of 2.0 mmol/l (3.5-5.2), bicarbonate 14 mmol/l (24-30), creatinine 140 mmol/l (60-100), anion gap 21 mmol/l (7-17). A diagnosis of hypokalemia with renal tubular acidosis was made. The patient was treated and discharged on buprenorphine.

Case 3

A 22 year old female, with a one year history of taking 60 Nurofen Plus per day, was admitted for emergency laparotomy for a perforated pre pyloric ulcer and peritonitis. The patient required ICU care and the pathology showed she was acidotic and hypoalbuminemic. She had initially started Nurofen Plus for post IUD insertion pain, at recommended doses. Discovering euphoric effects from high doses, she escalated the dose after two weeks. The patient has been treated for depression. She had been abstinent from Nurofen Plus for 15 months and had been treated in a residential D&A facility. A relatively brief relapse of 60 Nurofen Plus tablets per day precipitated acute abdominal pain and urgent hospital admission.

Other Cases

Case 4: A 32 year old male presented to D&A services with a 2 year history of Nurofen Plus use: 40-60 tablets per day. He commenced use initially for dental pain and found escalating doses decreased anxiety. After point-of-sale changes, he was forced to reduce the dose. He is now stable on buprenorphine 8mg daily.

Case 5: A 28 year old female with a 2 year history of using 75 Nurofen Plus per day presented to hospital requesting withdrawal. This was driven by inability to purchase high amounts in a rural area, due to point-of-sale changes. Gastroscopy and other pathology was normal. Symptomatic opioid withdrawal was conducted as the patient declined maintenance pharmacotherapy.

Discussion

There is a growing recognition of NSAID use with codeine dependence among health workers. Health services are identifying abuse of OTC codeine preparations more effectively with case exposure.

Cases 1, 2 and 3 were referred to D&A services by base hospitals, following serious medical complications. The patients had not sought help with codeine dependence and did not identify as having a SUD. In two of these the patients had been treated previously for OTC codeine dependence and had relapsed only for a brief time at lower doses. However the gastrointestinal complications were catastrophic.

Cases 4 and 5 presented directly to D&A services with opioid withdrawal symptoms post point of sale changes. The inability to procure sufficient OTC medications had prompted their self referral and neither patient has so far developed medical complications.

The patients in all cases were not cognisant of the risks of NSAID OTC medications. The lack of perceptions of dependence and risks to those dependent on OTC preparations are echoed in a recent large Australian report conducted on OTC dependence.[3]

The cases discussed share common bio-psycho-social considerations; predominantly young (22-32), females (4 of 5 cases) who had experienced prior trauma, with a history of pain issues preceding NSAID dependence, and did not identify as having a SUD.

Conclusions

This group of patients did not identify as having a SUD or were not cognisant of the risks of OTC NSAID –codeine misuse.

While referrals occurred following medical events and hospital admissions, the point-of-sale regulatory changes appear to have prompted some patients to self refer.

Biopsychosocial commonalities were noted prior to dependence in all 5 patients:

- predominantly female
- previous trauma
- high prevalence mental health diagnoses
- pain

Relapse, even for a brief duration, caused dramatic gastric damage in two cases.

References

1,2 Severe hypokalemia and weakness due to Nurofen plus misuse; Chetty et al; Annals of Clinical Biochemistry, July 2003, p422.

3 Over The Counter Codeine Dependence-Turning Point Report S Nielson et al., June 2010.

Consultation Submission to TGA around Re-scheduling codeine products

This submission is made on behalf of more than 40 Addiction Specialists, Addiction Psychiatrists and Addiction Medicine practitioners who are members of the Queensland Addiction Medicine Collaborative (QAMC). QAMC members represent the majority of medical practitioners working exclusively in Addiction Medicine in Queensland. We strongly support the proposed deletion of the Schedule 3 entry for codeine products, and the rescheduling of all codeine containing compound products to Schedule 4. We do not support the suggestion that only codeine containing compound analgesic products should be rescheduled, therefore we support the amendment of the Schedule 2 entry for codeine also.

Much of our work involves the medication assisted treatment of opioid dependence. There are currently more than 6,000 patients in treatment in Queensland. Over the past 10 years we have observed a growing number of patients accessing codeine products, either as their primary drug of concern or when their regular opioid is unavailable. Acute and longer term harms then result from excessive consumption of the compound mixed with codeine. There is a particular irony in the current Scheduling arrangement. Only lower dose codeine products are available, in combination form, 'over the counter', thus patients are consuming large quantities of medication each day, sometimes 60-100 tablets of products such as paracetamol / codeine and ibuprofen / codeine, in order to treat their opioid dependence. Colleagues visiting from USA and parts of Europe often express surprise that codeine can be obtained on Schedule 2 or 3, since in their own country it is a prescription only medication.

Codeine is a prodrug which is converted by liver enzymes (mainly cytochrome 2D6) to morphine (1). Thus in using codeine, patients need to be aware that they are effectively taking morphine, which is recognised as a strong painkiller with significant potential to cause opioid use disorders and other harms. There is no easy way to predict which patients will convert codeine to morphine efficiently and conversely no way to predict the 10% (or even 20%) of the population where the enzyme responsible does not convert codeine to morphine at all (1). Case reports describe young children overdosing and even dying after 'therapeutic' doses of codeine in the post-operative period, as well as a breast feeding mother on a 'therapeutic' dose of a codeine containing analgesic whose baby died from an opioid overdose due to the efficiency of their combined 2D6 activity (2,3). Authorities have suggested codeine should no longer be prescribed for children under 12 years (4).

The harms which result from excessive consumption of codeine containing analgesic products are well described (5). In Queensland we too have patients who have suffered from a range of complications. These include perforated peptic ulcer requiring emergency surgery; stercoral ulceration of the colon leading to peritonitis requiring emergency laparotomy and temporary defunctioning colostomy; recurrent presentations with anaemia requiring admissions and blood transfusions over a 10 year period; NSAID related small bowel enteropathy leading to emergency admission with severe anaemia and hypoalbuminaemia with peripheral oedema and weight loss; and paracetamol overdose requiring emergency treatment with N-acetyl-cysteine. Excessive consumption of paracetamol is of particular concern in many of our patients who have an increased incidence of viral hepatitis, as this may further increase their risk of liver damage.

When confronted with the dangers of using excess ibuprofen or paracetamol, patients sometimes disclose the steps they have taken (such as cold water separation or mixing paracetamol and ibuprofen containing compound analgesics) to reduce the risk of overdose on paracetamol and or ibuprofen. However in most cases, opioid use disorder has 'driven' patients to ever increasing codeine consumption to gain enough morphine to address their growing opioid tolerance, regardless of the concomitant risks to their health.

If codeine was an effective analgesic product, re-Scheduling might be more challenging, i.e. re-Scheduling might be said to be denying patients the right to timely pain relief. However in the Oxford League Table of Analgesic Efficacy (6), a meta-analysis of many studies of a range of analgesics treating acute pain, codeine 60 mg came last in the list. In this analysis codeine was reported to have a 'number needed to treat' (NNT) of 16.7 for a 50% reduction in pain scores, compared with the most effective analgesics with NNT between 1.5 and 2.5 (some Cox 2 selective inhibitors and typical NSAIDs such as ibuprofen). Many NSAIDS are already available as Schedule 2 product even for young children in the case of ibuprofen. This indicates that codeine is a very poor analgesic product, and when used a compound analgesic it is likely the major benefit comes from the other component in the medication, typically ibuprofen or paracetamol.

MIMS currently lists 72 codeine containing products, almost all are in compound form with other medications. Should the TGA imagine that simply rescheduling the codeine containing compound analgesics will address this growing problem, we would like to highlight another patient who managed their severe opioid use disorder with a compound cough suppressant liquid containing pseudoephedrine and dihydrocodeine (equivalent to codeine), drinking up to 400 ml or 2 bottles each day (containing up to 760 mg of codeine equivalent). This suggests that patients may switch to other over-the-counter codeine containing products if the codeine containing compound analgesic products alone are rescheduled.

Of great concern is the likelihood of powerful lobbying from the pharmacy industry, fearing loss of sales and profits. However it must be recognised that there is a greater good at stake and the welfare of patients is paramount. While there are effective treatments available for opioid use disorder (with more than 47,000 patients on Opioid Treatment Programs around Australia), 'prevention is much better than cure', thus steps, such as rescheduling codeine, which reduce the amount of opioid available in the community will in turn lead to fewer patients developing opioid use disorder. Finally members of the QAMC will be happy to provide more details of harms caused with de-identified individual patient histories, if this would be helpful for the Scheduling meeting.

Yours faithfully

[redacted]
on behalf of the Queensland Addiction Medicine Collaborative
[redacted] Metro North Mental Health - Alcohol and Drug Service

(1) Iedema, Joel. Cautions with codeine. Australian Prescriber (2011); 34:133-135

(2) Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, Ultra-rapid-Metabolism Genotype and Postoperative Death. NEJM (2009); 361:827-828

(3) Madadi P, Ross CJD, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G. Pharmacogenetics of neonatal opioid toxicity following Maternal Use of Codeine During Breastfeeding: A Case-Control Study. Clinical Pharmacology and Therapeutics (2009); 85:31-35

(4) MacDonald N, MacLeod SM. Has the time come to phase out codeine? Can Med Assoc J. (2010); 182:1825

(5) Frei MY, Neilson S, Dobbin MD, Tobin CL. Serious morbidity associated with misuse of over the counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust (2010); 193:294-6

(6) The Oxford Pain Research Group. The Oxford League Table of Analgesic Efficacy (2007). Accessed on 15/4/15 from http://www.medicine.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/lftab.html

I support the need for codeine combination analgesics being available only with prescription.

Working in a large [redacted] in the [redacted] I witness first-hand the damage these preparations are doing not only physically but emotionally to patients. The trends appear to be rising with patients presenting with dependence to codeine combinations and life threatening conditions. Common presentations are bleeding duodenal ulcers and/or perforated ulcers requiring emergency lifesaving surgery. Since my time working in Addiction Medicine I have had to alter my assessment questioning format; now including questions about OTC opioid preparations.

Patients appear to be unaware of the severe side effects of taking large quantities of these drugs, being focused more on the 'need' to satisfy their addiction, preventing withdrawal. Many patients describe the initially commencing of these drugs to manage a minor headache or toothache and the drug use escalated out of control, while being unaware of the risks associated.

It is not uncommon to expose the boxes of tablets patients are taking on a daily basis to maintain dependency levels to avoid withdrawal. Up to 80 tablets per day are sort by individuals to maintain function. This involves visiting multiple chemists both near and far to avoid suspicion of their drug use. The extensive process is described by patients in which they calculate chemists they have visited, and which are safe to purchase from on a daily basis.

Patients that present to [redacted] have often been following the method of 'chemist shopping' for years. This is having a huge impact on self-esteem and emergent guilt relating to ones secret addiction. The addiction/dependency eventually impacting the individual's ability to maintain employment, relationships and having severe health implications.

One patient I recall after lifesaving surgery to stop a bleeding ulcer cried with relief that something had finally happened to expose his dirty secret of addiction to Nurofen Plus. While he reported trying many times to reduce his consumption, the power of his addiction meant he never succeeded. I recollect him saying he had wished he was able to face the addiction and seek professional support but felt shame and very isolated being addicted to what he thought was a 'soft drug'. He was commenced on pharmacotherapy while in hospital and was pleased that each day now meant his medication was prescribed and ready, rather than remembering which chemists could be visited today without suspicion of being caught overusing such medications.

The impact to the individual is massive, both from physical dependency view point and emotionally crippling with the shame and daily struggle to meet ones needs. The families often feel the impact of this addiction once it is discovered, and at times have been part of the 'chemist shopping' ritual to avoid debilitating withdrawal symptoms for loved ones.

If codeine combinations were re-scheduled requiring prescriptions it may significantly reduce the harms associated with such medications. Patients would require medical consultation and assessment for the need for appropriate analgesia. RE-scheduling codeine preparations would reduce the access to these potent drugs and ensure patients are not self-medicating acute/chronic pain, and potentially masking serious symptoms of illness or disease.

3. Isn't it enough that the country is screaming because there isn't enough GPs and there is major talk about how to get more to meet demand?
4. Isn't it enough that every time a normal full-time working person is sick they have to wait days and weeks to get an appointment to get their GP to write a letter to a specialist that one knows they are going to be lucky to get to see in six to 12 months time; BUT, when you have this letter you then find the specialist is so full they aren't taking patients and you have to start the whole process again. WHY?

   WHY does the medical system strangle the whole process with delays, tight controls and payments to their professional colleagues, their GPS. Is this some medical pyramid selling scheme set up in Australia to keep the rich richer and the poor poorer; it seem like it to the normal full-time tax paying working folk.

AND NOW – because an extremely small section of the population abusing Codeine the majority of the population has yet to suffer again.

Stop this NONSENSE!.

This is the codeine that on occasions my family has a hacking cough during the night they cannot sleep that we buy to stop.
This is the codeine/Panadol mix that on rare occasions my family has an extremely sore muscle complaint and that the only thing that works and you want to stop.
Hence, you want to make my family wait through sleepless nights to get a GP's appointment WHICH ARE ALMOST NON EXISTENT when you need them, pay a small fortune for the appointment and then to get to the pharmacy to pay some government extortionist Government Price. WHY – because an extremely small section of the population has a problem with codeine. Why should the large proportion of the population be punished because of the silly few?

There will always be a small section of the population abusing something – stop this nonsense and do NOT put Codeine products on any listing. Leave us adults alone to make our own decisions when we need or don't need codeine.

Kind regards

[redacted]

From: [redacted]
Sent: Tuesday, 28 April 2015 11:15 AM
To: TGA Info
Subject: Contacting the TGA

Hello
I have heard that the TGA are considering a change in regulations to remove the availability of over-the-counter products containing codeine (panadeine etc) and making them only available by prescription. I urge you to re-consider this.

While, I acknowledge that there may be some over-use and self-abuse, for many people, ready access to a strong pain killer is essential.

For my self, I am a [redacted] old male who has suffered from tension headaches and migraines since a teenager. These occur without warning three to four time a year and with each episode lasting two to three days. They are extremely debilitating with the effects being severe nausea and sensitivity to lights and noise. Visits to my GP, numerous tests, brain scans, monitoring of "triggers", foods etc have failed to find a cause. Otherwise I am considered to be fit, active and healthy for my age. I am not taking any prescribed or complementary medicines.

An over-the-counter product containing codeine is the the only product that provides me with relief from this condition and it distresses me to think that I may now have to visit my doctor to seek a prescription. This is especially so, as you will be well aware that it is almost impossible to see a doctor on-demand, unless one takes ones chances at a walk-in doctors supermarket or queues at a hospital emergency department. The thought of having to wait three days to get an appointment to see my GP when I have a series of severe headaches, which I know can be eased, is distressing. I of course, know that if the condition doesn't ease within 24-48 then I should seek medical advice.

Yes, I agree that there may be some people who are addicted to codeine and some who may over-medicate leading to injury. But there also those who are responsible for their own actions.

In pure economic term, perhaps one should attempt to quantify the cost of addiction and self harm against the cost to the medical sector and the broader economy. I imagine that continuing to make these products available without prescription would win.

Restricting availability to packets of 20 or 24 may be a good compromise, along with reinforcing the need for pharmacists to assess the need for this medication. In my experience, they already do this.

Thank you

[redacted]

Albury Wodonga Health
Community MHDA Albury | NEBMHS
475 Townsend Street, Albury NSW 2640
Tel. (02) 6058 1750 | Fax. (02) 6058 1751

The Secretary, Advisory Committee on Medicines Scheduling.

07/05/2015

Dear Sir / Madam,

I write to support the rescheduling of Codeine Combination Analgesic Agents (CCAA), as **prescription only categorisation.**

My background is consultation liaison nursing in addiction medicine specialty settings across medical, drug & alcohol and psychiatric services over the last 14 years. I have worked in both metropolitan acute and community based settings.

My opposition to the current scheduling is based on clinical experience and the development of a case studies series published in 2010.The purpose of this modest work were to inform and educate the serious medical consequences for persons dependent on Nurofen plus, the most common analgesic abused. Our findings are in line with bigger and more detailed reports such as turning points research on pharmacy acquired codeine combination analgesic medications. I will not repeat the abstract, as it is attached to this submission.

We have had many near fatal outcomes associated with these agents. We have also lost a 27 year old female who died as the direct result of [redacted] dependence, who relapsed after abstinence assisted by opioid pharmacotherapy. The relative ease of acquiring 60-70 tablets per day still disturbs me to this very day. This young lady consumed no other substances (licit or illicit) and this is a common theme in the codeine dependent. People can, and are, acquiring these drugs with relative ease, even in a regional setting.

The other point I wish to be considered, is that there is significant evidence that will be submitted by other concerned contributors, **that these drugs efficacy vs safety to the individual are highly questionable.** They are not strong enough for acute severe pain yet, have poor effect for moderate pain and again, the risk vs gain aspects are a worry.

I appreciate the pharmaceutical companies will oppose this, but respectfully suggest a combination NSAID /paracetamol agent may be more helpful than CCAA. If a patient is suffering moderate severe acute pain there are many more effective and safe option for doctors to consider.

[redacted]

Over The Counter and into the Grave: Morbidity and mortality related to NSAIDs & codeine dependence

Lisa Ferguson, Robert Batey, Charles Clarke, Gail Legg, Alan Fisher
Greater Southern Area Health Service (GSAHS) Albury, Wagga, Goulburn and Batemans Bay Hospitals, New South Wales (NSW), Australia.

Background & Aim

Misuse of Over-The-Counter (OTC) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) containing codeine has been associated with serious medical consequences including nephrotoxicity, hypokalemia[1], gastric perforation and haemorrhage.[2]

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Aim: To present a case series highlighting complications from misuse of these drugs.

Method

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A total of 5 cases were identified. Three patients are presented in more detail as they were more complex and in one case fatal.

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A 27 year old female with past history of sexual abuse and unplanned pregnancy commenced NSAIDs (Nurofen Plus) to relieve right sided abdominal pain following a termination. Use escalated to over 50 tablets per day. She presented with anaemia Hb 79, confusion, malnutrition, Alb 16 and BMI of 16. She had a history of admissions for blood and iron transfusions, with previous gastroscopy revealing a duodenal ulcer. The patient had been treated, after each of these admissions with pharmacotherapy for codeine dependence, and had been well and abstinent from NSAIDs for 8 months. About one month prior to the last admission she lapsed into Nurofen Plus use of unknown quantities. The patient underwent a laparotomy. However she suffered hypoxic brain injury from cardiac arrest due to lactic acidosis, sepsis, malnutrition and gastrointestinal bleeding. She died several days after the surgery.

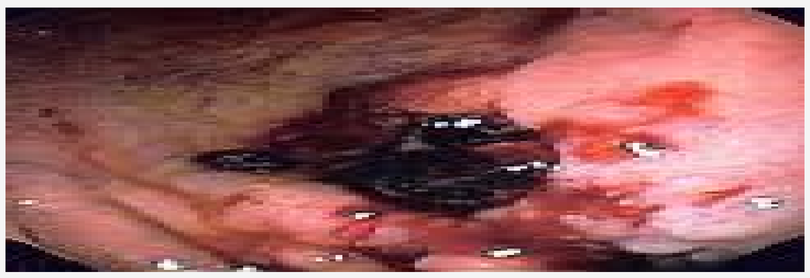

Figure 1. Bleeding gastric ulcer

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A 31 year old female presenting with severe muscle weakness, taking >50 Nurofen Plus per day, stating neck pain as the indication. She had been dependent for several months. The patient had a history of sexual assault and had been diagnosed with depression and anxiety. She was treated in ICU and biochemistry included: serum potassium of 2.0 mmol/l (3.5-5.2), bicarbonate 14 mmol/l (24-30), creatinine 140 mmol/l (60-100), anion gap 21 mmol/l (7-17). A diagnosis of hypokalemia with renal tubular acidosis was made. The patient was treated and discharged on buprenorphine.

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- previous trauma
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Relapse, even for a brief duration, caused dramatic gastric damage in two cases.

References

1,2 Severe hypokalemia and weakness due to Nurofen plus misuse; Chetty et al; Annals of Clinical Biochemistry, July 2003, p422.

3 Over The Counter Codeine Dependence-Turning Point Report S Nielson et al., June 2010.

From: [redacted]
Sent: Wednesday, 29 April 2015 12:49 PM
To: OTC Medicines
Subject: Frightened. A miniscule minority will destroy my quality of life.

Dear Sir/Madam,
I am deeply distressed that my excellent management of my pain issues is to be destroyed by the usual tiny minority who these days run the show and hold us all to ransom. I am an ex nurse and I know that people like this will ALWAYS find something to abuse. Take one away and they will replace it with another, often much more dangerous. So you wont be preventing that tiny number from overdoing things. Usually it will involve more alcohol and its extremely dangerous. But you can get it on every 2nd street corner with no questions asked. [redacted] as it is a pain reliever. I can have a bottle of gin every day if I want and I haven't had any alcohol for 26 years. But I will if I have too and its a million times worse for the body than properly used painkillers. I have a perfect liver after 35 years of pain killer use. Nurses get damaged backs and joints from the job constantly.

It just isn't fair that the majority continually must suffer for these appalling idiots and it wont change it ANYHOW. Those people will just move to other stuff most likely alcohol which is what causes a great number of the crap in our ER's every day. Its a joke that this could happen. I am so sick of it and so distressed. ITS NOT FAIR that we are terrorised by a minute number of fools. You will be causing so many more problems. The black market will be just one of them, considering millions of Australians use and need these drugs to maintain life quality and be useful.

But I smell a big rat and will be writing several letters to the health minister. Because there is ONE GROUP WHO STANDS TO BENEFIT FROM THIS GREATLY. That's the doctors. It will put huge excessive costs on the government as we all line up to make fortnightly visits to the doctor's to get scripts. It will be an enormous cost. I am so upset, I am going to start doing that RIGHT NOW. Then the price of the meds will be higher and the government will cop that too and how ironical is THAT considering what they have been saying about having just [redacted] on scripts. But the doctors will make a lot of money and considering how they have been getting a lot of pressure over price of consultations and reducing the times their patients go visit them, plus the pressure to greatly reduce the tests done unless there is a direct need I am not surprised at this because it will greatly boost their incomes. I know doctors, I have worked long time with them. They will say other stuff to cover it but no, believe me they are ALL worrying about maintaining their incomes. I remember last time this idiotic nonsense blew up the TGA tended to think it was the Pharmacists who had other 'motives' but NO it isn't the Pharmacists, they don't need it. It's the doctors as they know the pressure will be on them soon to reduce their income from medicare sources and are preparing.

You see the countries who have the most serious issues with pain killers are the ones where they can only be got by scripts. America is drenched in it. Because its true, the doctors will start giving stronger ones but people have to keep going to the doctors to get them and that's the reason they are on script in America because it gives the doctors a lot of income. More than half of Americans use them. Its well known and very common.

I will be informing the government of the huge cost they will be expected to cover. In other cases, people will lose their quality of life if they just give up and will give up work if they are doing it because of constant chronic pain issues. Unless you have lived with constant pain you have NO idea of what it does and without relief that you don't need to jump through firey hoops or swear away your house for it will destroy your life. Many people will resort to alcohol as its a pain reliever of sorts. This will in due course make shocking health issues as it rots your insides. Its FAR MORE DANGEROUS THAN A PAINKILLER. Besides the potential violent and anti social behaviour it will kill you. The chemical in painkillers that's the problem ISNT THE CODIENE. Its the paracetamol, or ibruprofen. The man made chemicals and they can be bought in supermarkets.

People will combine the alcohol with the toxic paracetamol from the supermarket and severely harm themselves, just trying to get a bit stronger pain relief with out having to swear on the bible and feel like a criminal. I am so sick of it, its so depressing. You cant do anything. The 'nanny state' is right out of control and its almost not worth living. I mean it. I think it might be better just to end it all and get away from the nightmare of today's world. These painkillers have been around for 80 years in this country and there's been v little trouble. When I used to be in the ER, it wasn't painkillers that caused the probs in it, that would be less then one a week, sometimes much less, IT WAS ALCOHOL. Which will get much worse now. I will drinking it too. I can get a bottle a day easy.

We are surrounded by thought police, appalling people on the lookout for slips of the tongue, you cant even say the Irish like to have a few Guinness on St Pat's day without a charge of 'casual racism'. Is this a world we want??? Is this a world I want to live in????NO. I don't. It's awful. It's horrible. A nightmare. A young friend of mine was crying over the 'nanny state' crap the other day. We are all treated like we are 5 years old. So the options are, look at what the black market situation will be, (if it is like America there will be a big black market for these things), start drinking spirits again, and start today getting scripts from the doctor and go every fortnight so the government has to pay for the visit and the scripts because a very small number of people do the usual and will just have moved on to something else any way. So you wont be helping those tiny number of idiots at all and just making the enormous number of people who are responsible lives a misery. Not worth living really is it???? I think that will be my solution. I cant stand it anymore, just waiting for the next oppression. Thankyou, [redacted]

[redacted]

01 May 2015

Therapeutic Goods Administration
Sent via Email to medicines.scheduling@tga.gov.au

Consultation Submission on Proposed Amendments to the Poisons Standard (Medicines)

I call for protection of my right as a consumer to obtain Codeine-containing medications quickly, conveniently and relatively cheaply at normal retail outlets.

I am aware through news media that [redacted] plans to submit that Codeine-containing products be reclassified to become prescription-only. They cite organ damage 'and even death' by those who take 'well over the recommended dose' and become addicted to Codeine.

I am not certain of the extent to which decisions by the Therapeutic Goods Administration will control or influence New Zealand regulations, but since New Zealand anaesthetists are lobbying for restriction of Codeine I offer my submission also. While I have sympathy for the distress experienced by medical practitioners faced with concentrated exposure to suffering addicts, the anaesthetists' view may not reflect accurately the overall picture including the vast majority of safe, responsible consumers.

As a migraine sufferer who uses Codeine-containing painkillers from time to time, I oppose making such medications prescription-only. Although I have other management options that can be sufficient on some occasions, they require me to have on hand a supply of prescribed medication. There are times when adding Codeine is the minimum medicine capable of managing my migraine, and there are also times when being able to buy Codeine-containing compounds locally is the only way that I can get medicine into my system quickly in order to contain a developing migraine. Forcing me to endure the additional time and expense of having to obtain a prescription from a medical practitioner would be unfair, and would also often lead to a more severe migraine that can become very difficult to contain. Prior to developing my early response management of migraines, there were times when stronger injected opiates at a medical centre were the only effective intervention. When my migraine starts (on average about monthly), the ability to conveniently and quickly obtain Codeine-containing painkillers has often been a saviour, stopping the migraine from developing into a much more serious acute condition that can prevent me from working and otherwise functioning for several days.

The fact that a small proportion of consumers ignore recommended dosages and cause themselves health problems should not reduce the right of the vast majority of responsible consumers to be able to obtain the medicine conveniently and relatively cheaply. Restriction of Codeine in order to protect irresponsible users from the consequences of their own choices will expose a much greater number of responsible consumers to unnecessary prolonging and exacerbation of pain-related conditions and risks associated with that, such as loss of income, relationship damage and even suicide. Restriction of the rights of the responsible majority because of irresponsible behaviour by a small minority is a slippery slope that deserves to be avoided whenever possible.

Restricting Codeine will not be effective in protecting the irresponsible minority anyway, because those who abuse medications and/or ignore warnings and recommendations will simply apply the same behaviour to other substances. They are mainly people with addiction problems that will require intervention regardless of the particular medicine associated with their presentation at any one time.

Protecting the responsible majority's ability to obtain quick and convenient help from Codeine medications is, I contend, a paramount good. Other ways can be built upon to discourage others from misusing these medicines, such as increased education, warnings by chemists, detection of abusive patterns of purchase, and mental health intervention to overcome self-destructive addictive behaviour patterns.

As a currently practising retail pharmacist, I fully support any proposal to reschedule all codeine containing products to schedule 4. This especially includes combination analgesics, which are creating a great deal of problems and issues in the community pharmacy sector. Please let pharmacists focus on pharmaceutical care, that is, dispensing and counselling patients on their true over the counter issues and prescription medication, as this is what pharmacy is meant to be about. Why should we have to waste our precious time and resources dealing with drug seeking customers who could have already purchased multiple packets of codeine containing combination analgesics within recent days, or even on the same day (which often occurs). We are subjected to uncalled for abuse on a regular basis, even though we are actually looking out for the health and safety of customers. With no legal way of knowing about prior codeine purchases from other pharmacies, pharmacists are put in a very difficult position on numerous occasions each day, with suspicious customers entering the pharmacy with their preconceived pain stories already scripted within their own mind and answering our questions perfectly to make sure their sale goes ahead.

I believe that codeine dependence is a much more widespread problem in the community than anyone thinks. Customers repeatedly ignore requests from pharmacists to see their doctor about their 'pain' and often move to the next pharmacy for the next few months until that pharmacist then grows suspicious. Customers continually treat themselves inappropriately with codeine based products despite any advice given by the pharmaceutical industry as a whole. Therefore, I believe that the only answer is to reschedule all codeine containing products to prescription only.

Yours Sincerely,

[redacted]

I have only a question to ask of the TGA and, that is, are the deaths due to overdose with the concomitant paracetamol? If yes, then this is the issue to be addressed, is it not?

RE: Rescheduling of codeine from S3 to S4

As a Community Pharmacist practicing in a rural area, I oppose the rescheduling of codeine products from S3 to S4.

I agree that there is a big problem with misuse of codeine in the community and big changes need to happen, however I don't feel rescheduling is the answer.

Firstly, rescheduling will mean that patients will need to see a doctor for any supply of a mixed codeine/analgesic medication. This is not always possible in rural areas. Sometimes patients face a 3-4 week wait to see a doctor in our local area. There are no walk in clinics available in this area. This is contradictory to all the best principles of acute pain management. Access to medication will be severely limited, particularly in rural areas.

Secondly, this will put further pressure on GPs and hospitals, who are already stretched to meet the demands of the community, not to mention the cost to the government of extra bulk billing appointments and added pressures on Emergency Departments.

This is a job that pharmacists can do- we just need the tools to enable us to identify the patients who are struggling with addiction verses those who are using these preparations correctly for acute pain management. I would fully support a real time monitoring system (such as Project Stop used to record pseudoephedrine sales) as a solution. I feel the benefits would be two-fold - allowing us to see a codeine sales history for our patients, we will be in a good position to identify those who need referral to their doctors for a pain management review but we will also be able to detect those that may be struggling with codeine addiction. This will allow those who are using the medication correctly to access adequate analgesia when required.

Submission on Proposed Amendments to the Poisons Standard (Medicines)

[redacted]

I am a medical practitioner with qualifications and experience in Addiction Medicine and General Practice, and hold Honorary/Adjunct Chairs in General Practice at the [redacted] I have 43 years clinical experience in Australia, New Zealand, UK and Canada, and have been an Advisor to the World Health Organisation.

For the past eight years I have produced Practical Examples About Real Life Situations (PEARLS), summaries of Cochrane Reviews for primary care practitioners, which are published on the Cochrane Collaboration New Zealand and Primary Care Field websites and in New Zealand Doctor.

I strongly support removing over-the-counter (OTC) codeine analgesics from Schedule 3 (Pharmacist supply) and rescheduling them to Schedule 4 (prescription only).

My clinical work involves supporting clients engaged with community teams, pharmacotherapy programs and inpatient withdrawal units. In all these settings I have dealt with the consequences of OTC codeine analgesics. Having worked in Australia and New Zealand over the past 15 years I have seen a steady increase on both sides of the Tasman in the number of people seeking help for OTC codeine dependence. With colleagues I have collated and published data from New Zealand and Australia, confirming the extent and severity of the physical, psychological and social problems related to codeine addiction and concomitant harms from non-steroidal inflammatory drugs and paracetamol (please see attached articles from the Medical Journal of Australia and the New Zealand Medical Journal). In addition to the 99 cases described in these publications, with the assistance of the Hobart ADS Community Team, I have collected a further 28 cases in southern Tasmania (publication in preparation). These clients consumed an average of more than 30 tablets a day for many years, and there was an extremely high prevalence of a history of mental health disorder and suffering of significant emotional trauma. A substantial proportion had experienced gastrointestinal problems including bleeding ulcers. [redacted]

These experiences from the clinical coal face reflect the hard reality of the significant levels of harm arising from the ready and widespread availability of OTC analgesics. I believe that this personal perspective adds real-world context to the compelling evidence from the growing international literature supporting OTC codeine rescheduling:

- Increasing numbers of individuals are seeking help for OTC codeine analgesic addiction[1,2]
- Effective treatments are available for those with opioid addiction[3-5]
- Cochrane Collaboration Systematic Reviews conclude that adding codeine to non-opioid analgesics such as ibuprofen and paracetamol provides little analgesic benefit[6 -8]
- New OTC products such as Maxigesic and Nuromol are readily available for self-treatment of acute pain; these provide better analgesia than OTC codeine products without the risks of addiction[9]
- Despite rescheduling of OTC codeine analgesics from Schedule 2 to Schedule 3 in 2010, these products are still readily available, and pharmacists continue to face challenges in dealing with drug seekers[10-16]
- Patients report seldom or never being refused supply by a pharmacist, and if they do, are able to sustain this high dose addiction over years by identifying pharmacies who will supply[11]

I would strongly urge the Advisory Committee to remove OTC codeine analgesics from Schedule 3 and reschedule them to Schedule 4.

[redacted]

FAChAM, FRCP, FRACGP, FRNZCGP, FRCGP, MD, BSc

References

1. 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.
2. Nielsen S, Roxburgh A, Bruno R et al. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002-2011. (Drug Alcohol Depend 2015), http://dx.doi.org/10.1016/j.drugalcdep.2015.02.004
3. Australian Institute of Health and Welfare 2014. National opioid pharmacotherapy statistics 2013. Drug treatment series no. 23. Cat. no. HSE 147. Canberra: AIHW. Table A9.

4. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy. Cochrane Database Syst. Rev. 2009;7:CD002209.pub2.
5. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev. 2014;2:CD002207.pub4.
6. 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.pub2.
7. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol for acute postoperative pain. Cochrane Database Syst. Rev. 2013;6:CD010210.pub2.
8. Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. Cochrane Database Syst. Rev. 2015;2:CD010107.pub3.
9. 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.
10. Haggan M. Pharmacists worried by OTC codeine. Aust J Pharmacy 16 March 2015. http://ajp.com.au/news/pharmacists-worried-by-otc-codeine/
11. 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
12. 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 2014;10:669-678.
13. Cooper R. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. Health Soc Care Community 2013;21:254-62.
14. Ferner R, Beard K. Over the counter medicines: proceed with caution, BMJ 2008;336:694-696.
15. 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
16. Duffy C. Codeine abuse leads to calls for painkiller rethink. ABC 7.30. 6 Nov 2012. http://www.abc.net.au/news/2012-11-06/codeine-abuse-leads-to-calls-for-painkiller-rethink/4356816

Dear Medicines Delegate

PUBLIC SUBMISSION: PROPOSED AMENDMENT TO UP-SCHEDULE CODEINE FROM S3 TO S4

I do not support the proposal to up-schedule all current S3 codeine preparations to S4.

I currently suffer from chronic pain which doctors and specialists have yet been able to identify the cause. S3 products containing paracetamol, codeine phosphate and doxylamine succinate work very well for me to alleviate the severe pain I experience when the condition flares up. Codeine/aspirin combined products work equally well. However, single active ingredient products such as paracetamol and aspirin do absolutely nothing for my pain.

Through these medications being available **on demand** at pharmacies, I have immediate access to them, and am able to sleep that night and go to work the next day. If I had to obtain these preparations on prescription (as per the proposal), I would have to wait at least two weeks to get to see my GP just for that script – this is because there is so much demand on their time from the local population. The same applies to my alternate GP. This would mean I would be suffering in extreme pain for the whole waiting period, unable to sleep properly and no doubt would have to take sick leave as I would be unable to function effectively at work while in pain and lacking sleep.

The consequences for me (and many other Australians) having to go to a GP for a prescription for a codeine preparation would be:

- protracted and very distressing period of suffering until I could get in to see a GP;
- an increased financial burden;
- inflated cost of codeine preparations by pharmacies just because it is supplied on prescription;
- taking up critical medical appoints at a surgery which are needed by patients who are in much greater need to see a GP when I know how to alleviate my severe pain;
- taking off at least 2-3 hours from work for each medical appointment; and
- alternatively, having to attending an emergency department.

I would like to request that you consider the likely fact that the majority of the Australian population greatly benefit from S3 codeine preparations and uses them correctly; and that this strongly outweighs the very minute segment of our population that abuses these preparations. If you increase the restrictions on S3 codeine preparations, the addicts will only change to something or somewhere else to feed their addiction – it will not stop them from being addicts. Reduction of misuse of codeine preparations could be achieved through educational programs via pharmacies, media, schools etc. In my opinion, the benefits from codeine preparations remaining in S3, for the majority of the Australian population, strongly outweigh the risks.

Implementation of a monitoring and/or registration system at pharmacies/licenced outlets for sales of S3 codeine preparations would be a far more effective mechanism to restrict supplies to addicts while at the same time allowing the majority of the Australian population to have immediate access to these medications to alleviate their suffering. Addicts could receive further help by attending drug rehabilitation clinics as well as the Australian Government providing better funding to such clinics.

Thank you for considering my submission.

[redacted]

30.4.2015

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Tuesday 5th May 2015

Provided electronically to: medicines.scheduling@tga.gov.au

Proposed amendments to the Poisons Standard (Medicines)

To Whom It May Concern,

Firstly, we would like to thank the TGA for the invitation for public comment on the proposed amendments to the Poisons Standard (Medicines) – ACMS meeting, July 2015. AFT Pharmaceuticals agrees with the proposed amendment to the Poisons Standard (Medicines) "to delete the Schedule 3 entry for codeine and reschedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence".

Supporting Documentation

We would like to draw to the committee's attention the following key items:

(1) Results of Health Practitioner Research in Australia and New Zealand on codeine, conducted independent of AFT Pharmaceuticals., and
(2) A summary of articles recently published in the press outlining codeine abuse concerns in the community.
(3) Published efficacy data for codeine

Health Practitioner Research

AFT Pharmaceuticals Ltd commissioned Cannings Corporate Communications in Sydney to undertake an independent survey of pharmacists and General Practitioners (GPs) in Australia to characterize their views on the issue of codeine misuse/abuse.
Concurrently, AFT Pharmaceuticals contracted Dart Public Affairs, Wellington to conduct the same survey on New Zealand-based pharmacists and GPs.
To reduce bias, survey participants were identified via healthcare practitioner databases.

There were over 2500 respondents in total. The results showed that:

- ~70% of all respondents said they were either somewhat concerned, or very concerned, about the potential for adverse consequences resulting from the *ordinary* use of codeine-based analgesics.

- >98% of all respondents said they were either somewhat concerned, or very concerned, about the potential for adverse consequences resulting from the *misuse* of codeine-based analgesics.

- 92% of Australian pharmacists and 77% of Australia GPs either somewhat agreed, or strongly agreed, when asked whether they thought codeine combinations are used too often by consumers and patients in Australia.

- 74% and 57% of NZ pharmacists and GPs, respectively, either somewhat agreed, or strongly agreed, when asked whether the thought that codeine combinations are used too often by consumers and patients in New Zealand.

The details of the Australian survey were published as an advertorial in in the December 2014 Issue of Retail Pharmacy (pg 20-21) and the NZ survey results were publicized in NZdoctor.co.nz and Scoop.co.nz. The results of both surveys are appended to this letter [Attachments 1-4].

Clearly there a large number of Australian pharmacists and doctors that share the view that there are potential issues of morbidity, toxicity and dependence with normal use as well as misuse/abuse of codeine and codeine-based combination analgesics.

These views are also shared by NZ-based pharmacists and GPs, although to a somewhat lesser extent.

Concerns in the Public Arena

In addition, there is growing awareness in the public domain of the issue of misuse/abuse of codeine and codeine-containing combination analgesics and the dangers therein.

AFT Pharmaceuticals have followed the publication of codeine-related new articles in a number of different jurisdictions. A sample of recent publications are presented in the table below [Table 1].

Table 1: Recent news articles concerning codeine misuse/abuse

Title/Hyperlink	News Agency
Australia	
Doctors and Pharmacists call for tighter control on codeine due to rise in addiction	The Sydney Morning Herald, New South Wales
Codeine addicts abuse Pharmacists	The Age, Victoria
New Zealand	
A 100-a-day, over-the-counter addiction	stuff.co.nz
Code Red	stuff.co.nz
Canada	
Star Investigation: Canada's invisible codeine problem	theStar.com, Canada
Put all codeine under prescriptions	theStar.com, Canada
China	
China tightens codeine control over addiction concerns	ecns.cn

Furthermore a search of "codeine and misuse or abuse or addiction" on Google.co.nz under News (22 April 2015), yielded a large number of results in other jurisdictions such as the US and the UK. These, and the articles in the table above, suggest there is a clear concern in the public domain regarding the potential for codeine misuse/abuse.

Codeine Efficacy

There is also the concern that the misuse/abuse of codeine may be augmented by its poor analgesic efficacy profile. Moore et al. (2011) provided an overview of 35 Cochrane Reviews of randomized trails which assessed the analgesic efficacy of 46 single dose oral analgesics for moderate postoperative pain in adults. The efficacy of each drug/dose combination was presented as the number needed to treat (NNT) for at least 50% maximum pain relief over 4 to 6 hours, and also the percentage of patients achieving at least 50% maximum pain relief, and the time to re-medication.

Across each of the aforementioned endpoints, codeine was the least effective oral analgesic. The outcomes are tabulated in the table below and compared with the common OTC analgesics paracetamol and ibuprofen. For all types of surgery, the NNT for at least a 50% maximum pain relief over 4 to 6 hours compared to placebo was highest for codeine 60 mg compared to 45 other oral analgesics including paracetamol and ibuprofen (NNT 3.6 and 2.5, respectively). The majority of drug/dose combinations had NNTs below 3.

Table 2: Efficacy of codeine 60 mg, paracetamol 975/1000 mg and ibuprofen 400 mg from Moore et al. 2011

NNT for at least 50% maximum pain relief over 4 to 6 hours compared with placebo		
	NNT	95% CI
Codeine 60 mg	12	8.4-18
Paracetamol 975/1000 mg	3.6	3.2-4.1
Ibuprofen 400 mg	2.5	2.4-2.6

Percentages of patients achieving 50% pain relief	
Codeine 60 mg	Less than 15%
Paracetamol 1000 mg	Less than 40%
Ibuprofen 400 mg	Less than 55%

Time to Re-medication	
Codeine 60 mg	Less than 3 hours
Paracetamol 1000 mg	Less than 4 hours
Ibuprofen 400 mg	Less than 6 hours

These data suggest that codeine is a poorly effective oral analgesic. The drug is less effective than 46 other oral analgesic drugs/dose combinations including paracetamol and ibuprofen and has a higher risk of at least one adverse event relative to placebo than paracetamol 975/1000 mg or ibuprofen 400 mg. The poor efficacy of codeine may promote its misuse by encouraging increased dosing to achieve the desired level of efficacy while increasing the probability of opioid effects.

Furthermore it should be noted that the amounts of codeine contained in S3 combination products in Australia are below the minimally effective doses published in the literature i.e. less than 60mg/dose. The codeine entry from the TGA Poisons Standard 2015 under Schedule 3 is as follows:

CODEINE when:

a) not combined with any other opiate substance;
b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:

    (1) in divided preparations containing *12 mg or less of codeine per dosage unit*; or
    (2) in undivided preparations containing 0.25 per cent or less of codeine;

c) labelled with a recommended daily dose *not exceeding 100 mg of codeine*; and

d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,

Except when included in Schedule 2.

In summary, there is public evidence of harm, there is concern amongst grass roots healthcare practitioners over both the correct use and abuse of codeine, and in addition the benefit in terms of analgesic efficacy is very limited.

Kind Regards,

AFT Pharmaceuticals Ltd.

References

Australian Press Articles

http://www.smh.com.au/nsw/doctors-and-pharmacists-call-for-tighter-controls-on-codeine-due-to-rise-in-addiction-20140913-10g0um.html
https://au.lifestyle.yahoo.com/marie-claire/news-and-views/latest/a/25918663/why-codeine-addiction-has-never-been-so-easy/

http://www.theage.com.au/victoria/codeine-addicts-abuse-pharmacists-20140424-zqyjx.html

New Zealand Press Articles

http://www.stuff.co.nz/stuff-nation/assignments/the-reality-of-dealing-with-addiction/10509686/I-was-taking-over-100-painkillers-at-a-time

http://www.stuff.co.nz/waikato-times/life-style/7747033/Code-Red

Chinese Press Article

http://www.ecns.cn/2014/12-17/146938.shtml

Canadian Press Articles

http://www.thestar.com/news/canada/2015/01/17/star-investigation-canadas-invisible-codeine-problem.html

http://www.thestar.com/opinion/letters_to_the_editors/2015/01/20/put-all-codeine-under-prescriptions.html

Press articles of AFT Survey contracted to Dart Public Affairs, Wellington, NZ

http://www.nzdoctor.co.nz/un-doctored/2015/march-2015/05/nz-pharmacists-concerned-about-codeine-based-analgesics.aspx

http://www.scoop.co.nz/stories/GE1503/S00019/nz-pharmacists-concerned-about-codeine-based-analgesics.htm

Retail Pharmacy Advertorial of AFT commissioned survey by Cannings Corporate Communications, Sydney, Australia

Advertorial. *Retail Pharmacy*, December 2014, page 20-21.

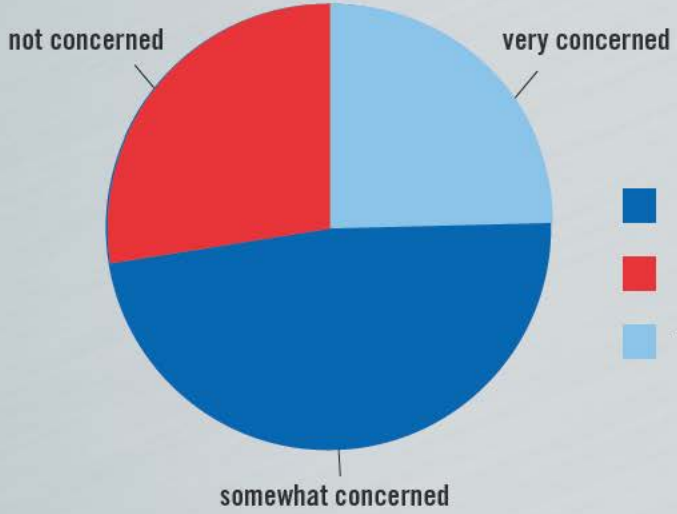
Australian Government, Department of Health, Therapeutic Goods Association: Poisons Standard 2015

http://www.comlaw.gov.au/Details/F2015L00128/Html/Text#_Toc408306129

Overview of Cochrane Systematic Reviews of single doses analgesic drugs/dose combinations for acute postoperative pain:

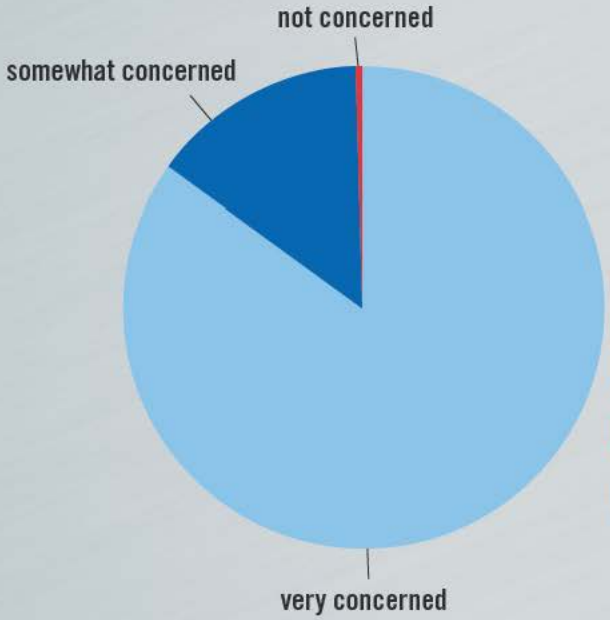
Moore, R. A., Derry, S., McQuay, H. J., & Wiffen, P. J. (2011). Single dose oral analgesics for acute postoperative pain in adults. In *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008659.pub2/abstract

Q2) To what extent are you concerned about the potential for adverse consequences resulting from the ordinary use of codeine-based analgesics (i.e. consumption within recommended guidelines)?



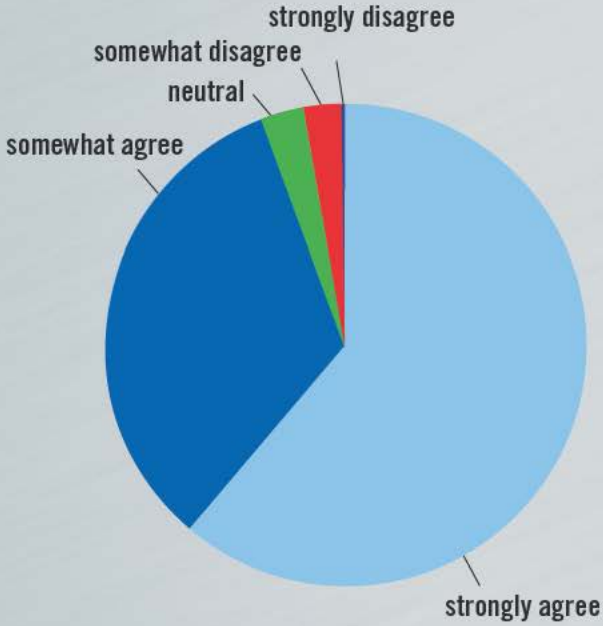
	Responses	
somewhat concerned	47.19%	478
not concerned	27.94%	283
very concerned	24.88%	252
	Total	1,013

Q3) To what extent are you concerned about the potential for adverse consequences resulting from the misuse of codeine-based analgesics (i.e. consumption in excess of recommended guidelines)?



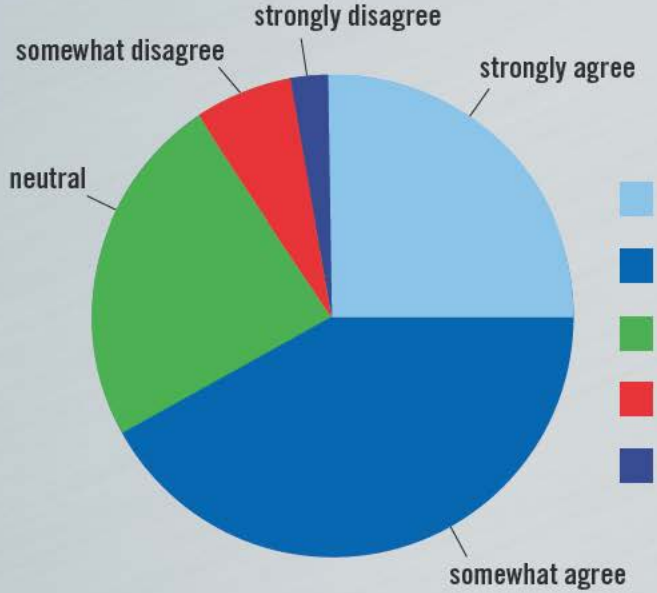
	Responses	
somewhat concerned	16.98%	172
not concerned	0.39%	4
very concerned	82.63%	837
	Total	1,013

Q4) Do you think that codeine combinations are used too often by consumers and patients in Australia?



	Responses	
strongly agree	61.87%	628
somewhat agree	29.85%	303
neutral	4.63%	47
somewhat disagree	3.35%	34
strongly disagree	0.30%	3
	Total	1,015

Q8) Do you think that paracetamol-ibuprofen combination products could be a suitable alternative to codeine-based combinations?



	Responses	
strongly agree	25.15%	254
somewhat agree	43.47%	439
neutral	17.23%	174
somewhat disagree	10.10%	102
strongly disagree	4.06%	41
Total		1,010

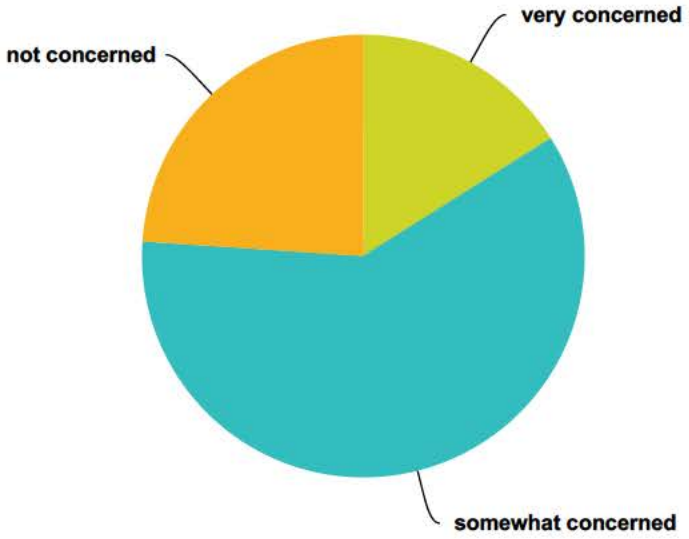
Q1 Address

Answered: 884 Skipped: 62

Answer Choices	Responses	
Name	**99.77%**	882
Company	**56.56%**	500
Address	**97.29%**	860
Address 2	**0.00%**	0
City/Town	**97.74%**	864
State/Province	**0.00%**	0
Z P/Postal Code	**94.46%**	835
Country	**0.00%**	0
Email Address	**70.48%**	623
Phone Number	**95.81%**	847

Q2 To what extent are you concerned about the potential for adverse consequences resulting from the ordinary use of codeine-based analgesics (i.e. consumption within recommended guidelines)?

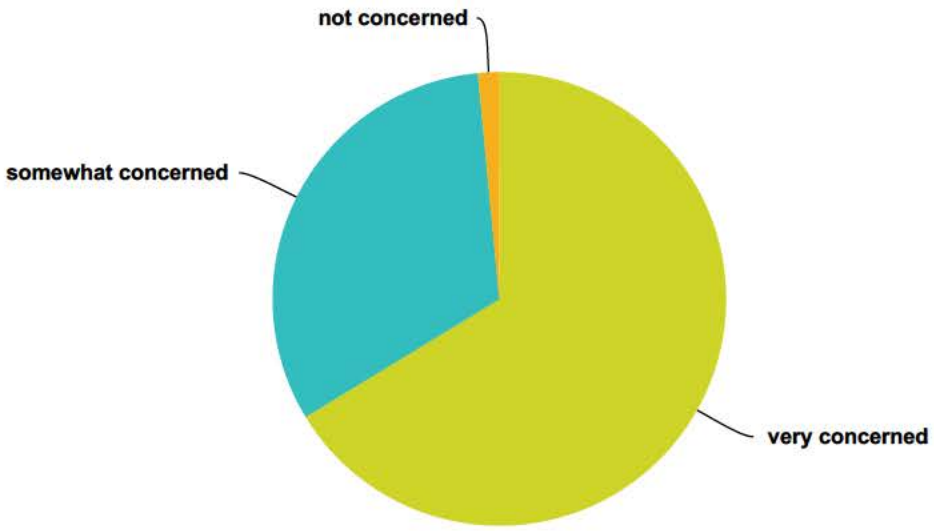
Answered: 927 Skipped: 19



Answer Choices	Responses	
very concerned	16.07%	149
somewhat concerned	59.98%	556
not concerned	23.95%	222
Total		927

Q3 To what extent are you concerned about the potential for adverse consequences resulting from the misuse of codeine-based analgesics (i.e. consumption in excess of recommended guidelines)?

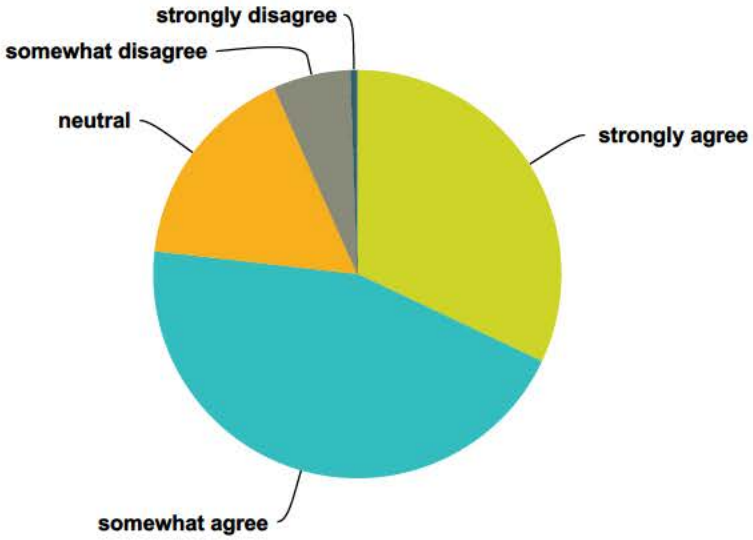
Answered: 929 Skipped: 17



Answer Choices	Responses	
very concerned	66.31%	616
somewhat concerned	32.19%	299
not concerned	1.51%	14
Total		929

Q4 Do you think that codeine combinations are used too often by consumers and patients in Australia?

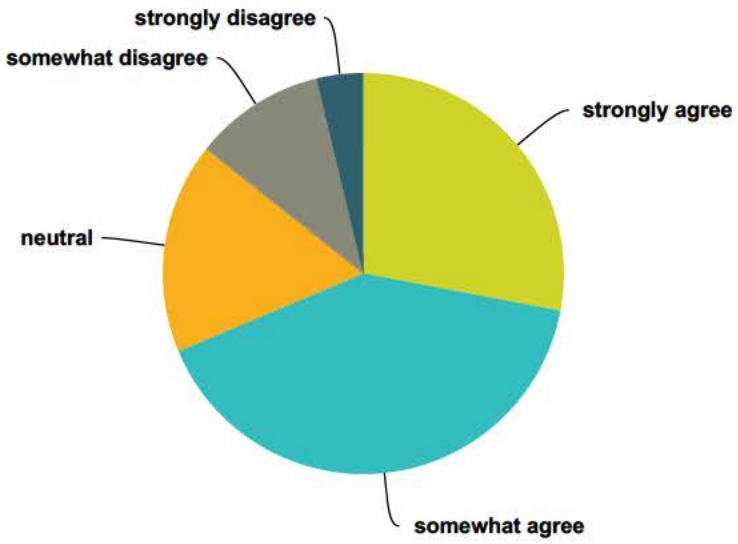
Answered: 927 Skipped: 19



Answer Choices	Responses	
strongly agree	32.04%	297
somewhat agree	44.77%	415
neutral	16.50%	153
somewhat disagree	6.15%	57
strongly disagree	0.54%	5
Total		927

Q5 Given the widespread use of codeine combination analgesics and concerns for misuse, do you think that further restrictions on availability should be instituted?

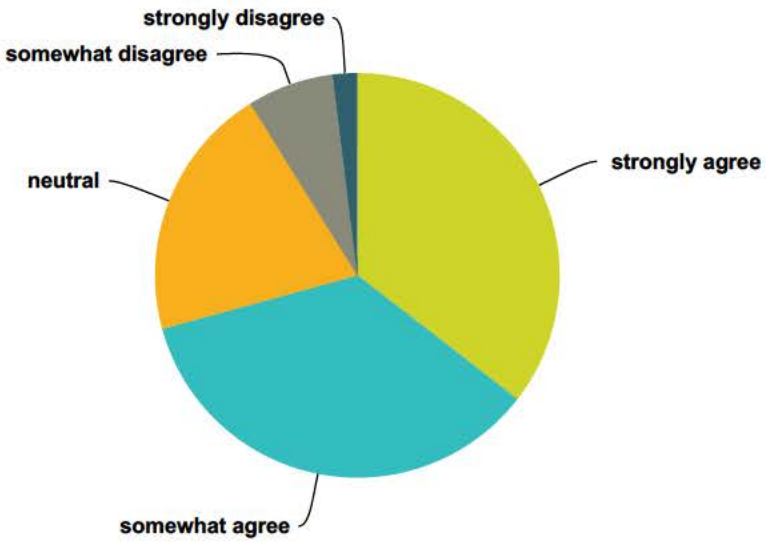
Answered: 929 Skipped: 17



Answer Choices	Responses	
strongly agree	27.99%	260
somewhat agree	40.69%	378
neutral	17.01%	158
somewhat disagree	10.55%	98
strongly disagree	3.77%	35
Total		929

Q6 Do you think that the Australian regulatory authority should be providing pharmacists with more accessible information about the potential risks associated with codeine-based analgesics?

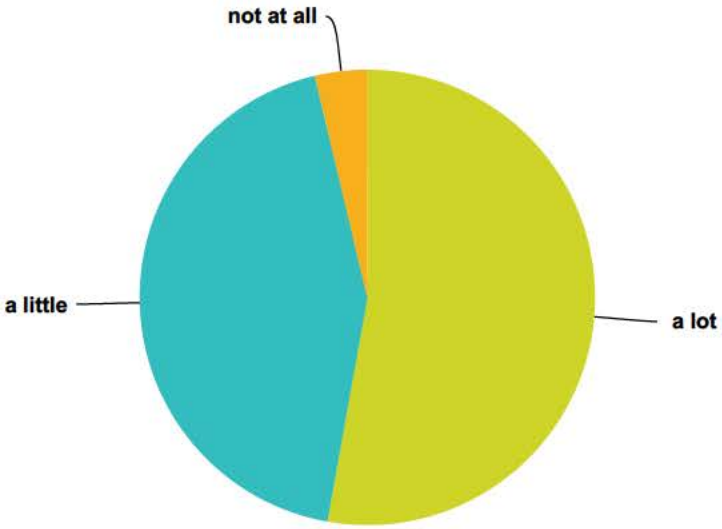
Answered: 868 Skipped: 78



Answer Choices	Responses	
strongly agree	35.48%	308
somewhat agree	35.25%	306
neutral	20.39%	177
somewhat disagree	6.91%	60
strongly disagree	1.96%	17
Total		868

Q7 To what extent would greater public awareness of the potential problems of codeine based analgesics influence their use?

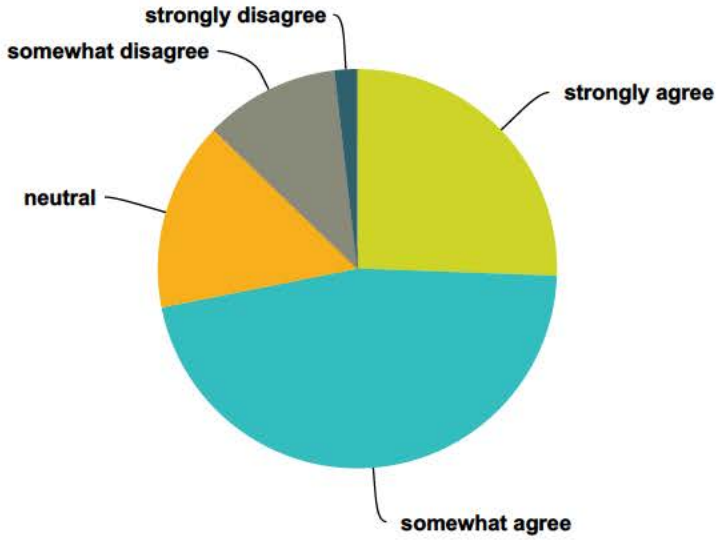
Answered: 867 Skipped: 79



Answer Choices	Responses	
a lot	52.83%	458
a little	43.48%	377
not at all	3.69%	32
Total		867

Q8 Do you think that paracetamol-ibuprofen combination products could be a suitable alternative to codeine-based combinations?

Answered: 868 Skipped: 78



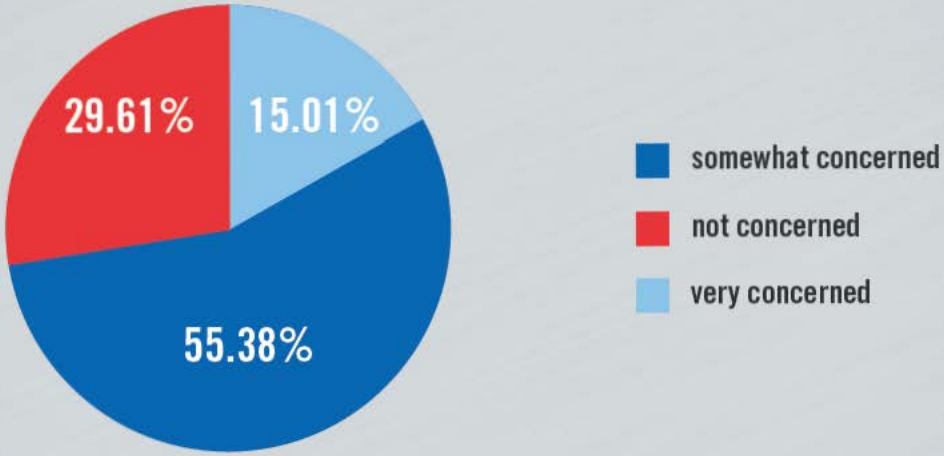
Answer Choices	Responses	
strongly agree	25.58%	222
somewhat agree	46.31%	402
neutral	15.32%	133
somewhat disagree	10.94%	95
strongly disagree	1.84%	16
Total		868

Q9 How surprised are you by the above-mentioned findings that paracetamol-ibuprofen combination products can be more effective at pain relief, and have fewer side-effects, than codeine-based analgesics?

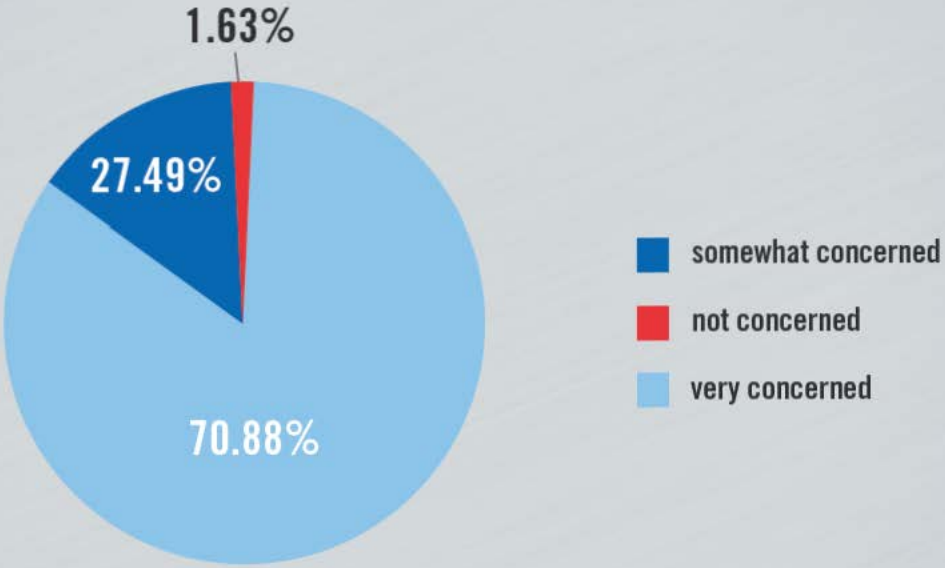
Answered: 870 Skipped: 76

Answer Choices	Responses	
very surprised	11.72%	102
somewhat surprised	35.40%	308
not surprised	52.87%	460
Total		870

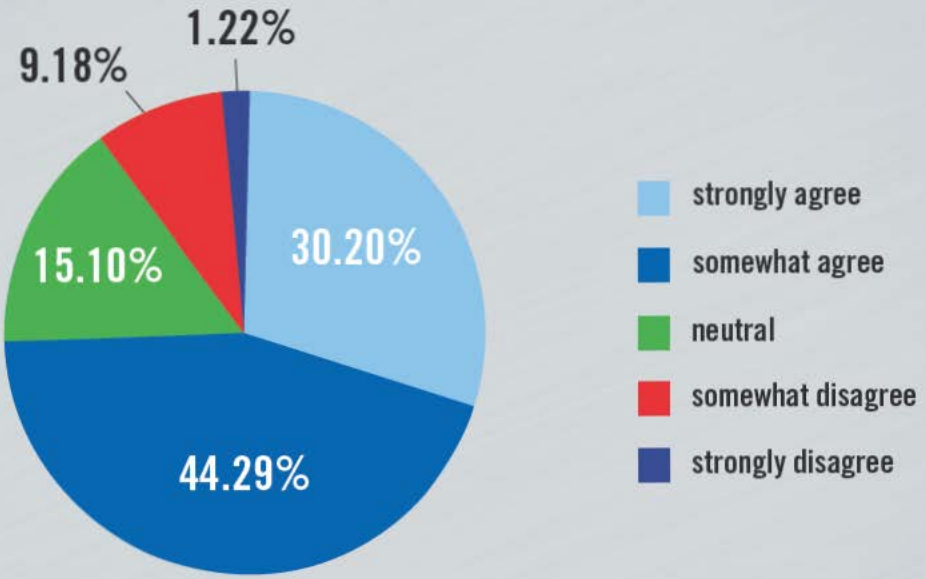
Q2 To what extent are you concerned about the potential for adverse consequences resulting from the ordinary use of codeine based analgesics (i.e. consumption within recommended guidelines)?



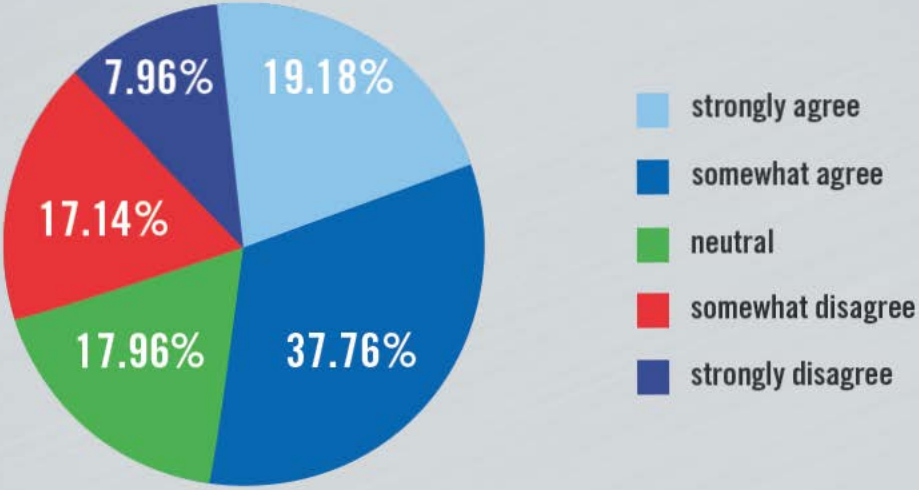
Q3 To what extent are you concerned about the potential for adverse consequences resulting from the misuse of codeine based analgesics (i.e. consumption in excess of recommended guidelines)?



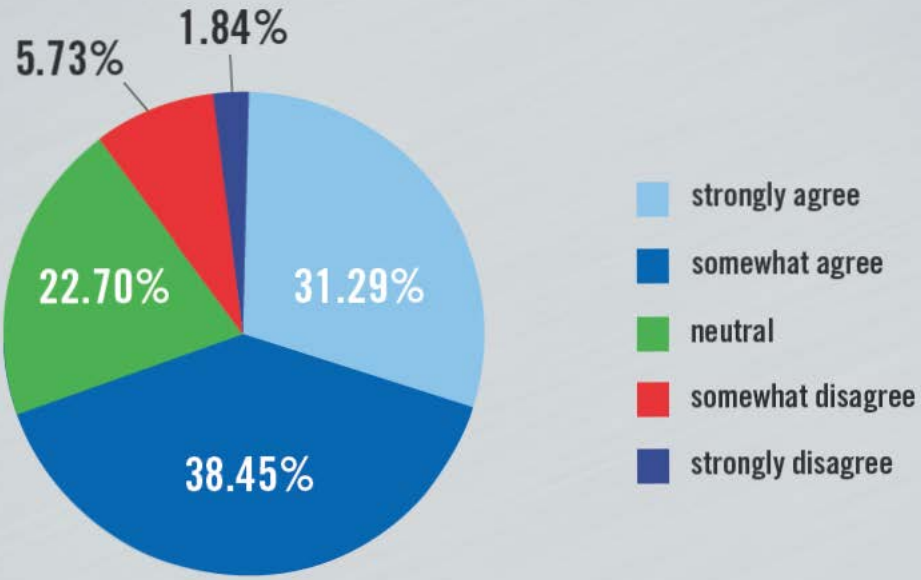
Q4 Do you think that codeine combinations are used too often by consumers and patients in New Zealand?



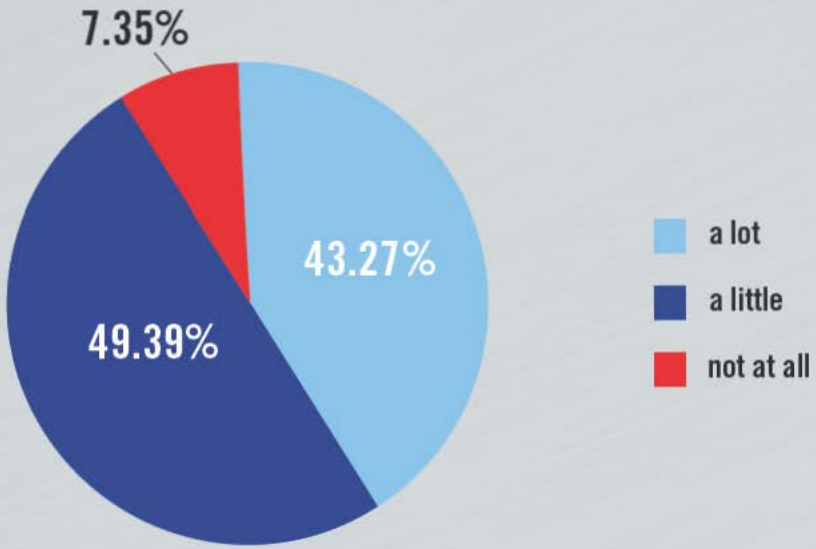
Q5 Given the widespread use of codeine combination analgesics and concerns for misuse, do you think that further restrictions on availability should be instituted?



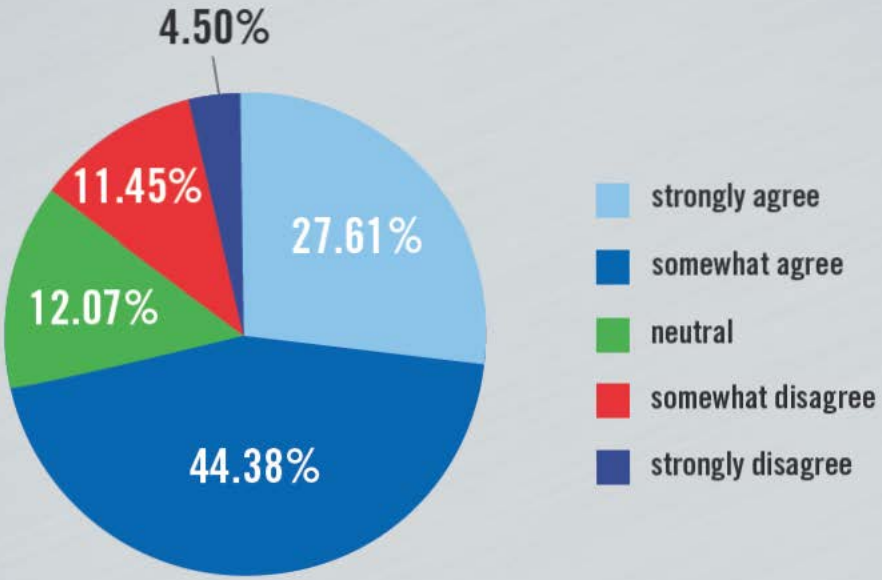
Q6 Do you think that the New Zealand regulatory authority should be providing pharmacists with more accessible information about the potential risks associated with codeine based analgesics?



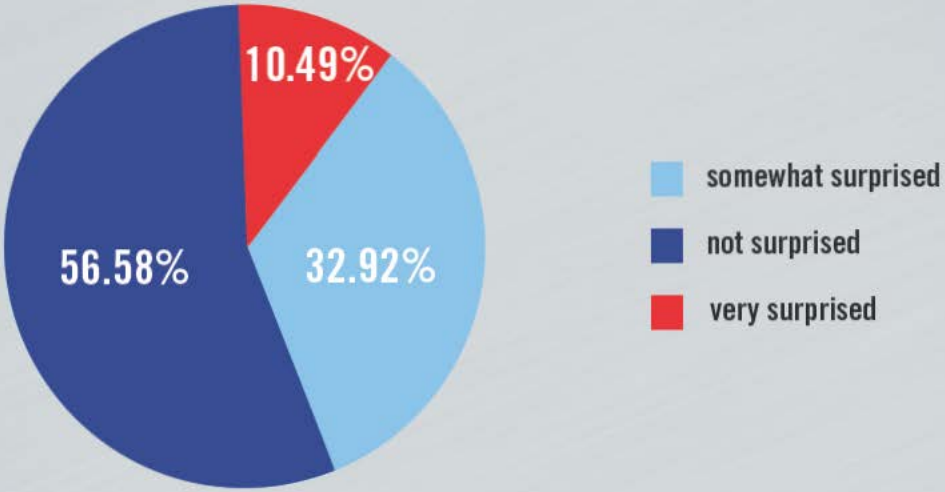
Q7 To what extent would greater public awareness of the potential problems of codeine based analgesics influence their use?



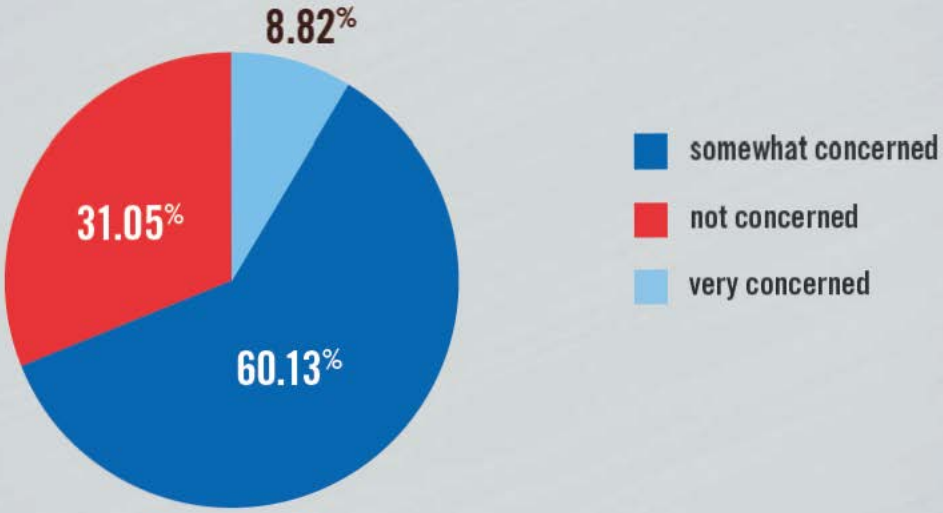
Q8 Do you think that paracetamol-ibuprofen combination products could be a suitable alternative to codeine based combinations?



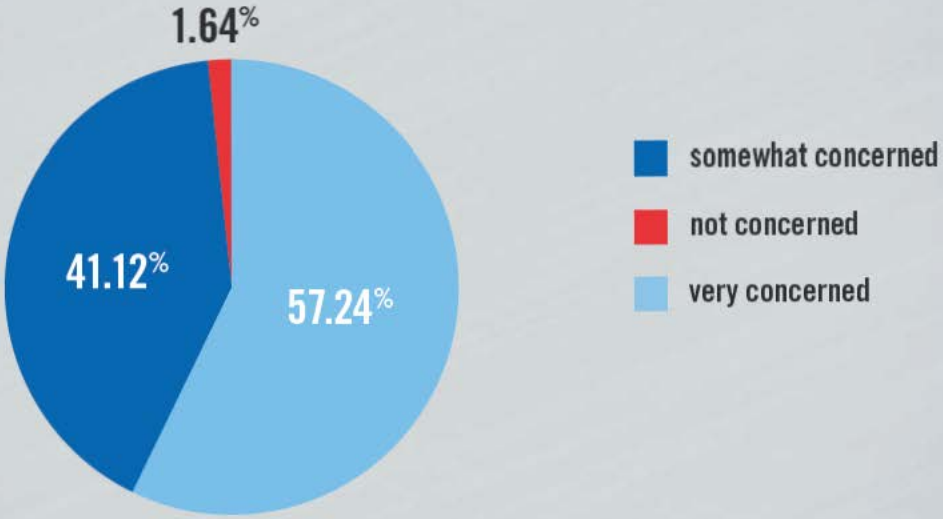
Q8 How surprised are you by the above-mentioned findings that paracetamol-ibuprofen combination products can be more effective at pain relief, and have fewer side-effects, than codeine based analgesics?



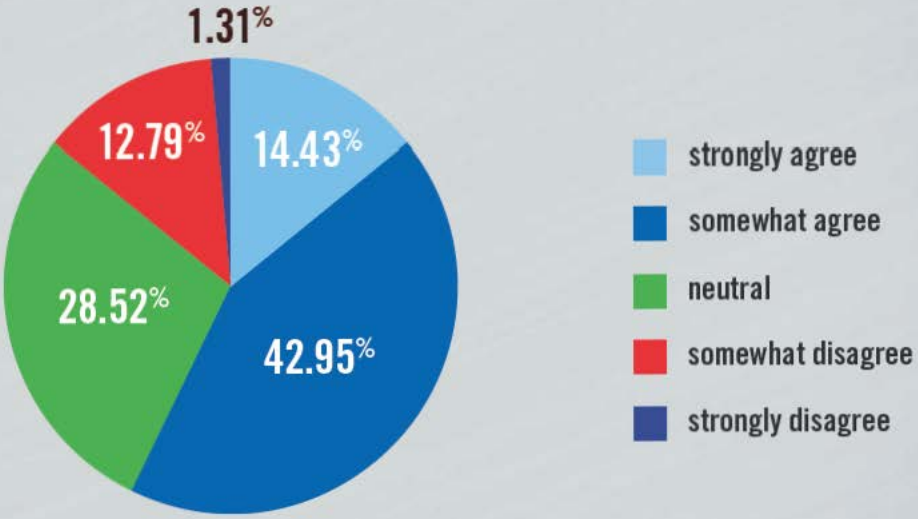
Q2 To what extent are you concerned about the potential for adverse consequences resulting from the ordinary use of codeine based analgesics (i.e. consumption within recommended guidelines)?



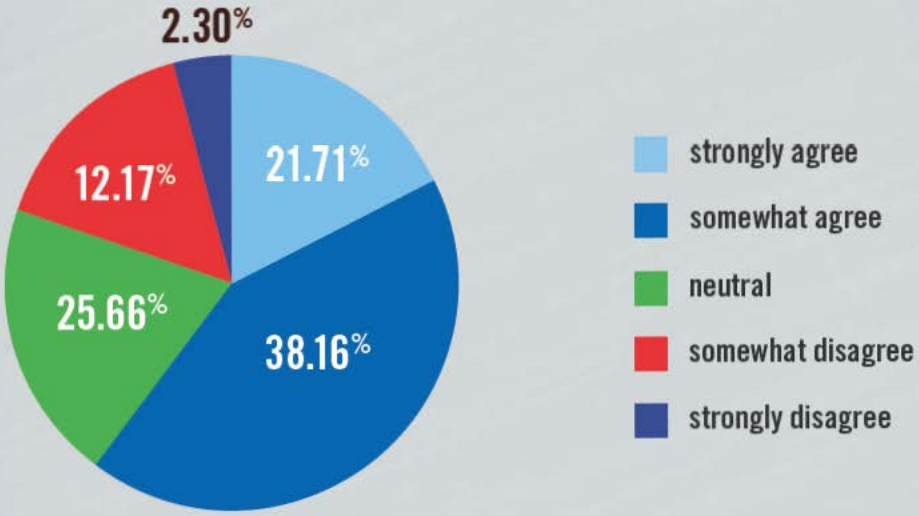
Q3 To what extent are you concerned about the potential for adverse consequences resulting from the misuse of codeine based analgesics (i.e. consumption in excess of recommended guidelines)?



Q4 Do you think that codeine combinations are used too often by consumers and patients in New Zealand?



Q6 Do you think that the New Zealand regulatory authority should be providing doctors with more accessible information about the potential risks associated with codeine based analgesics?



Single dose oral analgesics for acute postoperative pain in adults (Review)

Moore RA, Derry S, McQuay HJ, Wiffen PJ

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[Overview of Reviews]

Single dose oral analgesics for acute postoperative pain in adults

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ABSTRACT

Background

Thirty-five Cochrane Reviews of randomised trials testing the analgesic efficacy of individual drug interventions in acute postoperative pain have been published. This overview brings together the results of all those reviews and assesses the reliability of available data.

Objectives

To summarise data from all Cochrane Reviews that have assessed the effects of pharmaceutical interventions for acute pain in adults with at least moderate pain following surgery, who have been given a single dose of oral analgesic taken alone.

Methods

We identified systematic reviews in *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. For individual reviews we extracted the number needed to treat (NNT) for this outcome for each drug/dose combination, and also the percentage of participants achieving at least 50% maximum pain relief, the mean of mean or median time to remedication, the percentage of participants remedicating by 6, 8, 12, or 24 hours, and results for participants experiencing at least one adverse event.

Main results

The overview included 35 separate Cochrane Reviews with 38 analyses of single dose oral analgesics tested in acute postoperative pain models, with results from about 45,000 participants studied in approximately 350 individual studies. The individual reviews included only high-quality trials of standardised design and outcome reporting. The reviews used standardised methods and reporting for both efficacy and harm. Event rates with placebo were consistent in larger data sets. No statistical comparison was undertaken.

There were reviews but no trial data were available for acemetacin, meloxicam, nabumetone, nefopam, sulindac, tenoxicam, and tiaprofenic acid. Inadequate amounts of data were available for dexibuprofen, dextropropoxyphene 130 mg, diflunisal 125 mg, etoricoxib 60 mg, fenbufen, and indometacin. Where there was adequate information for drug/dose combinations (at least 200 participants, in at least two studies), we defined the addition of four comparisons of typical size (400 participants in total) with zero effect as making the result potentially subject to publication bias and therefore unreliable. Reliable results were obtained for 46 drug/dose combinations in all painful postsurgical conditions; 45 in dental pain and 14 in other painful conditions.

NNTs varied from about 1.5 to 20 for at least 50% maximum pain relief over four to six hours compared with placebo. The proportion of participants achieving this level of benefit varied from about 30% to over 70%, and the time to remedication varied from two hours (placebo) to over 20 hours in the same pain condition. Participants reporting at least one adverse event were few and generally no different between active drug and placebo, with a few exceptions, principally for aspirin and opioids.

Drug/dose combinations with good (low) NNTs were ibuprofen 400 mg (2.5; 95% confidence interval (CI) 2.4 to 2.6), diclofenac 50 mg (2.7; 95% CI 2.4 to 3.0), etoricoxib 120 mg (1.9; 95% CI 1.7 to 2.1), codeine 60 mg + paracetamol 1000 mg (2.2; 95% CI 1.8 to 2.9), celecoxib 400 mg (2.5; 95% CI 2.2 to 2.9), and naproxen 500/550 mg (2.7; 95% CI 2.3 to 3.3). Long duration of action (≥ 8 hours) was found for etoricoxib 120 mg, diflunisal 500 mg, oxycodone 10 mg + paracetamol 650 mg, naproxen 500/550 mg, and celecoxib 400 mg.

Not all participants had good pain relief and for many drug/dose combinations 50% or more did not achieve at last 50% maximum pain relief over four to six hours.

Authors' conclusions

There is a wealth of reliable evidence on the analgesic efficacy of single dose oral analgesics. There is also important information on drugs for which there are no data, inadequate data, or where results are unreliable due to susceptibility to publication bias. This should inform choices by professionals and consumers.

PLAIN LANGUAGE SUMMARY

Comparing single doses of oral analgesics for acute pain in adults postoperation

All analgesic drugs (painkillers) are tested in standardised clinical studies of people with established pain following surgery, and often after removal of third molar (wisdom) teeth. In all these studies the participants have to have at least moderate pain in order for there to be a sensitive measure of pain-relieving properties. *The Cochrane Library* has 35 reviews of oral analgesic interventions, with 38 different drugs, at various doses involving 45,000 participants in about 350 studies. This overview sought to bring all this information together, and to report the results for those drugs with reliable evidence about how well they work or any harm they may do in single oral doses.

For some drugs there were no published trials, for some inadequate amounts of information, and for some adequate information but with results that would have been overturned by just a few unpublished studies with no effect. None of these could be regarded as reliable. However, amongst the data there were still 46 drug/dose combinations with reliable evidence.

No drug produced high levels of pain relief in all participants. The range of results with single-dose analgesics in participants with moderate or severe acute pain was from 70% achieving good pain relief with the best drug to about 30% with the worst drug. The period over which pain was relieved also varied, from about two hours to about 20 hours. Typically adverse event rates were no higher with analgesic drugs than with placebo, except often with opioids (for example, codeine, oxycodone) where more participants experienced them.

Commonly used analgesic drugs at the recommended or licensed doses produce good pain relief in some, but not all, patients with pain. The reasons for this are varied, but patients in pain should not be surprised if drugs they are given do not work for them. Alternatives analgesic drugs or procedures should be found that do work.

BACKGROUND

Description of the condition

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical

component of patient care and is important for cost-effective use of healthcare resources. Good postoperative pain management helps to achieve a satisfied patient who is in hospital or at home and unable to carry out normal activities for a minimal amount of time.

Description of the interventions

Analgesics used for relief of postoperative pain include so called 'mild' or step 1 (WHO 2010) analgesics, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and celecoxib, 'moderate' or step 2 analgesics, which are weaker opioids such as codeine, and 'strong' or step 3 analgesics, which are strong opioids such as oxycodone and fentanyl.

Paracetamol has become one of the most used antipyretic and analgesic drugs worldwide, and is often also used in combination with other stronger analgesics. NSAIDs as a class are the most commonly prescribed analgesic medications worldwide and their efficacy for treating acute pain has been well demonstrated (Moore 2003). Opioids as a class have long been used to treat pain during and immediately after surgery, because they can be given parenterally, and because dose can be titrated to effect for immediate pain relief. Oral opioids are less often used alone, but are used in fixed-dose combination with drugs like paracetamol or ibuprofen (McQuay 1997).

This overview will consider only oral administration of analgesics. Parenteral administration by intravenous, intramuscular, or subcutaneous injections is useful for some drugs immediately following surgery, particularly for patients unable to swallow or where oral intake is not possible for other reasons (McQuay 1997). Most postoperative patients can swallow and oral administration is clearly the least technically demanding and cheapest method of drug delivery, especially when the benefits of injection over oral administration have not been demonstrated, as with NSAIDs (Tramer 1998).

Acute pain trials

Postoperative (after surgery) pain relief is part of a package of care that covers the preoperative (before surgery), perioperative (during surgery), and postoperative periods and involves using the best evidence at all times (Kehlet 1998). This overview involves only one aspect of one part of the patient journey, namely how well different oral drug interventions work to relieve pain. The choice of particular oral drug intervention depends on the clinical and operational circumstances and how any choice fits in with local care pathways. This overview only examined the efficacy of oral drugs: how to use them effectively in the relief of postoperative pain is a question not addressed here.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. To show that the analgesic is working, it is necessary to use placebo (McQuay 2005; McQuay 2006). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have acceptable pain relief. Approximately 18% of participants given placebo will have adequate pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. Therefore the use of additional or rescue analgesia is important for all participants in the trials.

Trials have to be randomised and double-blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following four to six hours for shorter-acting drugs, and up to 12 or 24 hours for longer-acting drugs. Half the maximum possible pain relief or better over the specified time period (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients 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. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Important characteristics of an analgesic include the proportion of patients who experience clinically useful levels of pain relief at a given dose, the duration of useful pain relief (which informs dosing intervals), and the drug's tolerability. Single dose studies can provide us with information on the number needed to treat (NNT) for at least 50% maximum pain relief over four to six hours compared with placebo and the proportions of participants achieving that outcome, the NNT to prevent (NNTp) use of rescue medication and the proportions needing rescue medication, the median (or mean) time to use of rescue medication, and the number needed to harm (NNH) for one or more adverse events, and the proportions experiencing adverse events. Additional information may also be available for the occurrence of serious adverse events and adverse event withdrawals, although the numbers of events captured in single dose trials are usually too few to allow statistical analysis.

How the intervention might work

Non-steroidal anti-inflammatory drugs

NSAIDs reversibly inhibit the enzyme cyclooxygenase (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 ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). Aspirin is a special case, in that it irreversibly blocks COX-1.

Paracetamol

Paracetamol lacks significant anti-inflammatory activity, implying a mode of action distinct from that of NSAIDs. Despite years of use and research, however, the mechanisms of action of paracetamol are not fully understood. Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but has recently been considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis' wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (Botting 2000; Chandrasekharan 2002; PIC 2008) now has little credibility and a central mode action of paracetamol is thought to be likely (Graham 2005).

Opioids

Opioids bind to specific receptors in the central nervous system (CNS), causing reduced pain perception and reaction to pain, and increased pain tolerance. In addition to these desirable analgesic effects, binding to receptors in the CNS may cause adverse events such as drowsiness and respiratory depression, and binding to receptors elsewhere in the body (primarily the gastrointestinal tract) commonly causes nausea, vomiting, and constipation. 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.

Why it is important to do this overview

Knowing the relative efficacy of different analgesic drugs at various doses, under standard conditions, can be helpful. Choice of drug for an individual patient will depend on relative efficacy and a number of other factors including availability, cost, tolerability, and individual considerations, such as the patient's history and contraindications to a particular medication, and their ability to remedicate orally. A large number of systematic reviews of individual oral analgesics versus placebo in acute postoperative pain have been completed, using identical methods. An overview is required to facilitate indirect comparisons between individual analgesics, providing estimates of relative efficacy which can help to inform treatment choices.

OBJECTIVES

To provide an overview of the relative analgesic efficacy of oral analgesics that have been compared with placebo in acute postoperative pain in adults, and to report on adverse events associated with single doses of these analgesics. This will be done using a number of different outcomes and ways of expressing results, which have been set by informed discussions with various groups of healthcare professionals, and using reviews newly published or updated Cochrane Reviews that incorporate these methods to give the best presentation of results.

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 ($\geq$ 15 years).

Search methods for identification of reviews

We searched the *Cochrane Database of Systematic Reviews* for relevant reviews. See Appendix 1 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 independently carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. Any disagreements were resolved 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 is an issue);
- pain model (dental, other surgical).

We sought relative risk (RR) and numbers needed to treat to benefit (NNT), to prevent an event (NNTp), and to harm (NNH) or calculated these for the following outcomes:

- $\geq$ 50% maximum pain relief over four to six hours (patient-reported): this outcome encapsulates both degree of pain relief and duration of the effect, and is a dichotomous measure of success over a defined period following drug ingestion;
- use of rescue medication (or mean or median if appropriate, for example for time to remedication);
- patients suffering one or more adverse events; and
- withdrawal due to an adverse event.

We also sought information on the proportions of individuals with the outcomes listed above, and median or mean time to use of rescue medication. We collected information concerning serious adverse events if present.

Assessment of methodological quality of included reviews

Quality of included reviews

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

Each review was required to:

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

For each review we assessed the likelihood of publication bias by calculating the number of participants in studies with zero effect (relative benefit of one) that would be needed to give a NNT too high to be clinically relevant (Moore 2008). In this case we considered a NNT of $\geq$ 10 for the outcome 'at least 50% maximum pain relief over four to six hours' to be the cut-off for clinical relevance. We used this method because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton 2000).

Quality of evidence in included reviews

All included reviews used only primary studies that were both randomised and double-blind, so minimising the risk of bias from these items. All used patients with at least moderate pain intensity at baseline, providing a sensitive assay of analgesic efficacy. All used standard methods and reported standard outcomes, or provided data from which they could be calculated using validated methods. For studies in acute pain lasting up to six hours, it has been shown that use of last observation carried forward rather than baseline observation carried forward does not significantly influence results (Moore 2005).

We assessed the strength of evidence for each outcome according to the total number of participants contributing data and the methodological quality of, and degree of clinical heterogeneity (pain condition mix) in, the primary studies, as reported in the reviews. We also considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNT for at least 50% maximum pain relief to an unacceptably high level (in this case the arbitrary NNT of 10) (Moore 2008). Where this number was less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable.

Data synthesis

We used information on the selected efficacy outcomesto 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). The trials used in these reviews have a high level of clinical and methodological homogeneity, having, for more than 50 years, used consistent validated methods of measuring pain in patients with established pain of at least moderate severity, over at least four to six hours, and with placebo as a common comparator. Some of these data have been used to demonstrate the superiority of indirect over direct comparison in circumstances where there are large amounts of indirect data and small amounts of direct data

(Song 2003). The one potential source of clinical heterogeneity is the case mix, namely dental versus other surgery, and while this has previously been shown to have minimal effect on some descriptors, like NNT, it can result in differences in other descriptors, like percentage of participants obtaining an outcome (Barden 2004). This is addressed by examining results for dental and other surgery separately and together, where there are sufficient data. Any differences between different analgesics for harmful outcomes are highlighted, but single dose studies are not designed to reliably demonstrate such differences.

Comparative results are expressed as:

1. patients achieving at least 50% maximum pain relief, as a percentage and as NNT, compared with placebo;
2. duration of analgesia, as mean or median duration, and percentage remedicating by various times after dosing; and
3. adverse events - given the nature of the studies, especially their short duration, the outcome most often reported was percentage reporting at least one adverse event.

RESULTS

The overview included 35 separate Cochrane Reviews investigating 38 analgesics or analgesic combinations given as single oral doses in acute postoperative pain conditions (Aceclofenac 2009; Acemetacin 2009; Aspirin 1999; Celecoxib 2008; Codeine 2010; Dexibuprofen 2009; Dextropropoxyphene ± Paracetamol 1999; Diclofenac 2009; Diflunisal 2010; Dihydrocodeine 2000; Dipyrone 2010; Etodolac 2009; Etoricoxib 2009; Fenbufen 2009; Fenoprofen 2011; Flurbiprofen 2009; Gabapentin 2010; Ibuprofen 2009; Indometacin 2004; Ketoprofen and Dexketoprofen 2009; Lornoxicam 2009; Lumiracoxib 2010; Mefenamic acid 2011; Meloxicam 2009; Nabumetone 2009; Naproxen 2009; Nefopam 2009; Oxycodone ± Paracetamol 2009; Paracetamol + Codeine 2009; Paracetamol 2008; Piroxicam 2000; Rofecoxib 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009). In total there were 448 studies, combining the number of studies in the individual reviews. However, many studies had both placebo and active comparators; ibuprofen, for example, was used as an active comparator in many of them. The number of unique studies was probably closer to 350.

All of the reviews used the same methodological approach and the same primary outcome of NNT for at least 50% maximum pain relief over four to six hours compared with placebo. The sum of the number of participants in the reviews was 50,456, but there will have been double-counting of placebo participants both within reviews (comparison of different drug doses separately against placebo) and between reviews (drugs like ibuprofen are commonly used as an active comparator for new test analgesics and placebo arms will be counted in reviews of both analgesics). In these circumstances the number of unique participants is more likely to be of the order of 45,000.

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 patient data (see Table 1). They all used the same criteria and typically these were as follows.

- Adult participants 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 patients using standard pain intensity and pain relief scales.
- Study duration of four hours or more.
- Searching included electronic searches, plus databases created by handsearching the older literature, now part of 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:

1. had *a priori* design;
2. performed duplicate study selection and data extraction;
3. had a comprehensive literature search;
4. used published and any unpublished studies included irrespective of language of publication, though not all reviews contacted companies or researchers for unpublished trial data;
5. provided a list of included and excluded studies;
6. provided characteristics of included studies;
7. assessed and documented the scientific quality of the included studies;
8. the scientific quality of the included studies was used 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));
9. used appropriate methods to combine findings of studies and importantly provided analyses according to drug dose; and
10. conflict of interest statements were universal.

The reviews all used validated methods for conversion of mean to dichotomous data (Moore 1996; Moore 1997b; Moore 1997c), 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), though 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

To assess the effects of interventions, we used a four-step process.

1. Note drugs for which no acute pain data could be found.
2. Note drug/dose combinations with inadequate amounts of information, where inadequate is defined as fewer than two studies and 200 participants - with limited flexibility around 200 participant limit).
3. Note drug/dose combinations with data but no evidence of effect, or with evidence of no effect.
4. Note drug/dose combinations with high susceptibility to publication bias, as defined in the Methods section.

Any remaining results would be of effective drug/dose combinations, backed by high-quality data not subject to bias, of sufficient size for random chance effects to be unimportant, and not susceptible to publication bias.

All extracted information on all reviews is available in Table 1.

1. Drugs for which Cochrane Reviews found no information

No clinical trial information was available for seven drugs (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009).

2. Drugs for which Cochrane Reviews found inadequate information (< 200 patients in comparisons, in at least two studies)

We found only limited information for six drugs, namely:

- Dexibuprofen 200 and 400 mg (176 participants with the two doses in one study) (Dexibuprofen 2009).
- Dextropropoxyphene 130 mg (50 participants in one study) (Dextropropoxyphene ± Paracetamol 1999).
- Diflunisal 125 mg (120 participants in two studies) (Diflunisal 2010).
- Etoricoxib 60 mg (124 participants in one study) (Etoricoxib 2009).
- Fenbufen 400 mg and 800 mg (46 participants with the two doses in one study) (Fenbufen 2009).
- Indometacin 50 mg (94 participants in one study) (Indometacin 2004).

3. Drugs for which Cochrane Reviews found no evidence of effect or evidence of no effect

There was evidence for lack of effect for three drug/dose combinations, with no difference between active drug and placebo:

- Aceclofenac 150 mg (217 participants in one study) (Aceclofenac 2009).
- Aspirin 500 mg (213 participants in two studies) (Aspirin 1999).
- Oxycodone 5 mg (317 participants in three studies) (Oxycodone ± Paracetamol 2009).

4. Drug/dose combinations for which Cochrane Reviews found evidence of effect, but where results were potentially subject to publication bias

Summary table A shows the drug/dose combinations in all types of surgery, and in dental and other postoperative pain situations separately, where our judgement was of high susceptibility to publication bias. These tended to have larger (less effective) NNTs, small numbers of participants, or both. The appropriateness or otherwise of this categorisation is discussed below, but these results are the least reliable of those available from the reviews. For gabapentin, the NNT was above 10, and based on a relatively small number of participants.

Summary table A: Results potentially subject to publication bias

		At least 50% maximum pain relief over 4 to 6 hours		
	Number of	Number with outcome/total	Percent with outcome	

(*Continued*)

Drug	Dose (mg)	Studies	Participants	Active	Placebo	Active	Placebo	Relative benefit (95% CI)	NNT (95% CI)	Susceptibility to publication bias
All types of surgery										
Codeine + paracetamol	30/300	6	690	123/379	56/311	32	18	1.9 (1.4 to 2.5)	6.9 (4.8 to 12)	310
Dextropropoxyphe	65	6	440	85/214	60/226	40	27	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)	131
Diflunisal	250	3	195	49/98	16/97	47	16	2.9 (1.8 to 4.6)	3.3 (2.3 to 5.5)	396
Dihydrocodeine	30	3	194	31/97	19/97	32	20	1.6 (1.01 to 2.5)	8.1 (4.1 to 540)	46
Etodolac	50	4	360	44/154	34/206	29	17	1.7(1.1 to 2.6)	8.3 (4.8 to 30)	74
Gabapentin	250	3	327	26/177	8/150	15	5	2.5 (1.2 to 5.0)	11 (6.4 to 35)	NNT over 10
Ibuprofen	50	3	316	50/159	16/157	31	10	3.2 (1.9 to 5.1)	4.7 (3.3 to 8.0)	356
Mefenamic acid	500	2	256	60/126	29/130	48	22	2.1 (1.5 to 3.1)	4.0 (2.7 to 7.1)	384
Naproxen	200/220	2	202	54/120	13/82	45	16	2.9 (1.6 to 5.1)	3.4 (2.4 to 5.8)	392
Oxycodone	15	3	228	61/113	37/115	54	32	1.7 (1.2 to 2.3)	4.6 (2.9 to 11)	268
Oxycodone + paracetamol	5/325	3	388	60/221	14/167	27	8	3.6 (2.1 to 6.3)	5.4 (3.9 to 8.8)	331
Dental pain only										
Etodolac	50	4	360	44/154	34/206	29	17	1.7 (1.1 to 2.6)	8.3 (4.8 to 30)	74

(*Continued*)

Flurbiprofen	25	2	145	24/70	5/75	34	7	5.2 (2.1 to 13)	3.6 (2.5 to 6.6)	258
Lornoxicam	4	2	151	29/73	13/78	40	17	2.4 (1.3 to 4.1)	4.3 (2.7 to 11)	200
Other postoperative only										
Codeine	60	18	1265	232/626	157/639	37	25	1.5 (1.3 to 1.8)	8.0 (5.7 to 13)	316
Dexketoprofen	10/12.5	2	201	43/99	21/102	43	21	2.1 (1.4 to 3.3)	4.4 (2.8 to 9.7)	256
Dexketoprofen	10/12.5	2	201	47/99	21/102	47	21	2.3 (1.6 to 3.5)	3.7 (2.5 to 7.0)	342
Dextropropoxyphe	65	5	410	77/199	54/211	39	26	1.5 (1.1 to 2.0)	7.7 (4.5 to 24)	122
Ketoprofen	50	5	434	90/216	50/218	42	23	1.8 (1.4 to 2.4)	5.3 (3.7 to 9.9)	385
Naproxen	500/550	4	372	83/195	45/187	43	24	1.8 (1.3 to 2.4)	5.4 (3.6 to 11)	317
Rofecoxib	50	3	628	127/346	62/282	37	22	1.7 (1.3 to 2.2)	6.8 (4.6 to 13)	296

5. Drug/dose combinations for which Cochrane Reviews found evidence of effect, where results were reliable and not subject to potential publication bias

Reliable results are presented by pain condition for the primary outcome of NNT compared with placebo for at least 50% maximum pain relief over four to six hours: firstly all types of surgery together, then dental pain only, and finally by other painful conditions. The results contain all available data. Some of the data are from doses of drugs not typically used clinically, such as 180/240 mg etoricoxib or ibuprofen 100 mg, or from drugs not commonly available in many parts of the world, like rofecoxib. All data are presented so that readers can use that which is relevant for them.

All types of surgery

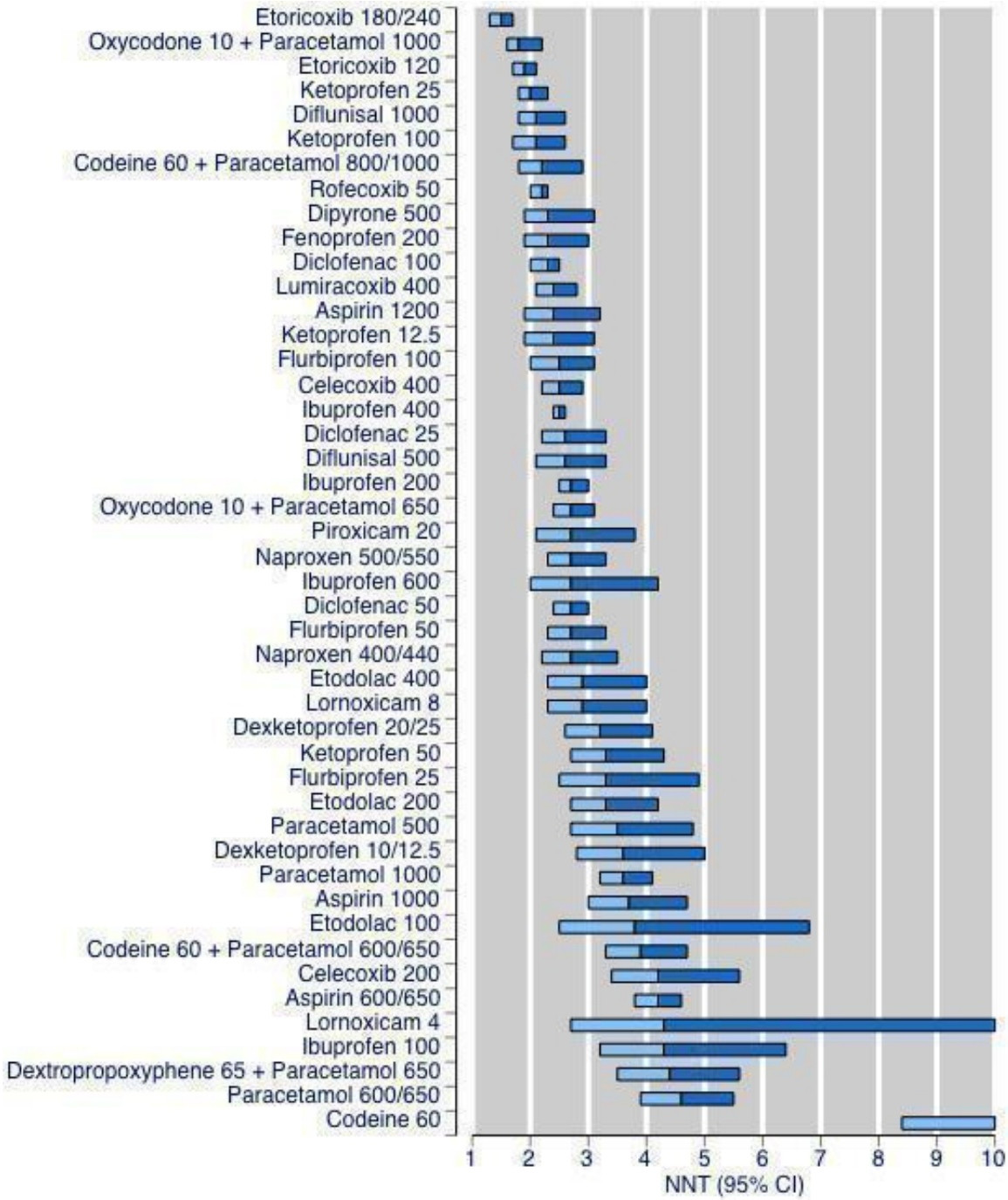
For all types of surgery, the results judged to be reliable are shown in Summary table B. Overall, about 45,000 participants contributed data. For lornoxicam 4 mg only 151 participants from two studies provided data, but more than 400 participants would have been needed in zero effect studies to overturn the result; our judgement was that this result was on the borderline of being reliable. For codeine 60 mg, although the NNT was above 10, it was based on over 2400 participants and we deemed that a reliable result.

The number of participants was high (above 2000) with ibuprofen 400 mg and 200 mg, aspirin 600/650 mg, paracetamol 975/1000 mg, and rofecoxib 50 mg. Results with high numbers of participants and low (good) NNTs were particularly robust, with almost 20,000 participants needed in zero effect studies to overturn the result for ibuprofen 400 mg and over 13,000 to overturn that for rofecoxib 50 mg.

NNTs varied from as low as 1.5 for high doses of etoricoxib, to as high as 12 for codeine 60 mg. The majority of drug/dose combina-

tions had NNTs below 3. A listing by rank order is shown in Figure 1. Higher doses of the same drug tended to have lower (better) NNTs, though this was not particularly evident with paracetamol.

Figure 1. All types of surgery: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.



Summary table B: Results judged to be reliable in all types of surgery

				At least 50% maximum pain relief over 4 to 6 hours						
		Number of		Number with outcome/total		Percent with outcome				
Drug	**Dose (mg)**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Aspirin	600/650	65	4965	983/2496	379/2469	39	15	2.5 (2.3 to 2.8)	4.2 (3.8 to 4.6)	6856
Aspirin	1000	8	770	178/416	55/354	43	16	2.7 (2.1 to 3.5)	3.7 (3.0 to 4.7)	1311
Aspirin	1200	3	249	85/140	25/109	62	19	3.3 (1.8 to 6.3)	2.4 (1.9 to 3.2)	789
Celecoxib	200	4	705	149/423	32/282	35	11	3.5 (2.4 to 5.1)	4.2 (3.4 to 5.6)	974
Celecoxib	400	4	620	184/415	9/205	34	4	11 (5.9 to 22)	2.5 (2.2 to 2.9)	1860
Codeine	60	33	2411	311/1199	209/1212	26	17	1.5 (1.3 to 1.7)	12 (8.4 to 18)	NNT above 10
Codeine + paracetamol	60 + 600/650	17	1413	370/857	96/556	43	17	2.6 (2.2 to 3.2)	3.9 (3.3 to 4.7)	2210
Codeine + paracetamol	60 + 800/1000	3	192	64/121	5/71	53	7	6.3 (2.9 to 14)	2.2 (1.8 to 2.9)	681
Dexketoprofen	10/12.5	5	452	104/230	38/222	45	17	2.7 (2.0 to 3.7)	3.6 (2.8 to 5.0)	804
Dexketoprofen	20/25	6	523	129/225	38/248	47	15	3.3 (2.4 to 4.5)	3.2 (2.6 to 4.1)	1111

(*Continued*)

Dextropropoxyphe + paracetamol	65 + 650	6	963	184/478	74/485	38	15	2.5 (2.0 to 3.2)	4.4 (3.5 to 5.6)	1226
Diclofenac	25	4	502	131/248	37/254	53	15	3.6 (2.6 to 5.0)	2.6 (2.2 to 3.3)	1429
Diclofenac	50	11	1325	441/780	102/545	57	19	3.0 (2.5 to 3.6)	2.7 (2.4 to 3.0)	3582
Diclofenac	100	7	787	231/416	44/371	56	12	4.8 (3.6 to 6.4)	2.3 (2.0 to 2.5)	2635
Diflunisal	500	6	391	104/198	27/193	53	14	3.8 (2.6 to 5.4)	2.6 (2.1 to 3.3)	1113
Diflunisal	1000	5	357	112/182	26/175	62	15	4.1 (2.9 to 6.0)	2.1 (1.8 to 2.6)	1343
Dipyrone	500	5	288	106/143	45/145	74	31	2.4 (1.8 to 3.1)	2.3 (1.9 to 3.1)	964
Etodolac	100	5	498	103/251	50/247	41	20	2.0 (1.5 to 2.7)	4.8 (3.5 to 7.8)	540
Etodolac	200	7	670	145/333	44/337	44	13	3.3 (2.5 to 4.5)	3.3 (2.7 to 4.2)	1360
Etodolac	400	3	222	52/134	4/88	39	5	9.0 (3.4 to 24)	2.9 (2.3 to 4.0)	544
Etoricoxib	120	5	655	259/406	26/249	64	11	6.1 (4.1 to 9.0)	1.9 (1.7 to 2.1)	2792
Etoricoxib	180/240	2	199	129/150	6/49	79	12	6.4 (3.1 to 14)	1.5 (1.3 to 1.7)	1128
Fenoprofen	200	4	287	83/146	19/141	57	13	4.2 (2.7 to 6.4)	2.3 (1.9 to 3.0)	961
Flurbiprofen	25	3	208	36/102	5/106	35	5	7.0 (2.9 to 16)	3.3 (2.5 to 4.9)	422
Flurbiprofen	50	10	692	245/353	108/339	69	32	2.2 (1.9 to 2.6)	2.7 (2.3 to 3.3)	1871

(*Continued*)

Flurbiprofen	100	7	416	139/215	48/201	65	24	2.8 (2.2 to 3.6)	2.5 (2.0 to 3.1)	1248
Ibuprofen	100	4	396	60/192	16/204	31	8	3.7 (2.3 to 5.9)	4.3 3.2 to 6.4)	525
Ibuprofen	200	20	2690	718/1572	101/1118	46	9	4.6 (3.9 to 5.6)	2.7 (2.5 to 3.0)	7273
Ibuprofen	400	61	6475	2013/3728	375/2747	54	14	3.9 (3.6 to 4.4)	2.5 (2.4 to 2.6)	19425
Ibuprofen	600	3	203	88/114	36/89	77	40	2.0 (1.5 to 2.6)	2.7 (2.0 to 4.2)	549
Ketoprofen	12.5	3	274	77/138	18/136	56	13	4.2 (2.7 to 6.6)	2.4 (1.9 to 3.1)	868
Ketoprofen	25	8	535	175/281	31/254	62	12	4.9 (3.5 to 6.9)	2.0 (1.8 to 2.3)	2140
Ketoprofen	50	8	624	151/314	56/310	48	18	2.7 (2.0 to 3.5)	3.3 (2.7 to 4.3)	1267
Ketoprofen	100	5	321	106/161	28/160	66	18	3.6 (2.5 to 5.1)	2.1 (1.7 to 2.6)	1208
Lornoxicam	4	2	151	29/73	13/78	40	17	2.4 (1.3 to 4.1)	4.3 (2.7 to 11)	478
Lornoxicam	8	3	273	71/155	13/118	46	11	4.7 (2.7 to 8.1)	2.9 (2.3 to 4.0)	668
Lumiracoxib	400	4	578	183/366	17/212	50	8	6.9 (4.1 to 11)	2.4 (2.1 to 2.8)	1830
Naproxen	400/440	3	334	103/210	14/124	49	11	4.8 (2.8 to 8.4)	2.7 (2.2 to 3.5)	903
Naproxen	500/550	9	784	200/394	59/390	52	15	3.4 (2.6 to 4.4)	2.7 (2.3 to 3.3)	2120
Oxycodone + paracetamol	10/650	10	1043	346/680	49/363	51	14	3.9 (2.9 to 5.2)	2.7 (2.4 to 3.1)	2820

(*Continued*)

Oxycodone + paracetamol	10/1000	2	289	100/147	19/142	68	13	4.9 (3.2 to 7.6)	1.8 (1.6 to 2.2)	1317
Paracetamol	500	6	561	176/290	86/271	61	32	1.9 (1.6 to 2.3)	3.5 (2.7 to 4.8)	1042
Paracetamol	600/650	19	1886	358/954	145/932	38	16	2.4 (2.0 to 2.8)	4.6 (3.9 to 5.5)	2214
Paracetamol	975/1000	28	3232	876/1906	241/1329	46	18	2.7 (2.4 to 3.0)	3.6 (3.2 to 4.1)	5746
Piroxicam	20	3	280	89/141	36/139	63	26	2.5 (1.8 to 3.3)	2.7 (2.1 to 3.8)	757
Rofecoxib	50	25	3688	1458/2519	134/1169	58	11	5.1 (4.3 to 6.1)	2.2 (2.0 to 2.3)	13076

Dental conditions

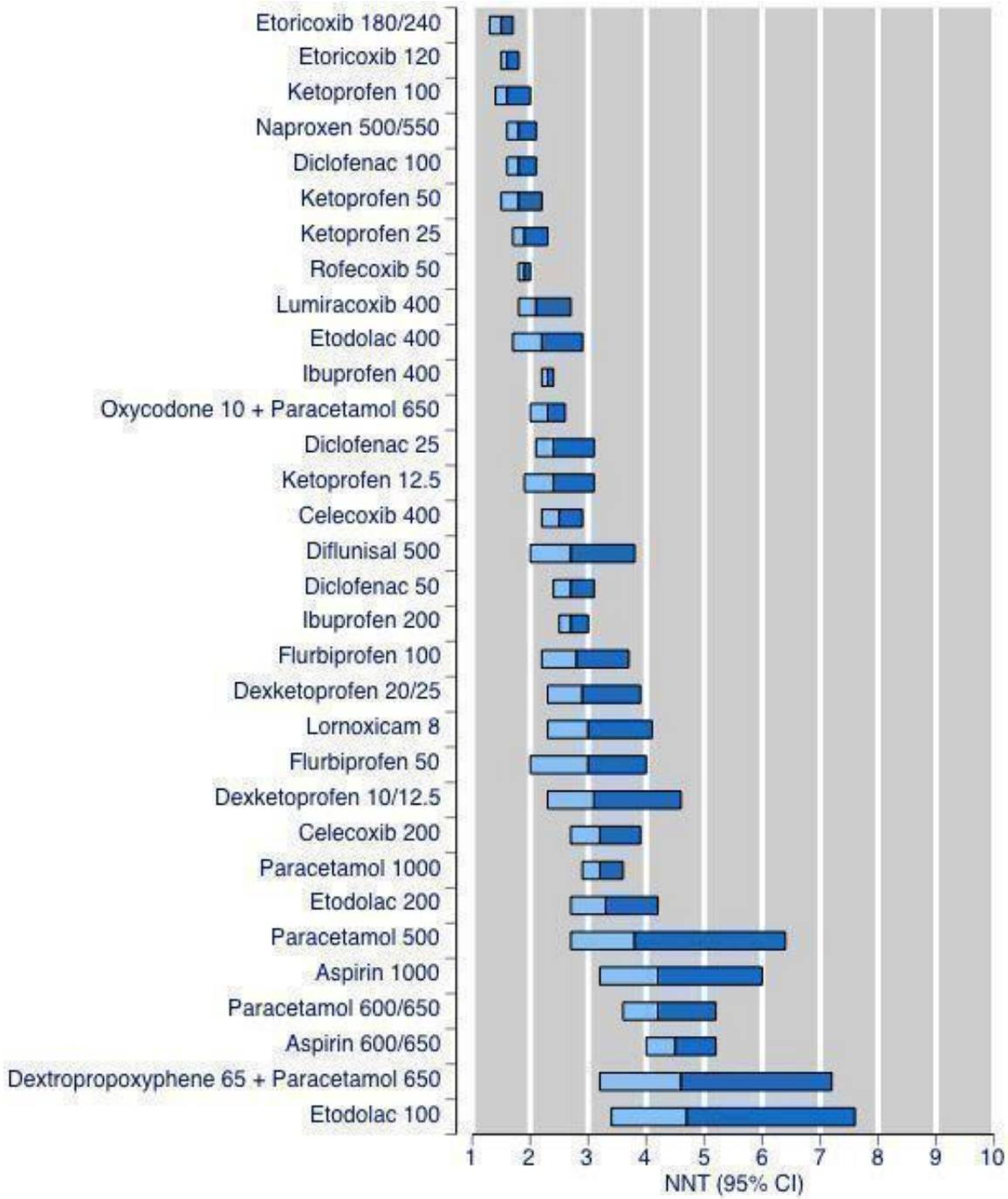
In practice this means almost exclusively the third molar extraction model, with minor differences in the number of teeth removed, and the extent of any bone involvement during surgery. Results judged to be reliable are shown in Summary table C; overall, about 29,000 participants contributed data.

For etodolac 400 mg, and ketoprofen 50 and 100 mg, fewer than 200 participants provided data, but many more than 400 participants would have been needed in zero effect studies to overturn the result; our judgement was that this result was on the borderline of being reliable. For codeine 60 mg, although the NNT was above 10, it was based on over 1146 participants and we deemed that a reliable result.

The number of participants was high (above 2000) with ibuprofen 400 mg and 200 mg, aspirin 600/650 mg, paracetamol 975/1000 mg, and rofecoxib 50 mg. Results with high numbers of participants and low (good) NNTs were particularly robust, with about 18,000 participants needed in zero effect studies to overturn the result for ibuprofen 400 mg, and over 13,000 to overturn that for rofecoxib 50 mg.

NNTs varied from as low as 1.5 for high doses of etoricoxib to as high as 21 for codeine 60 mg. The majority of drug/dose combinations had NNTs below 3. A listing by rank order is shown in Figure 2. Higher doses of the same drug tended to have lower (better) NNTs, though this was not particularly evident with paracetamol.

Figure 2. Dental pain: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.



Both Summary of results C and Figure 2 give all results for a particular dose of a particular drug, irrespective of drug formulation. There can be important differences between formulations, and examples of this are shown in Summary table C for sodium and potassium salts of diclofenac, and soluble and standard formulations of ibuprofen. These results show that, based on reasonable and reliable evidence, formulation has a major impact on efficacy in acute pain for diclofenac (Diclofenac 2009) and ibuprofen (Ibuprofen 2009).

Summary table C: Results judged to be reliable in painful dental conditions

		At least 50% maximum pain relief over 4 to 6 hours								
		Number of		Number with outcome/total		Percent with outcome				
Drug	**Dose (mg)**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Aspirin	600/650	45	3581	634/1763	251/1818	36	14	2.6 (2.3 to 2.9)	4.5 (4.0 to 5.2)	4377
Aspirin	1000	4	436	87/250	20/186	35	11	2.8 (1.9 to 4.3)	4.2 (3.2 to 6.0)	602
Celecoxib	200	3	423	94/282	2/141	41	1	16 (5.1 to 49)	3.2 (2.7 to 3.9)	899
Celecoxib	400	4	620	184/415	9/205	34	4	11 (5.9 to 22)	2.5 (2.2 to 2.9)	1860
Codeine	60	15	1146	79/573	52/573	14	9	1.5 (1.1 to 2.1)	21 (12 to 96)	NNT above 10
Dexketoprofen	10/12.5	3	251	61/131	17/120	47	14	3.3 (2.0 to 5.3)	3.1 (2.3 to 4.6)	559
Dexketoprofen	20/25	4	322	82/176	17/146	47	12	4.5 (2.8 to 7.2)	2.9 (2.3 to 3.9)	788
Dextropropoxyphe + paracetamol	65 + 650	3	353	61/173	23/180	35	13	2.8 (1.8 to 4.2)	4.6 (3.2 to 7.2)	414

(*Continued*)

Diclofenac	25	3	398	99/196	22/202	51	11	4.7 (3.1 to 7.1)	2.5 (2.1 to 3.2)	1194
Diclofenac	50	9	1119	378/678	82/441	56	19	3.0 (2.4 to 3.7)	2.7 (2.4 to 3.1)	3025
Diclofenac	100	4	413	151/228	19/185	66	10	6.6 (4.3 to 10)	1.8 (1.6 to 2.1)	1881
Diflunisal	500	3	220	62/112	19/108	55	18	3.1 (2.0 to 4.8)	2.7 (2.0 to 3.8)	595
Etodolac	100	4	418	80/211	34/207	38	16	2.3 (1.6 to 3.3)	4.7 (3.4 to 7.6)	471
Etodolac	200	7	670	145/333	44/337	44	13	3.3 (2.5 to 4.5)	3.3 (2.7 to 4.2)	1360
Etodolac	400	2	149	43/85	3/64	51	5	11 (3.5 to 18)	2.2 (1.7 to 2.9)	528
Etoricoxib	120	4	500	233/326	16/174	71	9	8.0 (5.0 to 13.0)	1.6 (1.5 to 1.8)	2625
Etoricoxib	180/240	2	199	129/150	6/49	79	12	6.4 (3.1 to 14)	1.5 (1.3 to 1.7)	1128
Flurbiprofen	50	7	473	161/245	74/228	66	32	2.1 (1.7 to 2.5)	3.0 (2.0 to 4.0)	1104
Flurbiprofen	100	6	354	119/184	48/170	65	29	2.4 (1.9 to 3.1)	2.8 (2.2 to 3.7)	910
Ibuprofen	200	18	2470	680/1462	100/1008	47	10	4.5 (3.7 to 5.4)	2.7 (2.5 to 3.0)	6678
Ibuprofen	400	49	5428	1746/3148	271/2280	55	12	4.3 (3.8 to 4.9)	2.3 (2.2 to 2.4)	18172
Ketoprofen	12.5	3	274	77/138	18/136	56	13	4.2 (2.7 to 6.6)	2.4 (1.9 to 3.1)	868
Ketoprofen	25	6	452	153/239	26/213	64	12	5.2 (3.6 to 7.5)	1.9 (1.7 to 2.3)	1927
Ketoprofen	50	3	190	61/98	6/92	62	6	9.0 (4.2 to 19)	1.8 (1.5 to 2.2)	866

(*Continued*)

Ketoprofen	100	3	195	79/97	10/98	72	10	7.3 (4.0 to 13)	1.6 (1.4 to 2.0)	1024
Lornoxicam	8	3	273	71/155	13/118	46	11	4.7 (2.7 to 8.1)	2.9 (2.3 to 4.0)	668
Lumiracoxib	400	3	460	163/307	7/153	53	2	9.7 (4.3 to 2.2)	2.1 (1.8 to 2.7)	1730
Naproxen	500/550	5	402	122/199	14/203	61	7	8.7 (5.2 to 14)	1.8 (1.6 to 2.1)	1831
Oxycodone + paracetamol	10/650	6	673	252/496	11/177	51	6	6.8 (3.9 to 12)	2.3 (2.0 to 2.6)	2253
Paracetamol	500	3	305	84/150	46/155	56	30	1.9 (1.4 to 2.5)	3.8 (2.7 to 6.4)	498
Paracetamol	600/650	10	1276	225/638	74/638	35	12	3.1 (2.4 to 3.8)	4.2 (3.6 to 5.2)	1762
Paracetamol	975/1000	19	2157	545/1335	82/822	41	10	4.1 (3.3 to 5.2)	3.2 (2.9 to 3.6)	4584
Rofecoxib	50	22	3060	1332/2173	73/887	61	8	7.3 (5.9 to 9.2)	1.9 (1.8 to 2.0)	13045
Formulation comparisons										
Diclofenac sodium	50	3	313	58/193	18/120	30	15	2.0 (1.3 to 3.3)	6.7 (4.2 to 17)	154
Diclofenac potassium	50	5	622	237/367	40/255	65	16	3.8 (2.8 to 5.0)	2.1 (1.9 to 2.4)	2340
Diclofenac sodium	100	2	211	30/114	4/97	26	4	5.3 (1.9 to 15)	4.5 (3.2 to 7.6)	258
Diclofenac potassium	100	6	591	200/302	39/289	66	13	5.0 (3.7 to 6.8)	1.9 (1.7 to 2.2)	2520

(*Continued*)

Ibuprofen	200 soluble	7	828	270/478	34/350	56	10	5.7 (4.2 to 7.9)	2.1 (1.9 to 2.4)	3115
Ibuprofen	200 standard	15	1883	406/984	62/899	41	7	5.9 (4.7 to 7.6)	2.9 (2.6 to 3.2)	4610
Ibuprofen	400 soluble	9	959	361/550	41/409	66	10	6.5 (4.8 to 8.9)	1.8 (1.7 to 2.0)	4369
Ibuprofen	400 standard	46	4772	1385/2598	230/2174	53	11	5.2 (4.6 to 5.9)	2.3 (2.2 to 2.5)	15,976

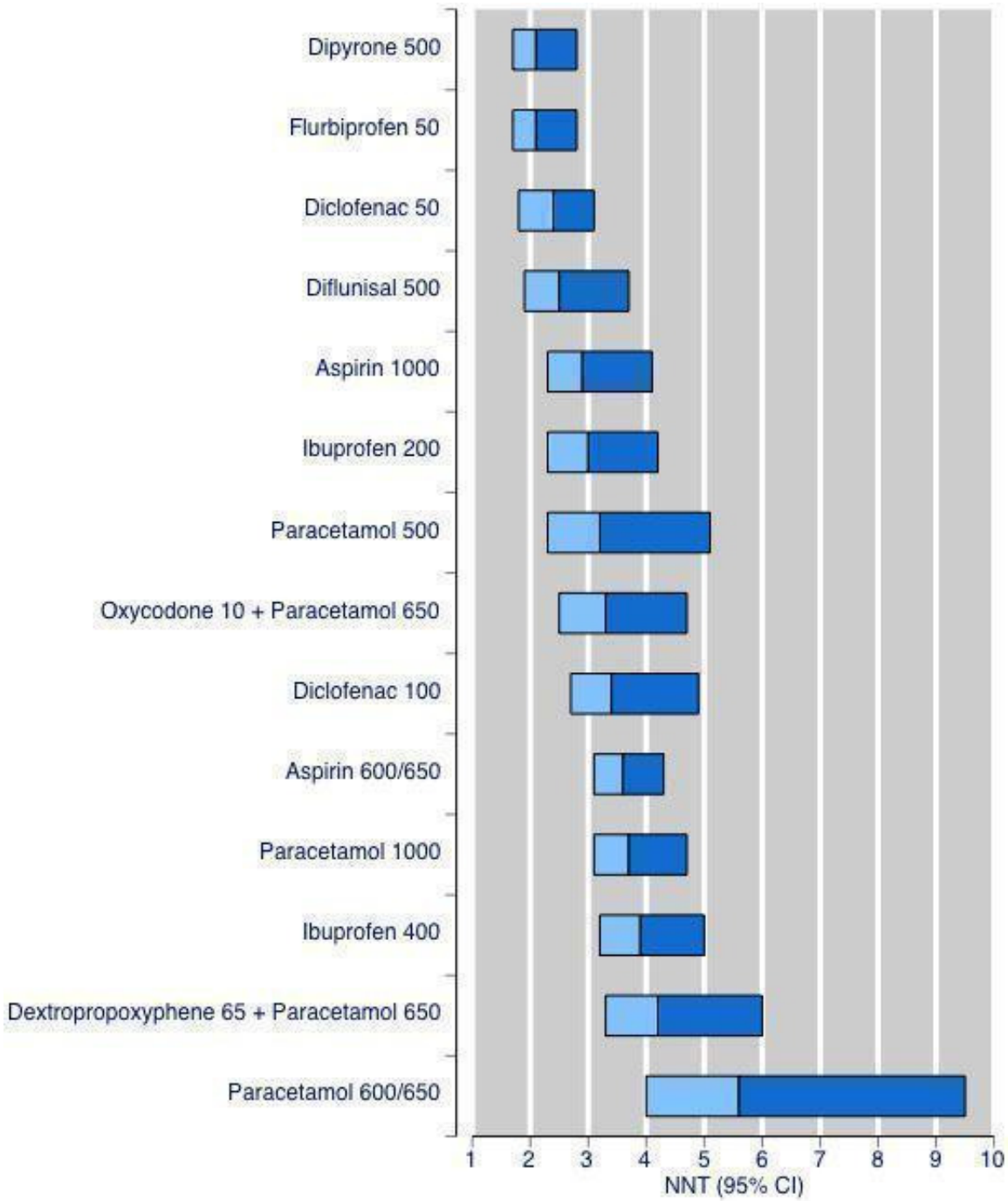
Other painful conditions

This grouping included all acute postoperative pain that is not dental; it includes conditions like episiotomy, orthopaedic, and abdominal surgery, where the pain is of at least moderate in intensity and oral analgesics are indicated. There were insufficient data to allow further subgrouping according to type of surgery. Results judged to be reliable are shown in Summary table D; overall, about 7000 participants contributed data.

For diflunisal 500 mg fewer than 200 participants provided data, but more than 400 participants would have been needed in zero effect studies to overturn the result; our judgement was this result was on the borderline of being reliable.

The number of participants was above 1000 with aspirin 600/650 mg, ibuprofen 400 mg, and paracetamol 975/1000 mg. NNTs varied from as low as 2.1 for dipyrone 500 mg and flurbiprofen 50 mg to as high as 5.6 with paracetamol 1000. A listing by rank order is shown in Figure 3. Higher doses of the same drug tended to have lower (better) NNTs, though this was not particularly evident with paracetamol or ibuprofen.

Figure 3. Other painful conditions: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.



Summary table D: Results judged to be reliable in other painful conditions

				At least 50% maximum pain relief over 4 to 6 hours						
		Number of		Number with outcome/total		Percent with outcome				
Drug	**Dose (mg)**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Aspirin	600/650	19	1384	349/733	128/651	48	20	2.4 (2.0 to 2.8)	3.6 (3.1 to 4.3)	2460
Aspirin	1000	4	334	91/166	35/168	55	21	2.6 (1.9 to 3.6)	2.9 (2.3 to 4.1)	818
Dextropropoxyphe + paracetamol	65 + 650	3	610	123/305	51/305	40	15	2.4 (1.8 to 3.2)	4.2 (3.3 to 6.0)	842
Diclofenac	50	2	206	63/102	20/104	62	19	3.2 (2.1 to 4.9)	2.4 (1.8 to 3.3)	652
Diclofenac	100	3	374	79/188	24/186	42	13	3.3 (2.2 to 4.9)	3.4 (2.7 to 4.9)	726
Diflunisal	500	3	171	42/86	8/85	49	9	5.3 (2.7 to 10)	2.5 (1.9 to 3.7)	513
Dipyrone	500	4	210	78/104	29/106	75	27	2.7 (2.0 to 3.8)	2.1 (1.7 to 2.8)	790
Flurbiprofen	50	3	219	84/108	34/111	78	31	2.5 (1.9 to 3.3)	2.1 (1.7 to 2.8)	824
Ibuprofen	200	2	220	42/110	5/110	38	5	7.7 (3.2 to 18)	3.0 (2.3 to 4.2)	513
Ibuprofen	400	12	1047	277/580	103/467	48	22	2.2 (1.8 to 2.6)	3.9 (3.2 to 5.0)	1638
Oxycodone + paracetamol	10/650	4	370	93/184	37/186	51	20	2.5 (1.9 to 3.4)	3.3 (2.5 to 4.7)	751

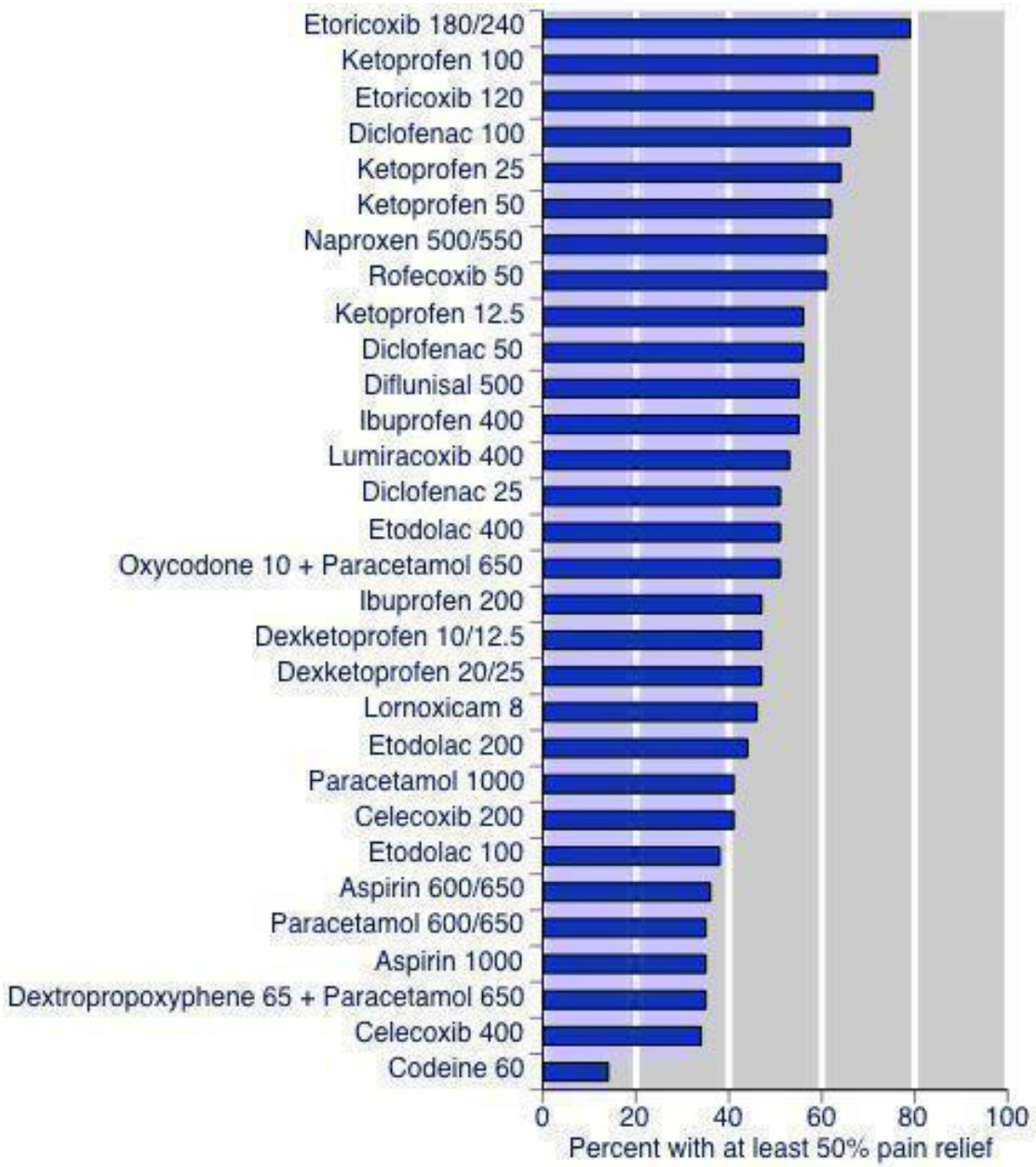
(*Continued*)

Paracetamol	500	3	256	92/140	40/116	66	34	1.9 (1.5 to 2.5)	3.2 (2.3 to 5.1)	544
Paracetamol	600/650	9	610	136/316	74/294	43	25	1.8 (1.4 to 2.3)	5.6 (4.0 to 9.5)	479
Paracetamol	975/1000	10	1075	333/568	161/507	59	32	1.7 (1.5 to 2.0)	3.7 (3.1 to 4.7)	1830

6. Percentage of patients achieving target of at least 50% maximum pain relief

These results are described in Summary tables B, C, and D for each drug/dose combination. There was very wide variation between drugs even in the same painful condition, and where there were consistent responses with placebo. Figure 4 shows that in dental pain, while some drugs achieved a high level of pain relief in over 60 to 70% of participants, in others it was as low as about 30%. The response with placebo in dental pain averages about 10% to 15%, but tends to be higher in other surgical conditions.

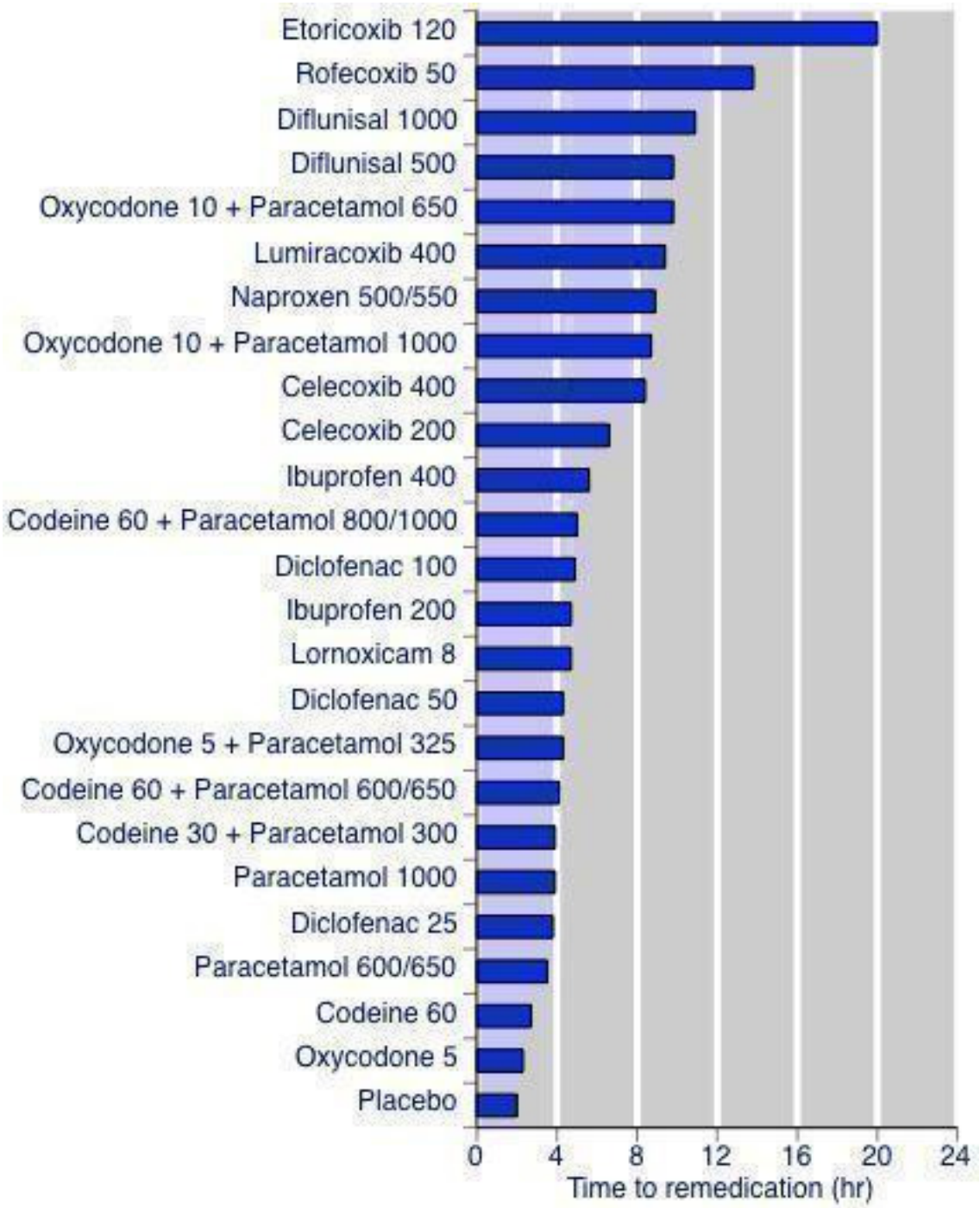
Figure 4. Percentage of patients achieving at least 50% maximum pain relief (dental pain).



7. Time to remedication

A number of reviews reported the mean of the mean or median time to remedication, a useful secondary outcome indicating the duration of effective analgesia before the pain intensifies to the point where additional analgesia is required. For placebo, averaging over all reviews, the mean time to remedication is two hours; trials typically have a one to two-hour period before which additional analgesia is not allowed, to allow time for any analgesic to work. For active drugs in dental pain, the mean duration varied between below three hours for codeine 60 mg and oxycodone 5 mg, up to 20 hours for etoricoxib 120 mg (Figure 5; Appendix 3).

Figure 5. Mean time to remedication in painful dental conditions.



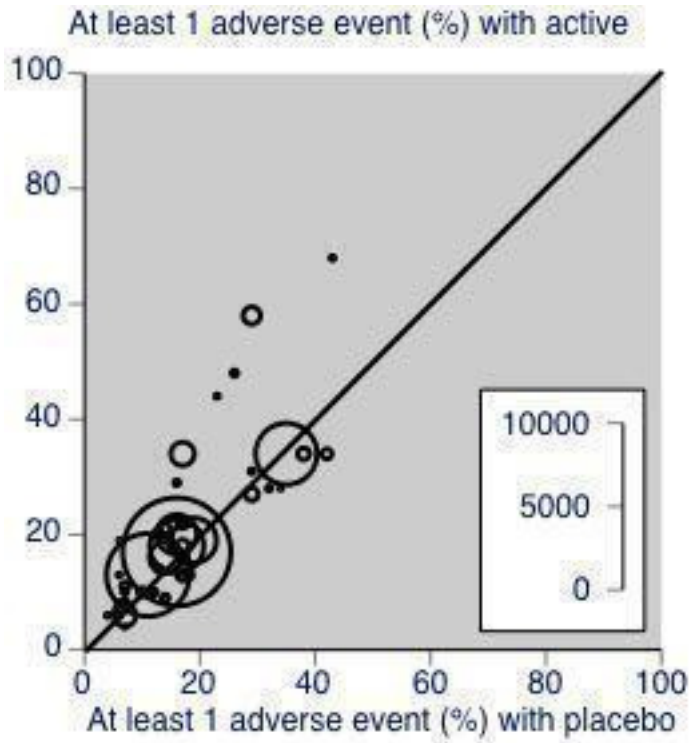
8. Percentage remedicated with time

We collected information on the percentage of patients who had remedicated with active treatment and placebo at various times after the start of therapy and this is reported in Appendix 3. This was sparsely reported in a small subsection of studies. In brief, typically 70% to 90% of participants given placebo had used rescue medication by six hours, and this tended to increase further at longer durations, though it never reached 100%. With analgesics, the numbers remedicating at six hours were always lower than with placebo.

9. Experience of adverse events

Adverse event reporting in acute pain studies is known to be heavily influenced by the methods used (Edwards 2002). Most reviews reported no serious adverse events and the only common report was that of participants experiencing at least one adverse event during the period of the study. These results are shown in Summary table E. The usual finding was no difference in adverse event rates between active and placebo groups (Figure 6). Statistical differences were found only for aspirin 600/650 mg (NNH 44), codeine + paracetamol 60/650 mg (NNH 6.0), diflunisal 1000 mg (NNH 7.7), dihydrocodeine 30 mg (NNH 7.4), and oxycodone ± paracetamol combinations (NNH 3.5 to 4.5).

Figure 6. Plot of percentage of participants reporting at least one adverse event with active drug and placebo. Each symbol represents results from one drug/dose combination, and the size of the size of the symbol is proportional to the number of participants (inset scale).



Summary table E: Participants experiencing at least one adverse event (AE)

		At least one AE							
		Number of		Number on		Percent with outcome			
Drug	**Dose (mg)**	**Studies**	**Patients**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative risk (95% CI)**	**NNH (95% CI)**
Aspirin	600/650	64	4965	19/76	20/88	13	11	1.2 (1.0 to 1.4)	44 (23 to 345)
Celecoxib	200	4	705	64/406	44/263	16	17	0.90 (0.63 to 1.28)	
Celecoxib	400	4	620	107/315	87/206	34	42	1.05 (0.85 to 1.3)	
Codeine	60	33	2411	81/399	63/399	20	16	1.3 (0.9 to 1.7)	
Codeine + paracetamol	60 + 600/650	17	1413	266/779	83/479	34	17	1.6 (1.3 to 1.9)	6.0 (4.6 to 8.3)
Dexketoprofen	10/12.5	5	452	12/132	18/126	9	14	0.6 (0.3 to 1.3)	
Dexketoprofen	20/25	6	523	43/220	26/193	20	13	1.3 (0.8 to 2.1)	
Diclofenac	25	4	502	20/248	18/254	8	7	1.2 (0.6 to 2.1)	
Diclofenac	50	11	1325	41/643	34/473	6	7	1.0 (0.7 to 1.5)	
Diclofenac	100	7	787	18/419	64/373	18	17	1.0 (0.8 to 1.4)	
Diflunisal	250	3	195	4/98	7/97	4	7	0.6 (0.2 to 1.8)	
Diflunisal	500	6	391	38/235	33/227	18	15	1.3 (0.8 to 1.9)	
Diflunisal	1000	5	357	61/208	34/209	29	16	1.8 (1.2 to 2.6)	7.7 (4.8 to 20)

(*Continued*)

Dihydrocodeine	30	3	194	13/67	4/69	19	6	3.4 (1.2 to 9.8)	7.4 (4.1 to 38)
Etodolac	50	4	360	10/132	12/188	8	6	1.4 (0.6 to 3.2)	
Etodolac	100	5	498	26/230	16/229	11	7	1.6 (0.9 to 2.8)	
Etodolac	200	7	670	67/314	54/319	22	17	1.2 (0.9 to 1.7)	
Etodolac	400	3	222	43/154	37/109	28	34	0.8 (0.6 to 1.2)	
Etoricoxib	120/180/240	5	725	190/551	67/174	34	38	0.9 (0.7 to 1.1)	
Fenoprofen	200	4	287	9/146	9/141	6	6	0.94 (0.4 to 2.1)	
Flurbiprofen	25	3	208	15/109	17/112	14	16	0.95 (0.5 to 1.7)	
Flurbiprofen	50	10	692	37/284	50/290	13	17	0.75 (0.5 to 1.1)	
Flurbiprofen	100	7	416	20/200	24/203	10	12	0.86 (0.5 to 1.5)	
Gabapentin	250	3	327	49/177	49/152	28	32	0.9 (0.7 to 1.3)	
Ibuprofen	50	3	316	11/114	8/111	10	7	1.3 (0.6 to 3.0)	
Ibuprofen	100	4	396	22/152	20/158	14	13	1.2 (0.7 to 2.1)	
Ibuprofen	200	20	2690	208/1102	137/706	19	19	0.9 (0.7 to 1.02)	
Ibuprofen	400	61	6475	476/2870	326/1997	17	16	0.9 (0.8 to 1.04)	
Ketoprofen	12.5	3	274	8/138	6/136	6	4	1.3 (0.5 to 3.6)	

(*Continued*)

Ketoprofen	25	8	535	27/259	22/231	10	10	1.2 (0.7 to 2.0)	
Ketoprofen	50	8	624	29/141	18/137	21	14	1.6 (0.9 to 2.6)	
Ketoprofen	100	5	321	19/86	16/89	22	18	1.2 (0.7 to 2.2)	
Lornoxicam	8	3	273	84/190	16/70	44	23	1.4 (0.9 to 2.2)	
Lumiracoxib	400	4	578	40/307	28/153	13	18	0.7 (0.4 to 1.3)	
Mefenamic acid	500	2	256	7/53	3/53	13	6	2.2 (0.7 to 7.2)	
Naproxen	400/440	3	334	38/173	14/84	22	17	1.3 (0.8 to 2.2)	
Naproxen	500/550	9	784	80/291	83/290	27	29	0.96 (0.7 to 1.2)	
Oxycodone	5	3	317	48/157	46/160	31	29	1.1 (0.8 to 1.6)	
Oxycodone + paracetamol	5/325	3	388	107/221	44/167	48	26	1.6 (1.2 to 2.1)	4.5 (3.2 to 7.9)
Oxycodone + paracetamol	10/650	10	1043	199/343	61/209	58	29	1.8 (1.4 to 2.3)	3.5 (2.7 to 4.8)
Oxycodone + paracetamol	10/1000	2	289	100/147	61/141	68	43	1.6 (1.3 to 2.0)	4.0 (2.8 to 7.3)
Paracetamol	500	6	561	10/158	12/161	7	6	0.9 (0.4 to 1.9)	
Paracetamol	600/650	19	1886	121/775	102/747	16	14	1.2 (0.9 to 1.5)	

(*Continued*)

Paracetamol	975/1000	28	3232	259/1423	145/919	18	16	1.1 (0.9 to 1.3)	
Rofecoxib	50	25	3688	750/2236	409/1168	34	35	0.96 (0.87 to 1.1)	

DISCUSSION

Summary of main results

We have reliable efficacy estimates of 46 drug/dose combinations in all types of surgery: 45 in painful dental conditions (overwhelmingly following third molar extraction) and 14 in other postoperative conditions. These estimates of efficacy have all been obtained using essentially the same clinical trial methods since they were first set out (Beecher 1957), and both trial and review methods have been standardised based on good evidence. The original philosophy concerning acute pain trials has been tested subsequently in a number of analyses using individual patient data (Moore 1997a; Moore 2005; Moore 2011) and those and other analyses also underpin the trials and reviews. This makes the results of studies comparable and that has previously included finding no significant difference between different pain models (Barden 2004).

We also know that there are a number of drugs for which there are no available trial data on how effective they are in acute pain (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009), as well as drug/dose combinations with inadequate evidence of benefit, or definite evidence of no benefit.

Placebo responses in the different meta-analyses - the percentage achieving at least 50% maximum pain relief with placebo over four to six hours - were consistent, with most falling between 5% and 15%, especially with larger numbers of participants given placebo for dental conditions (Figure 7) and all postoperative conditions (Figure 8). For other postoperative conditions the numbers of participants given placebo tended to be small and the range of responses somewhat higher (Figure 9). The degree of variability is what is expected by the random play of chance (Moore 1998).

Figure 7. Plot of percent with outcome with placebo versus number of participants given placebo - dental only.

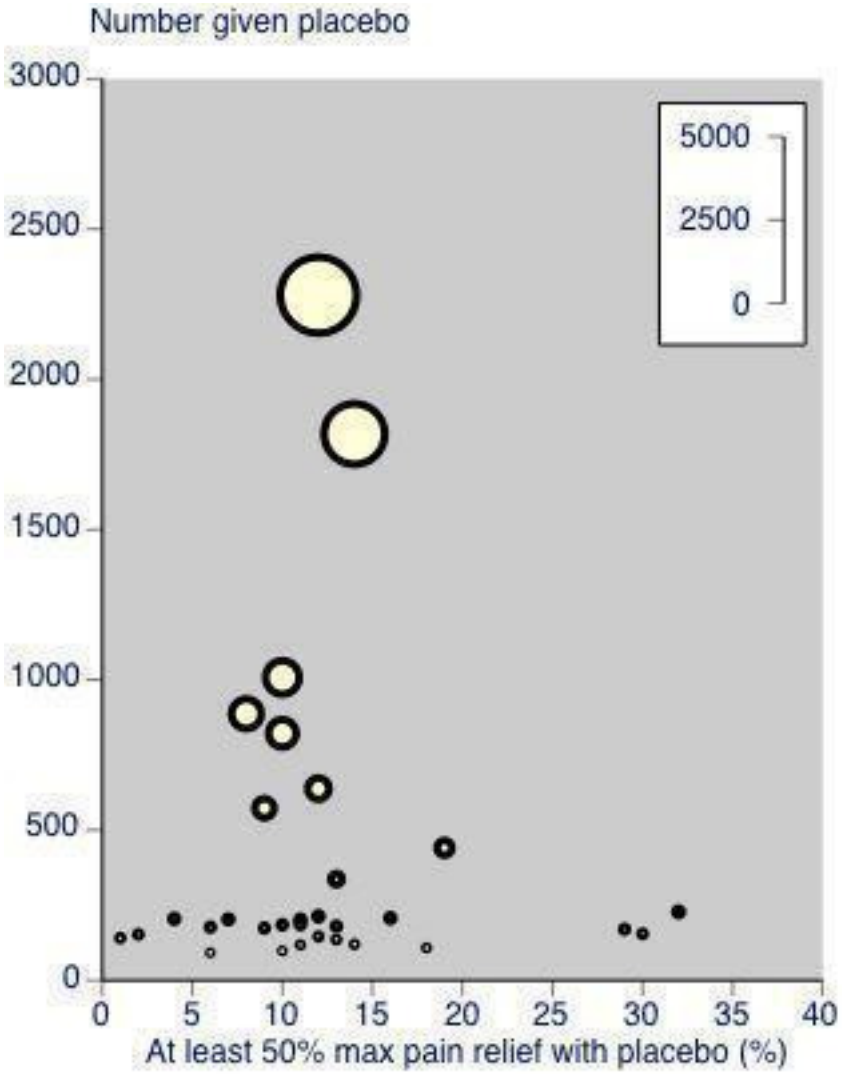


Figure 8. Plot of percent with outcome with placebo versus number of participants given placebo - other conditions only.

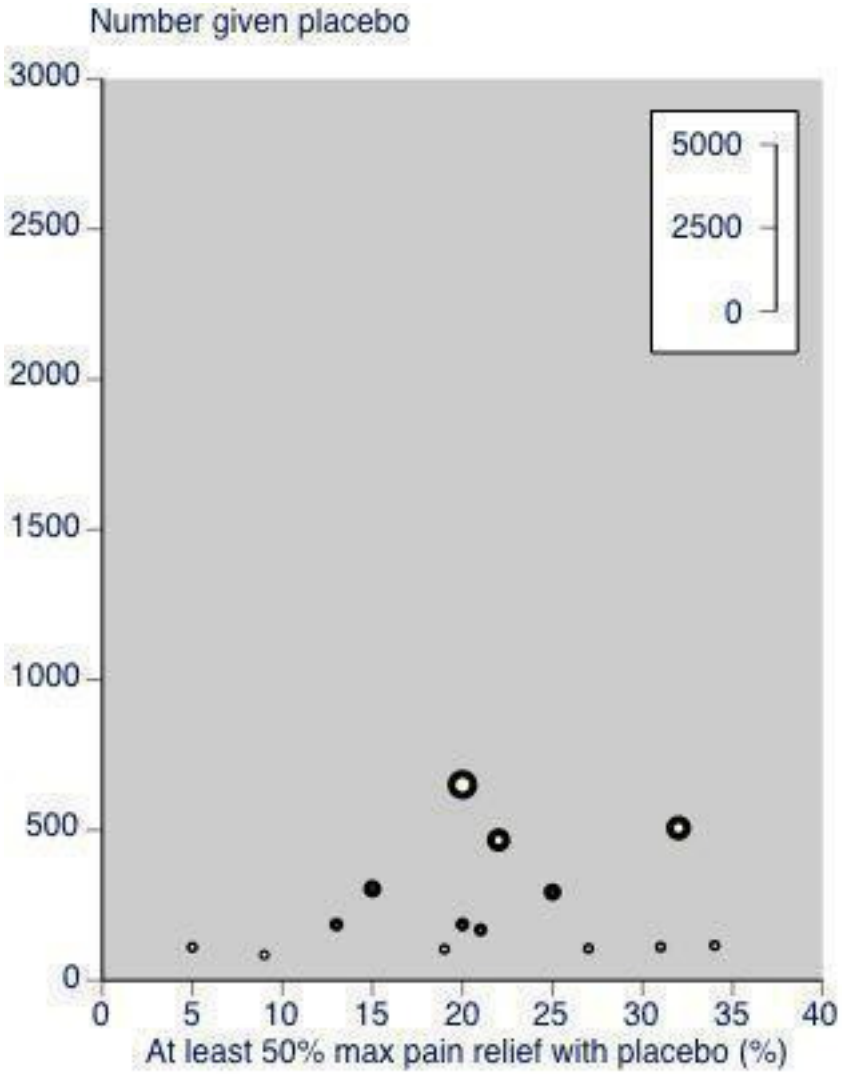
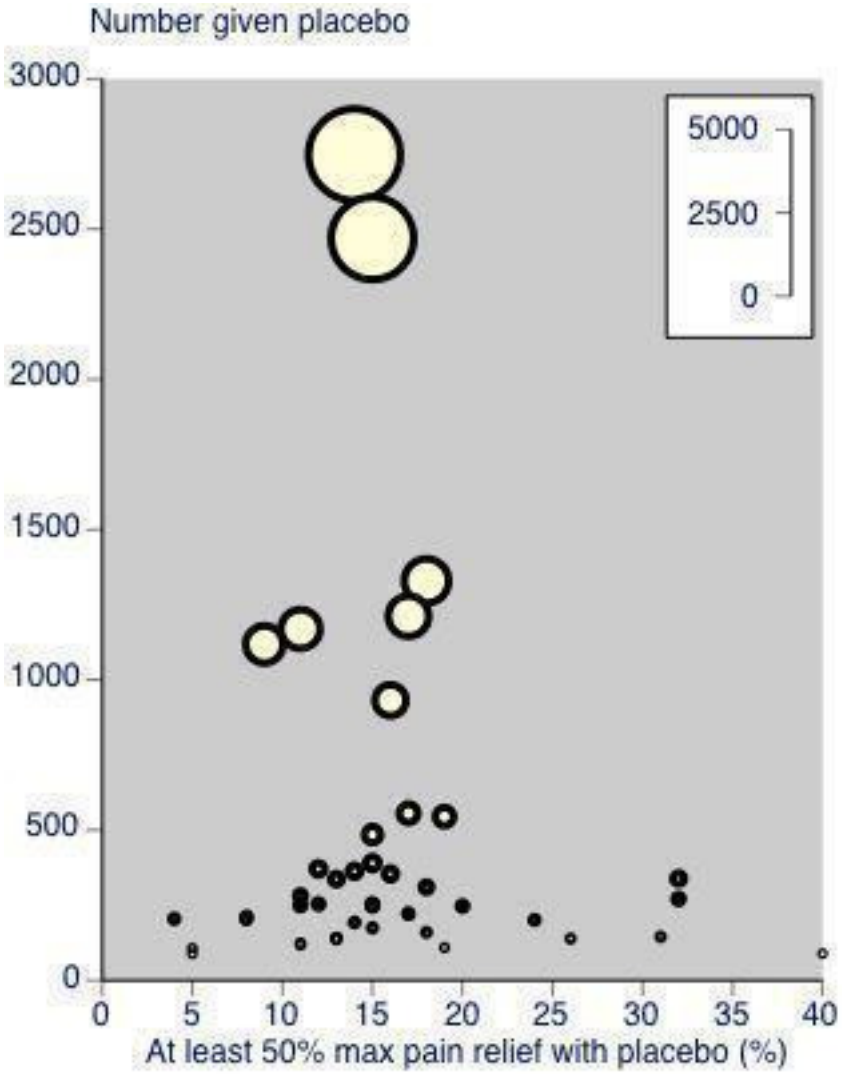


Figure 9. Plot of percent with outcome with placebo versus number of participants given placebo - all types of surgery.

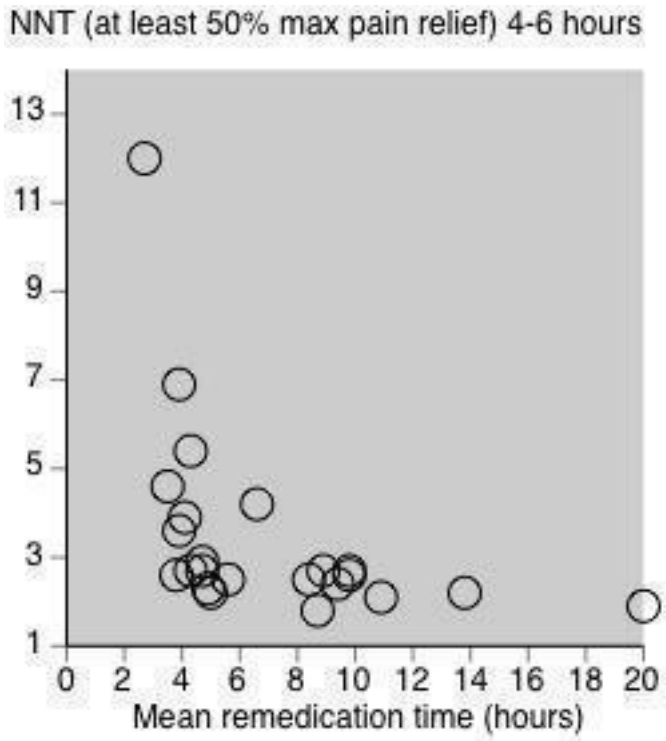


The efficacy results with adequate evidence show a range of values, whether measured relative to placebo in terms of a number needed to treat (NNT) for at least 50% maximum pain relief over four to six hours, in terms of the percentage of participants obtaining this level of benefit, or in terms of time before additional analgesia is required. Some drugs could be shown to not have any beneficial effects at some doses. Adverse events in these short-duration studies were generally not different between active drug and placebo, with a few exceptions, principally opioids.

The results also show clearly that even the most effective drugs fail to deliver good analgesia to a proportion of patients, meaning that a degree of analgesic failure is to be expected. Figure 4 shows that with many interventions, it is to be expected in more than half of patients treated.

There was also an interesting relationship between efficacy over four to six hours and duration of analgesia measured by mean time to remedication (Figure 10). Drugs with short duration of action tended to have higher (worse) NNTs, while drugs with longer duration of action had universally lower (better) NNTs, typically of two or below in those where mean remedication time was eight hours or longer. While not unexpected, this relationship implies that drugs with longer effects are likely to be more useful and effective in clinical practice.

Figure 10. Plot of NNT over four to six hours versus mean time to remedication.



Overall completeness and applicability of evidence

The 35 Cochrane Reviews cover almost all oral analgesics, although throughout the world many different combination analgesics can be found, typically without any published clinical trials. The review found that for seven drugs there were no clinical trial data and for a further six drugs there was inadequate information for any reliable basis of efficacy. In both these cases there are probably unpublished clinical trials. The authors' (unpublished) experience is that obtaining clinical trial data for older drugs is difficult and often impossible - though not always, as the eventual publication of 14 unpublished clinical trials of tramadol in a meta-analysis demonstrated (Moore 1997a). None of the drugs or doses for which this was a concern are used commonly in treating acute pain.

Some reviews appear not to be recent; all had been updated since 2008, but without finding any new studies and so they have kept their original citation dates (Aspirin 1999; Dextropropoxyphene ± Paracetamol 1999; Dihydrocodeine 2000; Piroxicam 2000). Additional searches for these drugs revealed no new studies since the reviews were completed. For other drugs, like etoricoxib, one or two additional studies have very recently been published, but do not materially change the conclusions.

There are no Cochrane Reviews for some commonly used drugs. These include tramadol, though there is an extant protocol for this, tramadol + paracetamol, and the combination of ibuprofen + paracetamol, a recently released combination, and one where these commonly-available drugs are frequently taken together. Non-Cochrane reviews are available for these (Edwards 2002; Moore 1997a; Moore 2011), which used the same methods and standards as the Cochrane Reviews, but results of these have not been included in the comparative figures. For completeness, results for these non-Cochrane reviews are shown in Summary table F.

The results for tramadol 50 mg in dental pain and for tramadol 100 mg in other painful conditions are clearly not reliable, as they are subject to potential publication bias. Results for higher doses of tramadol, tramadol and paracetamol, and ibuprofen and paracetamol are reliable. It is worth noting that reviews of tramadol indicated high rates of adverse events, though they were not reported in ways comparable to Cochrane Reviews (Edwards 2002; Moore 1997a).

Summary table F: Data from non-Cochrane reviews

			At least 50% maximum pain relief over 4 to 6 hours								
			Number of		Number on		Percent with outcome				
Drug	**Dose (mg)**	**Pain condition**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Tramadol	50	Dental	6	471	41/246	13/225	17	6	2.9 (1.6 to 5.2)	9.1 (6.1 to 19)	47
Tramadol	100	Dental	7	578	89/300	22/278	30	8	3.8 (2.4 to 5.8)	4.6 (3.6 to 6.4)	679
Tramadol	100	Other	4	304	51/168	13/136	30	10	3.2 (1.8 to 5.6)	4.8 (3.4 to 8.2)	329
Tramadol	150	Other	5	371	106/184	31/187	60	17	3.5 (2.4 to 4.9)	2.4 (2.0 to 3.1)	1175
Tramadol + paracetamol	75/650	Dental	5	659	128/340	11/339	40	3	12 (6.4 to 21)	2.9 (2.5 to 3.5)	1613
Ibuprofen + paracetamol	200/500	Dental	2	280	130/176	10/104	74	10	7.7 (4.2 to 14)	1.6 (1.4 to 1.8)	1470

Adverse events

Acute pain studies using a single dose of analgesic and with limited duration represent a poor test of adverse events, which can also often be complicated by proximity to anaesthesia. They are particularly limited in speaking to serious adverse events that might occur following long-term use of any of the drugs in this review. Moreover, the populations of postoperative patients participating in these studies will have tended to be younger and without many of the comorbid conditions that can occur. The aim of the studies was solely to test whether the drugs were analgesics.

Quality of the evidence

The quality of the evidence was good, using standard reviews examining standard clinical trials designed to measure the analgesic efficacy of drugs in sensitive assays in acute painful conditions. The overview process further removed any results likely to be the object of potential publication bias, so that only reliable results remained. This leaves a very large body of efficacy results presented both by all types of surgery, and split by the main painful conditions of dental pain and other (non-dental) painful conditions.

These results report a clinically useful level of pain relief over a sensible period, and with the common comparator of placebo. Though indirect comparisons are often criticised, this is one circumstance where indirect comparison can be justified because of the clinical homogeneity of trials and outcomes, and because data

like these have been tested and indirect comparison found to be a reasonable approach (Song 2003).

Potential biases in the overview process

No obvious biases in the overview process exist, for the reasons given above. One possible concern would be if placebo responses varied extensively, as that would indicate a lack of clinical homogeneity, and some potential biases with high placebo responses in some studies or reviews limiting the measurement of efficacy of NNT, which measures absolute risk difference (Moore 2011). Figure 7, Figure 8 and Figure 9 show the placebo responses according to review and number of participants given placebo for dental studies, other postoperative studies, and all combined.

Small data sets are clearly more variable than larger, as would be expected (Moore 1998). However, with few exceptions placebo response rates were within limited ranges, typically between 5% and 20% for dental pain and 15% to 30% for other painful conditions.

Most studies in the individual reviews will have been sponsored or conducted by manufacturers. This is not likely to be a source of any bias, since specific analyses have been conducted on some of the larger data sets to demonstrate that no industry bias exists in like-for-like comparisons (Barden 2006).

Agreements and disagreements with other studies or reviews

The only other overview of this type known to exist for acute pain studies is a non-Cochrane overview in dental pain (Barden 2004). The general methods used were similar and there were no major differences.

Other important issues

This overview has brought together information on a very large number of participants and studies that have had one single aim, namely to test whether a particular drug at a particular dose had analgesic properties. The basic design of the individual studies was developed in the 1950s and 1960s, and rigorously tested at the time when randomised and double-blind studies were needed for objective assessment of analgesic efficacy (Houde 1960). Even the earliest studies emphasised large individual variability, and the variability in treatment groups of small size (Keats 1950).

These methods of analgesic testing have, with little change, become the standard way of demonstrating that a drug is an analgesic, and are typically performed early in the development of any new pain-relieving drug. A number of relatively recent individual patient analyses have examined various aspects of their design, conduct, and reporting (Barden 2004; Barden 2006; Moore 2005; Moore 1997a; Moore 2011). All of these investigations confirmed the success of the model, though adverse event reporting was inadequate (Edwards 1999). Other individual patient analyses of the postoperative period have demonstrated that patient satisfaction is highly correlated with good pain relief, showing the value of the outcome of at least 50% maximum pain relief (Mhuircheartaigh 2009).

While the reviews in this overview provide an excellent assessment of analgesic efficacy, both in the fact of the effects and often in its magnitude, there remains a distinction between measurement in trials and effectiveness in the clinic, and for different types of acute pain. Relative efficacy is, however, maintained between different painful conditions. For example, in dental pain ibuprofen 400 mg (NNT 2.3) is better than paracetamol 1000 mg (3.2) and aspirin 1000 mg (4.2). In migraine the same pattern is seen (Derry 2010; Kirthi 2010; Rabbie 2010), while NSAIDs are better than paracetamol for osteoarthritis (Towheed 2006). Information about analgesic efficacy from individual systematic reviews and overviews can be incorporated into schema for effective management of acute pain (Frampton 2009), or into other acute painful conditions.

It is the case that many of the individual studies used both a placebo and an active comparator. However, the actual drug and dose of active comparator varied so widely that useful direct comparisons between any two drugs was not available. Despite the fact that indirect comparisons have been shown to be reliable where sufficient high-quality data existed (Song 2003), one further step might be taken. That step would involve the use of network meta-analysis to confirm the assessment of relative efficacy in the overview, and to explore further methodological issues in this highly standardised and homogeneous data set (Caldwell 2005; Salanti 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The major implication for practice is the knowledge that there is a body of reliable evidence about the efficacy of 46 drug/dose combinations in acute pain. These results include information of immediate practical relevance including the percentage of patients likely to benefit in the short term, and comparative information about the likely duration of effect - a matter of pragmatic importance. However, not every patient will achieve good pain relief even with the most effective drugs, and analgesic failure is to be expected with a single dose, or perhaps with particular drugs in particular patients. Failure to achieve good pain relief should be actively and regularly sought and rectified.

Acute pain treatment is often part of a complex of interactions between patient, condition, and desired outcome; the overview helps by presenting evidence from which rational choices and decisions can be made. The evidence linking short-term benefit with longer duration of action is particularly important in this regard.

The overview also, and importantly, demonstrates where there are major absences of evidence. Where there is no evidence of efficacy, the drugs in question should probably not be used to treat acute pain.

Implications for research

Possibly the main implication for research is methodological. There will be few circumstances where such a body of information exists in such a clinically homogenous data set and it might appear to be an ideal opportunity to test new methods in meta-analysis, like network meta-analysis.

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REFERENCES

References to included reviews

Moore RA, Derry S, McQuay HJ. Single dose oral aceclofenac for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007588.pub2]

Moore RA, Derry S, McQuay HJ. Single dose oral acemetacin for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007589.pub2]

Rees J, Oldman A, Smith LA, Collins S, Carroll D, Wiffen PJ, et al.Single dose oral aspirin for acute pain. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD002067]

Derry S, Barden J, McQuay HJ, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004233.pub2]

Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008099.pub2]

Moore RA, Derry S, McQuay HJ. Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007550.pub2]

Moore RA, Collins S, Rees J, Derry S, McQuay HJ. Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database of Systematic Reviews* 1999, Issue 1. [DOI: 10.1002/14651858.CD001440]

Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004768.pub2]

Wasey JO, Derry S, Moore RA, McQuay HJ. Single dose oral diflunisal for acute postoperative pain in adults.. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD007440.pub2]

Moore RA, Rees J, Derry S, McQuay HJ. Single dose oral dihydrocodeine for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002760]

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. Single dose dipyrone for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2010, Issue 9. Art. No.: CD003227. [DOI: 10.1002/14651858.CD003227.pub2]

Tirunagari SK, Derry S, Moore RA, McQuay HJ. Single dose oral etodolac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007357.pub2]

Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD004309. [DOI: 10.1002/14651858.CD004309.pub2]

Moore RA, Derry S, McQuay HJ. Single dose oral fenbufen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007547.pub2]

Traa MX, Derry S, Moore RA. Single dose oral fenoprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD007556.pub2]

Sultan A, McQuay HJ, Moore RA, Derry S. Single dose oral flurbiprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007358.pub2]

Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD008183.pub2]

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001548.pub2]

Moore RA, Derry S, Mason L, McQuay HJ, Rees J. Single dose oral indometacin for the treatment of acute postoperative pain. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004308.pub2]

Barden J, Derry S, McQuay HJ, Moore RA. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007355.pub2]

Hall PE, Derry S, Moore RA, McQuay HJ. Single dose

oral lornoxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007441.pub2]
Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 7. [DOI: 10.1002/14651858.CD006865.pub2]
Moll R, Derry S, Moore RA, McQuay HJ. Single dose oral mefenamic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD007553.pub2]
Moore RA, Derry S, McQuay HJ. Single dose oral meloxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007552.pub2]
Moore RA, Derry S, Moore M, McQuay HJ. Single dose oral nabumetone for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007548.pub2]
Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004234.pub3]
Kakkar M, Derry S, Moore RA, McQuay HJ. Single dose oral nefopam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007442.pub2]
Gaskell H, Derry S, Moore RA, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002763.pub2]
Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD001547.pub2]
Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004602.pub2]
Moore RA, Rees J, Loke Y, Derry S, McQuay HJ. Single dose oral piroxicam for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002762]
Bulley S, Derry S, Moore RA, McQuay HJ. Single dose oral rofecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD004604.pub3]
Moore RA, Derry S, McQuay HJ. Single dose oral sulindac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007540.pub2]
Moore OA, McIntyre M, Moore RA, Derry S, McQuay HJ. Single dose oral tenoxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007591.pub2]
Moore RA, Derry S, MooreM, McQuay HJ. Single dose oral tiaprofenic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007542.pub2]

Additional references

Barden 2004
Barden J, Edwards JE, McQuay HJ, Andrew Moore R. Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain* 2004;**107**(1-2):86–90. [DOI: 10.1016/j.pain.2003.09.021]

Barden 2006
Barden J, Derry S, McQuay HJ, Moore RA. Bias from industry trial funding? A framework, a suggested approach, and a negative result. *Pain* 2006;**121**(3):207–18. [DOI: doi:10.1016/j.pain.2005.12.011]

Beecher 1957
Beecher HK. The measurement of pain; prototype for the quantitative study of subjective responses. *Pharmacology Reviews* 1957;**9**:59–209.

Botting 2000
Botting RM. Mechanism of action of acetaminophen: is there a cyclooxygenase 3?. *Clinical Infectious Diseases* 2000; **31**(5):S203–10. [DOI: 10.1086/317520]

Caldwell 2005
Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;**331**:897–900. [DOI: 10.1136/bmj.331.7521.897]

Chandrasekharan 2002
Chandrasekharan NV. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure and expression. *Proceedings of the National Academy of Sciences of the United States of America* 2002;**99**:13926–31. [DOI: 10.1073/pnas.162468699]

Collins 1997
Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres?. *Pain* 1997;**72**:95–7.

Derry 2010
Derry S, Moore RA, McQuay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD008040.pub2]

Edwards 1999
Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *Journal of Pain and Symptom Management* 1999;**18**(6):427–37. [DOI: 10.1093/bja/aep300]

Edwards 2002
Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis

of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *Journal of Pain Symptom Management* 2002;**23**:121–30. [DOI: 10.1002/14651858.CD002067]

Fitzgerald 2001
FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *New England Journal of Medicine* 2001;**345**(6):433–42. [PUBMED: 11496855]

Flower 1972
Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature* 1972;**240**:410–1.

Frampton 2009
Frampton C, Quinlan J. Evidence for the use of non-steroidal anti-inflammatory drugs for acute pain in the post anaesthesia care unit. *Journal of Perioperative Practice* 2009; **19**(12):418–23.

Glenny 2005
Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al.International Stroke Trial Collaborative Group. Indirect comparisons of competing interventions. *Health Technology Assessment* 2005;**9**(26):1-134, iii-iv.

Graham 2005
Graham GG, Scott KF. Mechanism of action of paracetamol. *American Journal of Therapeutics* 2005;**12**(1):46–55. [ISSN: 1075–2765]

Hawkey 1999
Hawkey CJ. Cox-2 inhibitors. *Lancet* 1999;**353**(9149): 307–14.

Hinz 2008
Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB Journal* 2008;**22**(2):383–90. [DOI: 10.1096/fj.07-8506com]

Houde 1960
Houde RW, Wallenstein Sl, Rogers A. Clinical pharmacology of analgesics. 1. A method of assaying analgesic effect. *Clinical Pharmacology and Therapeutics* 1960;**1**:163–74.

Keats 1950
Keats AS, Beecher HK, Mosteller FC. Measurement of pathological pain in distinction to experimental pain. *Journal of Applied Physiology* 1950;**3**(1):35–44.

Kehlet 1998
Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Annals of Surgery* 2008; **248**(2):189–98. [DOI: 10.1097/SLA.0b013e31817f2c1a]

Kirthi 2010
Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008040.pub2]

McQuay 1997
McQuay H, Moore A, Justins D. Treating acute pain in hospital. *BMJ* 1997;**314**(7093):1531–5.

McQuay 2005
McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005;**81**:155–60. [DOI: 10.1136/pgmj.2004.024737]

McQuay 2006
McQuay HJ, Moore A. Methods of therapeutic trials. In: McMahon SB, Koltzenburg M editor(s). *Textbook of Pain*. Fifth. Churchill Livingstone, 2006:415–26.

Mhuircheartaigh 2009
Mhuircheartaigh RJ, Moore RA, McQuay HJ. Analysis of individual patient data from clinical trials: epidural morphine for postoperative pain. *British Journal of Anaesthesia* 2009;**103**(6):871–81. [DOI: 10.1093/bja/aep300]

Moore 1996
Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. *Pain* 1996;**66**:229–37. [DOI: 10.1016/0304-3959(96)03032-1]

Moore 1997a
Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997; **69**:287–94. [DOI: 10.1016/S0304-3959(96)03291-5]

Moore 1997b
Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997;**69**:127–30. [DOI: 10.1016/S0304-3959(96)03251-4]

Moore 1997c
Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997;**69**:311–15. [DOI: 10.1016/S0304-3959(96)03306-4]

Moore 1998
Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**:209–16. [DOI: 10.1016/S0304-3959(98)00140-7]

Moore 2003
Moore RA, Edwards J, Barden J, McQuay HJ. *Bandolier's Little Book of Pain*. Oxford: Oxford University Press, 2003. [DOI: 0-19-263247-7]

Moore 2005
Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. *Pain* 2005;**116**(3):322–31. [DOI: 10.1016/j.pain.2005.05.001]

Moore 2006
Moore A, McQuay H. *Bandolier's Little Book of Making Sense of the Medical Evidence*. Oxford: Oxford University Press, 2006. [ISBN: 0–19–856604–2]

Moore 2008
Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). *Systematic reviews in pain research: methodology refined*. Seattle: IASP Press, 2008:15–23. [ISBN: 978–0–931092–69–5]

Moore 2011
Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;**152**(5):982–9.

PIC 2008
Paracetamol Information Centre. www.pharmweb.net (accessed 16 February 2010).

Rabbie 2010
Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD008039.pub2]

Salanti 2008
Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Statistical Methods in Medical Research* 2008;**17**(3):279–301. [DOI: 10.1177/0962280207080643]

Schwab 2003
Schwab JM, Schluesener HJ, Laufer S. COX-3: just another COX or the solitary elusive target of paracetamol? . *Lancet* 2003;**361**:981–2. [DOI: 10.1016/S0140-6736(03)12841-3]

Shea 2007
Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al.Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10. [DOI: 10.1186/1471-2288-7-10]

Song 2003
Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;**326**(7387):472. [DOI: 10.1136/bmj.326.7387.472]

Thornton 2000
Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *Journal of Clinical Epidemiology* 2000;**53**(2):207–16. [DOI: 10.1016/S0895-4356(99)00161-4]

Towheed 2006
Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD004257.pub2]

Tramer 1998
Tramèr MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiologica Scandinavica* 1998;**42**(1):71–9. [PUBMED: 9527748]

WHO 2010
WHO. Pain ladder. www.who.int/cancer/palliative/painladder/en/. Accessed 12 July 2011.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Characteristics of included reviews

Review	Date assessed as up to date	Population	Interventions	Comparison interventions	Outcomes for which data were reported	Review limitations
Aceclofenac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Acemetacin 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found

Table 1. Characteristics of included reviews (*Continued*)

Aspirin 1999	2011 (update in progress)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Celecoxib 2008	2008	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Codeine 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Dexibuprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	Limited numbers
Dextro-propoxyphene ± Paracetamol 1999	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Diclofenac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Diflunisal 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Dihydrocodeine 2000	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Dipyrone 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Etodolac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews (*Continued*)

Etoricoxib 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Fenbufen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Fenoprofen 2011	2011	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	Limited numbers
Flurbiprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Gabapentin 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Ibuprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Indometacin 2004	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	Limited numbers
Ketoprofen and Dexketoprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Lornoxicam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Lumiracoxib 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews (*Continued*)

Mefenamic acid 2011	2011	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Meloxicam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Nabumetone 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Naproxen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Nefopam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Oxycodone ± Paracetamol 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Paracetamol + Codeine 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Paracetamol 2008	2008	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Piroxicam 2000	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Rofecoxib 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews (*Continued*)

Sulindac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Tenoxicam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Tiaprofenic acid 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found

AE = adverse event; SPID = summed pain intensity difference; TOTPAR = total pain relief

APPENDICES

Appendix 1. Search strategy for Cochrane Reviews

1. (postoperative):ti,ab,kw or (post NEXT operative):ti,ab,kw
2. (pain):ti,ab,kw or (painful):ti,ab,kw or (analgesi*):ti,ab,kw
3. (1 AND 2) in Cochrane Database of Systematic Reviews

Appendix 2. Results for remedication in individual reviews

			Remedication time				Percent remedicated by:							
			Number of		Median/Mean time to remedication (hours)		6 hours		8 hours		12 hours		24 hours	
Drug	**Dose**	**Condition**	**Studies**	**Patients**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Celecoxib	200	All	5	805	6.6	2.6								
		Dental	4	523	6.1	1.5							74	94

(*Continued*)

		Other											
	400	All	4	620	8.4	1.6						63	91
		Dental	4	620	8.4	1.6						63	91
		Other											
Codeine	60	All	4	275	2.7	2	38	46					
		Dental											
		Other											
Codeine + Paracetamol	30/300	All	5	455	3.9	2.9	48	57					
		Dental											
		Other											
	60/600/650	All	10	995	4.1	2.4	59	80					
		Dental											
		Other											
	60/800/1000	All	2	127	5	2.3							
		Dental											
		Other											
Dexketopro-	10/12.5	All					54	74					

(*Continued*)

fen														
		Dental												
		Other												
	20/25	All					52	75						
		Dental	2		4.2	2.2								
		Other												
Diclofenac	25	All	4	502	3.8	1.5	51	71						
		Dental												
		Other												
	50	All	5	457	4.3	2	35	68						
		Dental												
		Other												
	100	All	6	683	4.9	1.9	37	73						
		Dental												
		Other												
Diflunisal	125	All												
	250	All												
	500	All			9.8	3.2	27	66			53	87		
		Dental												
		Other												
	1000	All			10.9	3.2	23	75			43	88		

(*Continued*)

Etodola	50	All												
		Dental												
		Other												
	100	All												
		Dental												
		Other												
	200	All					61	77						
		Dental					64	88						
		Other												
	400	All					63	77						
		Dental					59	88						
		Other												
Etoricoxib	60	All												
		Dental												
		Other												
	120	All			20	2	50	92						
		Dental			>24	2								
		Other												
	180/240	All												
		Dental												
		Other												

(*Continued*)

Flurbiprofen	25	All					35	70						
		Dental												
		Other												
	50	All					25	66						
		Dental												
		Other												
	100	All					16	68						
		Dental												
		Other												
Gabapentin	250	All	3	327	2.4	2.1	69	86						
		Dental												
		Other												
Ibuprofen	50	All					29	50						
		Dental												
		Other												
	100	All					38	64						
		Dental					59	80						
		Other												
	200	All	10	1807	4.7	2.1	48	76						

(*Continued*)

		Dental					53	83						
	200 soluble	Dental												
	200 standard	Dental												
		Other												
	400	All	31	3548	5.6	1.9	42	79						
		Dental					41	80						
	200 soluble	Dental												
	200 standard	Dental												
		Other												
	600	All												
		Dental												
		Other												
	800	All												
		Dental												
		Other												
Ketoprofen	12.5	All					80	98						
		Dental												
		Other												

(*Continued*)

	25	All					46	79						
		Dental												
		Other												
	50	All					48	81						
		Dental												
		Other												
	100	All					43	85						
		Dental												
		Other												
Lornoxicam	4	All												
		Dental												
		Other												
	8	All	2		4.7	1.4								
		Dental												
		Other												
Lumiracoxib	400	All	4	548	9.4	1.7					64	91		
		Dental												
		Other												
Mefenamic acid	500	All					47	62						

(*Continued*)

		Dental											
		Other											
Naproxe	200/220	All											
		Dental											
		Other											
	400/440	All											
		Dental											
		Other											
	500/550	All	8	711	8.9	2					67	82		
		Dental											56	96
		Other												
Oxycodone	5	All	2	237	2.3	2.1	83	88						
		Dental												
		Other												
	15	All												
		Dental												
		Other												
Oxycodone + paracetamol	5/325	All			4.3	2	66	85						

(*Continued*)

		Dental											
		Other											
	10/650	All			9.8	1.5	55	83	86	88			
		Dental											
		Other											
	10/1000	All			8.7	1.1						67	87
		Dental											
		Other											
Paracetamol	500	All					35	63					
		Dental											
		Other											
	600/650	All	7	461	3.5	2.4	52	65					
		Dental											
		Other											
	975/1000	All	16	1540	3.9	1.7	53	72					
		Dental											
		Other											
Rofecoxib	50	All	20	3182	13.8	1.9			27	74			

(*Continued*)

		Dental	18	2872	16.2	1.7			20	79	32	89	52	87
		Other												

Note that empty cells indicate absence of data

HISTORY

Protocol first published: Issue 9, 2010

Review first published: Issue 9, 2011

CONTRIBUTIONS OF AUTHORS

SD and RAM carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. HJM and PW acted as arbitrators. All authors were involved in discussing the results writing and approving the overview.

RAM/SD will be responsible for updating the overview.

DECLARATIONS OF INTEREST

All authors have received research support from charities, government and industry sources at various times. RAM, HJM, and PW have consulted for various pharmaceutical companies in the past. RAM and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics [*administration & dosage; adverse effects]; Pain, Postoperative [*drug therapy]; Review Literature as Topic; Tooth Extraction [adverse effects]

MeSH check words

Adult; Humans

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AMA submission – TGA/ACMS codeine schedule 4 proposal

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The Advisory Committee on Medicine Scheduling (ACMS) has not provided any summary of the evidence base underpinning the proposal to shift current Schedule 3 preparations of codeine to Schedule 4. No specific information about the current risks and harm, the problem that up-scheduling would solve, or the expected impact on health care of the regulatory change has been provided

The AMA is therefore unable to provide a definitive view but makes the following observations.

The AMA agrees that codeine dependence is a real concern and that the side effects from taking excessive amounts can be very serious. There have been several recent studies indicating an increase in misuse and harm.

This may justify a decision by the ACMS to up-schedule some codeine preparations, particularly the higher dose and combination compound products. There is also some inconsistency in current regulation which could be addressed, for example, two Panadeine Extra tablets (the recommended dose) available over the counter is equivalent to one Panadeine Forte which requires a prescription.

However up-scheduling in isolation is unlikely to address the problems of misuse. Improved education about effective and safe pain management options for the public, pharmacists and general practitioners is also necessary.

The AMA continues to advocate for the implementation of the Electronic Recording and Reporting of Controlled Drugs system in each state and territory. This system would allow doctors and pharmacists to monitor in real time the prescribing and dispensing a range of medicines with the potential for misuse and harm, not only Schedule 8 medicines.

There are also alternatives to up-scheduling that could be considered, for example, introducing pharmacy requirements to record codeine dispensing in the same way as for pseudoephedrine.

It is also worth noting that a decision to up-schedule would likely lead to increased Medicare and PBS costs through more numerous medical practitioner consultations and prescriptions, at a time when the Government is seeking to reduce its outlays in these areas.

MAY 2015

Contact

[redacted]

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6 May 2015

The Secretary
Scheduling Secretariat
GPO Box 9848
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RE: Proposal to reschedule the current Schedule 3 codeine entry to Schedule 4

I write in response to your invitation for public comment regarding a proposal to delete the Schedule 3 entry for codeine, and reschedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence.

Please find attached my submission in support of the proposal, which reflects my views as a Victorian coroner but does not necessarily reflect the views of Victoria's other coroners.

I will be pleased to consider any requests from you for further information or clarification regarding my submission. I can be contacted via my Solicitor Kate Hamilton on (03) 8688 0703 or < Kate.Hamilton@coronerscourt.vic.gov.au >.

Yours sincerely

[redacted]

Coroners Court of Victoria

[redacted]

Submission

Preliminary matters

Structure and composition

Under subsection 52D(2) of the *Therapeutic Goods Act 1989* (Cwth) ('the Act'), the Secretary of the Department of Health and Ageing may amend the current Poisons Standard. In exercising this power, the Secretary must take the following matters into account where relevant under subsection 52E(2) of the Act:

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

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

(c) the toxicity of a substance;

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

(e) the potential for abuse of a substance;

(f) any other matters that the Secretary considers necessary to protect public health.

My submission comprises a statement of support for the proposal to reschedule the current Schedule 3 codeine entry to Schedule 4, followed by a selection of case studies that illustrate the matters listed in (a), (c) and (e) above. A brief concluding section reiterates the importance of the rescheduling in the context of broader efforts to reduce pharmaceutical drug-related harms.

Acknowledgements

I thank Dr Jennifer Pilgrim (Department of Forensic Medicine, Monash University), Dr Malcolm Dobbin (Victorian Department of Health and Human Services) and Dr Jeremy Dwyer (Coroners Court of Victoria) for their assistance in preparing this submission.

Statement of support for the proposal

Victoria's coroners regularly investigate deaths where Schedule 3 codeine combination preparations are found to play a direct causal role, including deaths associated with both acute use (overdose) and chronic use (for example gastric ulcers, renal necrosis and liver failure). Dependence upon Schedule 3 codeine combination preparations is a common theme across these deaths, and also recurs in deaths from other causes including particularly non-overdose suicides.

For these reasons I support the proposed rescheduling as a means to assist prescribers and dispensers to monitor how patients access codeine combination preparations. I anticipate the rescheduling will create new opportunities for both prescribers and dispensers to detect patterns of dependent and harmful misuse, and intervene to reduce associated risks of harm and death.

Case studies

I include in my submission 10 brief de-identified case studies drawn from deaths that I and my colleagues have investigated. I selected these case studies because they are

representative of the circumstances in which Victorian deaths involving Schedule 3 codeine combination preparations occur. I hope they provide some insight for the Scheduling Secretariat into the individual stories that underpin my concerns about the use and misuse of Schedule 3 codeine combination preparations, the potential for developing dependence on these preparations, and the fatally toxic effects of the preparations when misused.

Case study 1

An older woman commenced using Mersyndol (a Schedule 3 codeine-paracetamol-doxylamine preparation) approximately eight years before her death to treat back pain, migraine and sleep issues. Over time she developed a significant Mersyndol dependence, using between 10 and 20 tablets per day. She would attend multiple pharmacies to purchase it, as well as asking others to purchase it on her behalf, which caused significant tensions in her relationships with family and friends; some family members eventually refused any contact with her because of her drug seeking behaviour.

The woman was found unconscious with several full and empty packets of Mersyndol nearby. She was transported to hospital, where she was found to be suffering shock, liver failure and kidney impairment with a toxic paracetamol level, and died without regaining consciousness. The forensic pathologist who conducted the post-mortem examination formulated her medical cause of death as: "1(a) Complications following paracetamol overdose."

Case study 2

A young man developed a dependence on Nurofen Plus (a Schedule 3 codeine-ibuprofen combination) after using it to assist in reducing his use of cannabis. At his peak, he was taking up to 60 Nurofen Plus tablets per day. With assistance from an addiction specialist and psychiatrist, he reduced his usage to approximately 24 tablets per day, and reported that he was feeling in control of the drug.

The man experienced severe stomach pain that he attributed to effects of withdrawal from the Nurofen Plus. Family members subsequently found him unconscious having vomited blood, and attending paramedics were unable to revive him. The forensic pathologist who conducted the post-mortem examination found that he suffered from several conditions including perforated peptic ulcer, peritonitis and acute tubular necrosis probably associated with the long-term ibuprofen use. The investigating coroner found that the cause of death was:

> 1(a) Peritonitis; 1(b) Perforated gastric ulcer; 1(c) Clinical history of use of non-steroidal anti-inflammatory medications

The coroner commented that:

> [his] death from the effects of long term abuse of Nurofen / Nurofen Plus should serve as a timely reminder that the abuse of readily available or over-the-counter medication can be just as harmful as the abuse of illicit substances, and potentially even fatal.

Case study 3

A young man with a diagnosed mental illness had a 15-year history of drug dependence including cannabis, heroin and alcohol. After he entered a methadone program for treatment of heroin dependence, he commenced abusing Schedule 3 codeine combination preparations including Panadeine (a codeine-paracetamol preparation), which he would take in large quantities together with alcohol and prescribed diazepam.

The man's poly-drug use was a contributing stressor in the breakdown of his relationships with his partner, child and family members, his loss of employment, and his ongoing mental ill health. He died in circumstances that were consistent with intentional self-harm.

Case study 4

A middle-aged man had no clinically documented history of drug dependence. He suffered a workplace injury approximately 20 years before his death, as well as a more recent cycling-related injury. He was found deceased in his bedroom with several medications nearby including Mersyndol (a Schedule 3 codeine-paracetamol-doxylamine preparation), metoprolol, oxazepam, paracetamol, rabeprazole, oxycodone and nitrazepam.

The forensic pathologist who conducted the post-mortem examination noted that the man had elevated levels of codeine, paracetamol and doxylamine in his blood, and therapeutic levels of amitriptyline, oxazepam and oxycodone. The investigating coroner found his cause of death was: "1(a) Mixed drug toxicity (codeine, paracetamol, doxylamine, amitriptyline, oxazepam, oxycodone)".

Case study 5

A young man who resided in a low-level care facility was prescribed a range of psychiatric medications including olanzapine and sertraline to treat his mental ill health. He was known to be dependent on alcohol, cannabis and amphetamine, and also took large quantities of Panafen Plus (a Schedule 3 codeine-ibuprofen preparation), often with alcohol.

Approximately 36 hours before the man was found deceased, he was observed to take around 60 Panafen Plus tablets while drinking a pre-mixed alcoholic beverage. The next day he remained in bed sleeping and refused to get up. Eventually he rose briefly to attend dinner and take his evening medications; he was observed to be somewhat dazed at this stage. He returned to his bedroom, and the next morning was found deceased with several medication packets (including empty packets of Panafen Plus) located nearby.

The forensic pathologist who conducted the post-mortem examination noted that several drugs were detected in the man's blood, including sertraline, diazepam, olanzapine, ibuprofen and codeine. The forensic pathologist concluded the cause of death was unascertained as autopsy findings were non-specific; however the possibility of drug-related respiratory depression was noted.

Case study 6

A middle-aged woman who was socially isolated attended a large number of different doctors to obtain prescribed drugs. Little is known of the circumstances of her death, as she resided alone and her body was found some days after death. Police noted a range of medication packets (both empty and partially used) in her apartment including Codalgin (a Schedule 3 codeine-paracetamol preparation), paracetamol, diazepam and promethazine.

The forensic pathologist who performed the post-mortem autopsy noted a very high level of codeine and paracetamol in blood samples, as well as an elevated level of promethazine. The investigating coroner found the cause of the woman's death was "1(a) Combined drug toxicity".

Case study 7

A middle-aged woman had, over the course of some years, developed a dependence on benzodiazepines and various Schedule 3 codeine combination preparations including Mersyndol (a codeine-paracetamol-doxylamine preparation) and Panafen

Plus (a codeine-ibuprofen preparation). She attended a number of doctors and pharmacies to support this dependence; however a persistent doctor and a drug treatment service assisted her in making significant progress towards stabilising and reducing her drug use.

In the two days leading up to the woman's death, she attended a pharmacy where she was not a regular customer to purchase packets of Panafen Plus. The available evidence suggests she consumed approximately 60 Panafen Plus caplets during these two days together with 50 diazepam tablets. She was found unconscious at home by family members who had seen her in a very drowsy state the previous evening; emergency services were unable to revive her.

The forensic pathologist who conducted the post-mortem examination noted a very elevated post-mortem codeine level in the woman's blood, along with citalopram, diazepam and ibuprofen. The coroner found that her cause of death was "1(a) Combined drug toxicity", and commented that the death occurred despite the progress doctors had made in treating her drug dependence:

> It is therefore at least noteworthy, that the main ingredient in her death was the codeine which she was able to buy "over the counter" in combination with ibuprofen, and that as a precaution she did so at another pharmacy, where she was not known.

Case study 8

A middle-aged man developed an addiction to pharmaceutical opioids over the course of approximately 15 years after first being prescribed them to treat migraine and back pain. He attended multiple doctors to obtain scripts for opioids including morphine and pethidine, and would frequently report he had lost scripts or medications in order to obtain further drugs.

When concerned family members attended the man's house and found him deceased, analgesic drugs were located including multiple empty packets of Codalgin and Chemists Own Pain Relief (both Schedule 3 codeine-paracetamol preparations). The indication in the circumstances was that he supplemented his prescribed opioids by purchasing these codeine combination preparations. The forensic pathologist who performed the post-mortem autopsy noted a range of drugs were detected including codeine and paracetamol, morphine, diazepam and sertraline. The investigating coroner concluded the death was caused by the combination of drugs in a setting of heart disease.

Case study 9

A middle-aged man developed a long-term addiction to prescribed and over-the-counter pharmaceutical drugs. According to his partner, he would travel between several towns in Gippsland visiting different doctors to obtain scripts for drugs in excess of clinical need, and visiting pharmacies to purchase "any type of codeine he could obtain". The man's partner observed that he would often pass out in the evening from "taking too many tablets", and his high-level drug use contributed to both financial and relationship difficulties. He died in circumstances that indicated probable intentional self-harm.

Case study 10

A young man had an established history of abusing Nurofen Plus (a Schedule 3 codeine-ibuprofen preparation) and Panadeine (a Schedule 3 codeine-paracetamol preparation) as well as multiple prescribed pharmaceutical drugs. At one stage, family members stated that he needed to take 80 codeine-containing tablets per day "just to feel normal", and was unable to overcome his addiction despite engagement with the drug and alcohol sector.

The man was found deceased at his parents' home, with several packets of medications nearby including multiple brands of Schedule 3 codeine-ibuprofen preparations (Nurofen Plus, Panafen Plus and a generic brand). The forensic pathologist who performed the post-mortem autopsy advised that oxycodone was detected at an elevated level in his blood, with therapeutic levels of codeine, paracetamol, tramadol, diazepam and temazepam. The investigating coroner determined the cause of death was: "1(a) Bilateral bronchopneumonia on the background of elevated levels of narcotic analgesics".

Concluding comment

Pharmaceutical drugs contribute to approximately 80% of fatal overdoses investigated by Victorian coroners every year. Additional deaths occur as a result of chronic pharmaceutical drug misuse, and/or in a context of pharmaceutical drug dependence. Coronial investigations confirm that for most deaths that directly or indirectly involved pharmaceutical drugs, the deceased accessed the drugs through the health system rather than via theft, diversion, importation, illegal manufacture or otherwise.

Reducing the harms associated with pharmaceutical drugs in Victoria requires significant changes in how drugs are made available to patients through the health system, and I believe the rescheduling of codeine combination preparations is one such change that will make a positive difference.

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May 6, 2015

Dr Paul Brent
Chair
Advisory Committee on Medicines Scheduling
c/o Medicines Scheduling Secretariat
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Dear Dr Brent

RE: Codeine - Public Consultation on proposed amendments to the Poisons Standard

As a clinical pharmacologist, anaesthetist with intensive care training and pain medicine specialist 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

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

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.

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.

- **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.

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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.

- **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 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.

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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.

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.

[redacted]

[redacted]

To: the Secretary, Advisory Committee on Medicines Scheduling

I am a pharmacist employed by the [redacted] as the GP and Pharmacy Liaison Officer and as a counsellor in the Opioid Treatment Program. The patients that we treat are there because of an addiction to opioids.

The majority of the new patients that are currently coming into treatment at our service have become addicted to pharmaceutical opioids, prescription opioid, and more often, to over-the-counter (OTC) medications containing codeine, which they can access very easily from pharmacies, and they do visit multiple pharmacies.

The issue with these OTC codeine containing medications is that the patients start increasing the dose (codeine being a very weak analgesic), because they have now become addicted to the codeine, thereby also increasing the amount of ibuprofen or paracetamol that they consume, with drastic consequences.

We have had patients transferred to us from hospital after suffering gastric bleeding, and one young male patient had been in renal failure when brought into hospital after regularly consuming about 70-80 ibuprofen/codeine combination tablets daily for a number of weeks, chasing his addiction to codeine.

We see patients who have been caught in this addiction cycle, trying to stop, sometimes managing to quit, but relapsing and starting the cycle again as these medication are so easily obtained. The effects on them and on their families can be catastrophic.

There have been a number of studies, eg Nielsen et al (2014)1, which show that for patients coming into treatment for opioid addiction, OTC codeine has been their source of opioid.

Given my experience with the problems that these codeine combination medications can cause**, I would strongly support that they be removed from the OTC market and made prescription only**. The codeine provides only a very limited advantage to the non-opioid analgesic, but can, and has, created serious problems.

Making them prescription-only would, at the very least, allow these medications to be monitored.

Regards

[redacted]

[1]. 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.

From: [redacted]
Sent: Wednesday, 6 May 2015 6:32 PM
To: Medicines Scheduling
Subject: Proposed Amendments to the Poisons Standard (Medicines)

Dear members of the TGA,

I would like to register my support for the rescheduling of Codeine containing products to Schedule 4.
I am a clinically trained professional (Prosthetist & Orthotists) who has worked within the pharmaceutical industry for 13 years.

In my submission I will not focus on the established issues that is attached to codeine. Instead, I would like to submit my comments on the common practice of dispensing codeine products in Australian retail pharmacies. My current role involves me visiting, along with my sales reps, anywhere between 5 – 9 pharmacies per day for most days in the week.

I have been astounded to see the ease at which patients can obtain codeine based products and the lack of pharmacist intervention that accompanies this dispensing.
On a daily occurrence, patient's requesting codeine based products such as [redacted], are able to have the product handed over to them with a simple 'wave' to the pharmacist by the retail assistant. The retail assistant, on more occasions than not, will simply call out to the pharmacist and inform them that pt. X would like to purchase said product and the pharmacist will either give the nod of approval or ask if they have used the product before. An answer in the positive will usually suffice for the product to be dispensed.

I challenge anyone, without disclosing their intentions, to visit a pharmacy and observe this practice in action.

It has been argued that pharmacists are trained to monitor and filter out the appropriate patients who genuinely would benefit from these codeine based products; and I agree.
However, this is not the issue. The issue is, as mentioned above, in practice there is little, if any, genuine consultation with the pharmacist.

Unfortunately, it is a commercial reality that pharmacists are required to keep the scripts churning out and the thought process is often biased by commercial pressures.
So, as I've heard before, if the pharmacist doesn't give the patient what they want, the patient will simply go elsewhere and buy it. That translates to a lost sale that is unacceptable to the majority of business owners.

I am in no way suggesting that every pharmacist behaves in this way, however, I genuinely believe that the majority do; I see it daily.

The argument that by making codeine an S4 would potentially mean Dr's. would now prescribe stronger pain relief, I feel is without foundation.
If anything, it would allow Dr's, who are not under the same commercial pressures as retail pharmacies, to diagnose whether a pt. genuinely has pain that isn't being controlled by their OTC medication.
If not, then there is a much stronger chance that the pt's pain will be further treated in a different way. This could ONLY be available through a GP's diagnosis, network of pain specialists or other medications etc.

It would also mean that Dr's. could deal with addiction in a much more appropriate clinical way, such as opioid addiction therapies etc.

At present, the lack of clinical intervention is frightening and potentially irresponsible on many different levels.

I look forward to your considerations and hopefully patient and community care is the winner.

Kind regards,
Artie

[redacted]

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