Codeine has little role in pain management so what do I use now?

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DECLARATION OF CONFLICT OF INTEREST

- Although I work for Queensland Health this presentation in no way indicates their support. The comments I make are my own, made as a clinical pharmacist academic.
- I do not represent either The Pharmacy Guild or Pharmaceutical Society of Australia
- I am a member of the Society of Hospital Pharmacists of Australia who support codeine rescheduling
- I have received no payments from any Pharmaceutical Company regarding this work.
- I have received no research grants from any Pharmaceutical Company

Painkillers with codeine won't be available over the counter from 2018

By political reporters Dan Conifer and Francis Keany

Updated 20 Dec 2016, 11:57am

Painkillers containing codeine will no longer be available over the counter from 2018, the federal drug regulator has announced.

The Therapeutic Goods Administration's (TGA) principal medical officer, Dr Tim Greenaway, said the medication will change from Schedule 2 or 3 to Schedule 4 in February 2018 because consumers frequently became addicted to codeine.

"It's important that people realise that the decision's been taken based on safety predominantly and based on the risk of abuse," Dr Greenaway said.

"Medication that are available over the counter or through pharmacies should be substantially safe and not subject to abuse."

"This is clearly not the case with codeine."

The move will bring Australia into line with the United States, Japan and most of Europe.

The decision has been criticised by a peak pharmaceutical group, Australian Self Medication Industry (ASMI), which argued the drug should be kept available over the counter but with real-time

PHOTO: Consumers can become addicted to codeine, the TGA says. (ABC News: Bridget Judd)

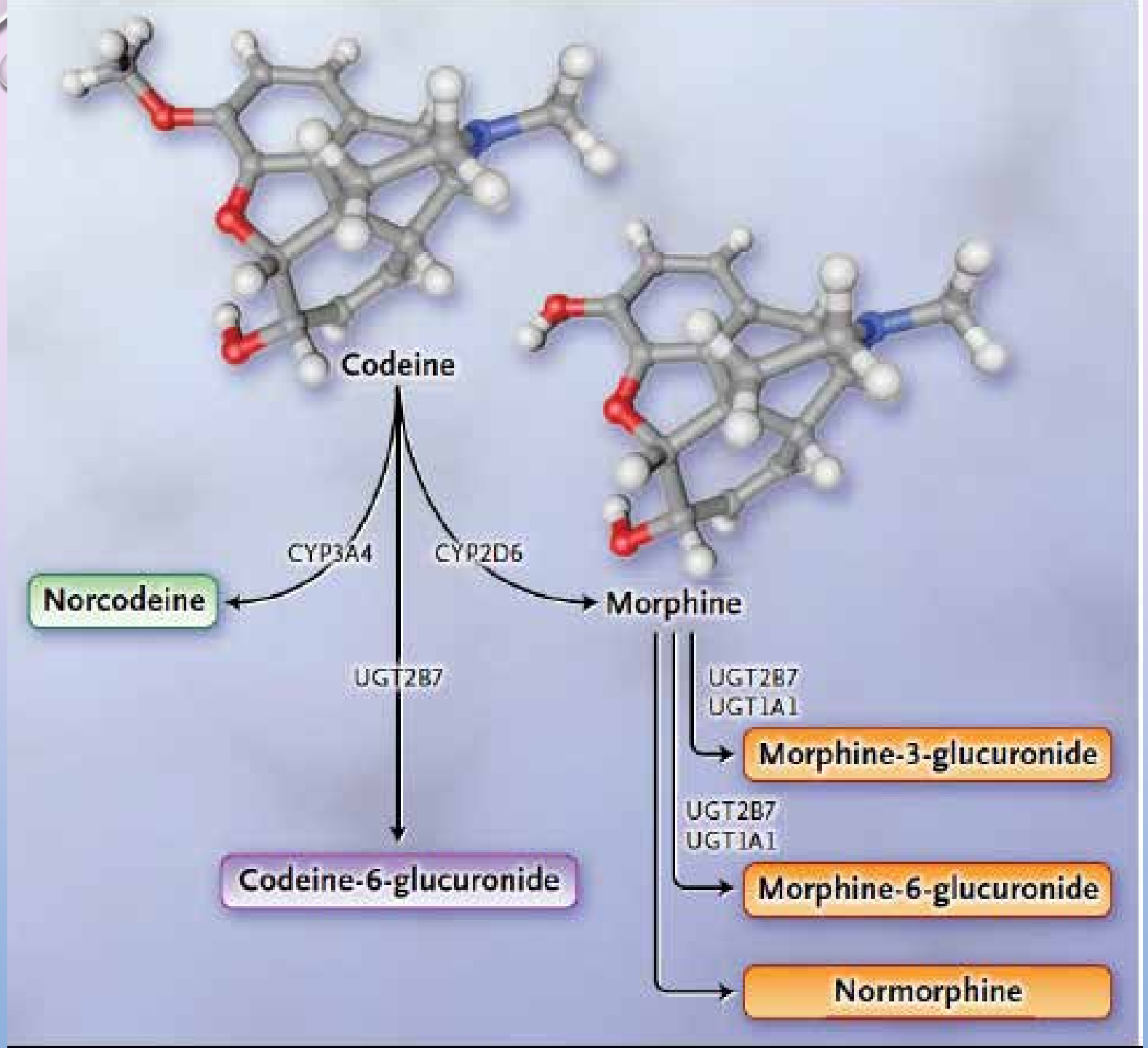
RELATED STORY: Push for mandatory national codeine database to prevent 'pharmacy shopping'

MAP: Australia

Key points:

- Painkillers containing codeine will no longer be available over the counter from 2018
- Extra regulation is already enforced in the United States, Japan and most of Europe
- TGA says the move is to reduce the number of consumers addicted to codeine

Pharmacogenetics


Codeine
CYP3A4
CYP2D6
Norcodeine
Morphine
UGT2B7
UGT2B7
UGT1A1
Morphine-3-glucuronide
UGT2B7
UGT1A1
Morphine-6-glucuronide
Codeine-6-glucuronide
Normorphine

Motherisk Update
Current Practice • Pratique courante

Safety of codeine during breastfeeding

Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine

Parvaz Madadi Gideon Koren, MD, FRCPC James Cairns, MD David Chitayat, MD Andrea Gaedigk, PHD
J. Steven Leeder, PHARMD, PHD Ronni Teitelbaum, MSC Tatyana Karaskov, MD Katarina Aleksa, PHD

ABSTRACT

QUESTION Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers?

ANSWER When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, newborns might be exposed to toxic levels of morphine when breastfeeding. Options to reduce this risk include discontinuing codeine after 2 to 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.

RÉSUMÉ

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 June 2013
EMA/385716/2013

Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation

The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by consensus a series of risk minimisation measures to address safety concerns with codeine-containing medicines when used for the management of pain in children. Codeine is an opioid that is authorised as a painkiller in adults and children. The effect of codeine on pain is due to its

Link to induction of severe respiratory depression in children with CYP2D6 ultra-metaboliser genotype and in children (younger than18years) with Obstructive Sleep Apnoea having a tonsillectomy and adenoidectomy.

Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

TO THE EDITOR: Obstructive sleep apnea is not rare in children with hypertrophic tonsils, and the common curative procedure is adenotonsillectomy.[1] Codeine is commonly prescribed for pain after adenotonsillectomy.[2] The respiratory depressant effects of opioids may influence the occurrence of respiratory complications.[3] An estimated one third of cases of apnea in children are not resolved after adenotonsillectomy.[4]

We report on the case of a healthy 2-year-old boy weighing 13 kg, with a history of snoring and sleep-study–confirmed sleep apnea, who underwent elective adenotonsillectomy. The outpatient surgery was uncomplicated, and 6 hours after surgery the boy received 10 mg of meperidine and 12.5 mg of dimenhydrinate intramuscularly and was sent home with instructions for 10 to 12.5 mg of codeine and 120 mg of acetaminophen syrup

detected in the femoral blood by means of gas chromatography–mass spectrometry; there was no evidence of other drugs or metabolites. Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the *CYP2D6* allele, resulting in the ultrarapid-metabolizer phenotype.

In this case, the prescribed and administered dose of codeine was within the recommended range of 1 to 3 mg per kilogram of body weight per day.[1,2] Increased conversion of codeine to morphine due to ultrarapid metabolism resulted in toxic accumulation of morphine. The concentration of 32 ng per milliliter of morphine at autopsy exceeded therapeutic levels and may have contributed to respiratory depression and death. Respiratory depression has been shown in young children with serum morphine concentrations exceeding 20 ng per milliliter.[3]

Incidence of the CYP 2D6 enzyme genotypes among different ethnic populations

Phenotype	% Caucasian	% Horn of Africa (Ethiopia, Somalia, Eritrea)	% Asian	% Hispanic
Poor Metaboliser (PM)	3-10	1.8-8.1	0-1.2	2.2-6.6
Intermediate Metaboliser (IM)	1-2	N/A	51	N/A
Ultrarapid/ extensive Metaboliser (EM)	0.8-4.3	29	0.9	1-7

N/A – not available

Analgesic Efficacy

Lack of evidence for efficacy at any dose <15mg

Efficacy in Acute Pain

- Oral codeine in a single dose of 60mg is not very effective in post operative setting (Derry 2010 Cochrane evaluation of 35 RCTS [n= 2475]) Effective for some individuals but does not compare favourably with alternatives e.g. paracetamol or NSAIDs alone
- There is NO data on combinations of oral paracetamol with doses <30mg
- 25.6-60mg Codeine improves analgesic efficacy of ibuprofen 400mg (Derry 2013 Cochrane evaluation of 6 RCTs [n=1342]) At least 50% maximum pain relief in 64% on combination c.f. 18% on placebo but very limited data to demonstrate combination better than either drug alone

ABDEL-SHAHEED et al. TGA review 2016

- 14 placebo-controlled RCTs (n=788) evaluated
  - 10 pain and 4 antitussive effects
- Data pooled using random effects model with strength of evidence assessed using GRADE assessment tool
- High quality evidence that in immediate low grade pain relief (MD ~12%)
- Effect declines at 4-6 hours in single dose studies (MD ~2.8%)

NB Modern IMMPACT guidelines for pain management only rate pain reduction (MD) of >30% significant and >50% highly significant

Low dose evidence that codeine products reduce cough severity but not frequency

Immediate term effects from OTC combination codeine at 3 hrs –SINGLE DOSE

Treatment, Follow Up Period and Reference	Treatment Mean	Treatment SD	Treatment Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference 95% CI
Paracetamol 300 mg + codeine 30 mg 3h [33]	54	22.2	40	65	22.2	40	20.8%	-11.00 [-20.73, -1.27]
Ibuprofen 400 mg + codeine 30 mg 3h [8]	30	22.2	46	40	22.2	47	24.2%	-10.00 [-19.02, -0.98]
Ibuprofen 200 mg + codeine 15 mg 3h [25]	30.4	22.2	32	42.8	22.2	9	7.3%	-12.40 [-28.82, 4.02]
Ibuprofen 400 mg + codeine 30 mg 3h [25]	27.6	22.2	33	42.8	22.2	9	7.4%	-15.20 [-31.56, 1.16]
Ibuprofen 200 mg + codeine 30 mg 3h [31]	27.5	22.2	36	43.8	22.2	35	18.5%	-16.30 [-26.63, -5.97]
Aspirin 375 mg + codeine 30 mg + caffeine 30 mg 3h [78]	15	20	30	23.8	16.3	26	21.8%	-8.80 [-18.31, 0.71]
Total (95% CI)			**217**			**166**	**100.0%**	**-11.67 [-16.11, -7.23]**

$I^2 = 0\%$

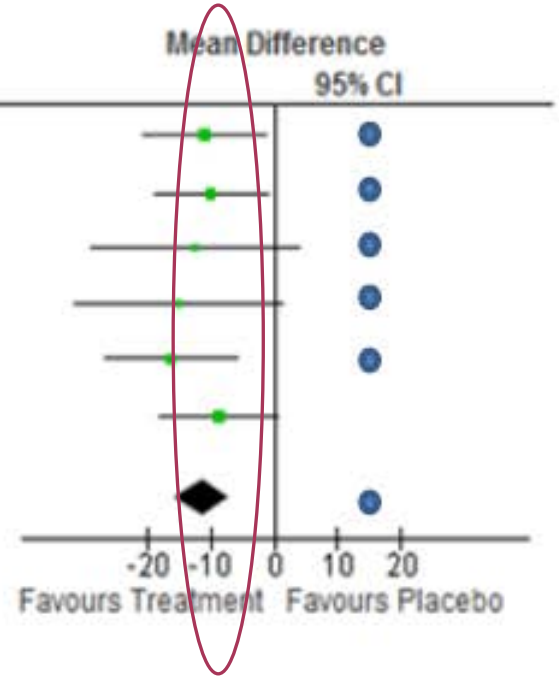


Figure 2: Pooled immediate term effects from OTC combination codeine medicines at 3 hours (3 h)

The pooled effect of -11.67 is considered a clinically important pain relieving effect. All single dose trials. The blue dots signify treatment effects >10 units which are considered clinically worthwhile.

11.7% DIFFERENCE

Short term effects from OTC combination codeine at 4-6 hrs

Treatment, Follow up period and reference	Treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference 95% CI
Paracetamol 300 mg + codeine 30 mg 6h [33]	71	22.2	40	68	22.2	40	26.6%	3.00 [-6.73, 12.73]
Ibuprofen 400 mg + codeine 30 mg 6h [8]	35	22.2	46	41.3	22.2	47	31.0%	-6.30 [-15.32, 2.72]
Ibuprofen 200 mg + codeine 15 mg 5h [25]	28.5	22.2	32	32	22.2	9	9.4%	-3.50 [-19.92, 12.92]
Ibuprofen 400 mg + codeine 30 mg 5h [25]	20.8	22.2	33	32	22.2	9	9.4%	-11.20 [-27.56, 5.16]
ibuprofen 200 mg + codeine 15 mg 5h [31]	30	22.2	36	31.3	22.2	35	23.6%	-1.30 [-11.63, 9.03]
Total (95% CI)			**187**			**140**	**100.0%**	**-2.84 [-7.86, 2.18]**
$I^2 = 0\%$								

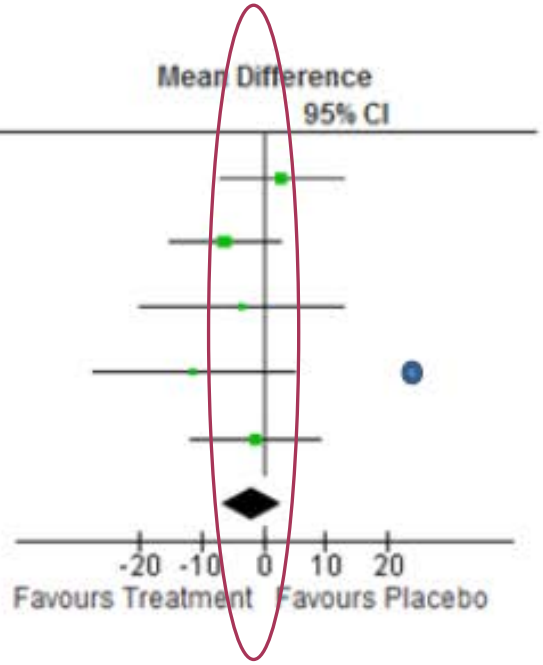


Figure 3: Pooled short term effects of combination OTC medicines containing codeine at time points from 4 hours (4h) to 6hours (6h)
The pooled effect of -2.84 was not considered clinically worthwhile. The blue dots signify treatment effects >10mm which are considered clinically worthwhile.

~3% DIFFERENCE

Problems with codeine-combination analgesic studies

Study	Country	Indication	Intervention	Mean Age yrs	Number	Outcome	Follow up
Ahlstrom 1985	Sweden	Removal impacted wisdom tooth	A Para1000 + C60 B Para500 + C30 C+ D Placebo	31 29 28 + 28	44 43 85	0-10 VAS 2nd dose could be taken	12hr
Cater 1985	UK	Post episiotomy	Ibu 400 + C 30 Placebo	23.1 22.7	46 47	0-8 VAS Single dose	8hr
Frame 1986	UK	Removal impacted 3rd molar tooth	C Ibu200 + C15 D Ibu400 + C30 E Ibu800 + C60 Placebo	23.6 25.1 23.7 23.6	33 All study	0-8 VAS Single dose	5hr
Gershman 1984	Denmark	TMJ pain syndrome	I Para450 + C9.75 Placebo	34.6 29.7	14 16	0-100mm VAS 2 tabs q4hrs	2weeks X-over study
Giles 1986	UK	Postop dental surgery	I Ibu200 + C15 Placebo	23.9 25.7	36 35	0-8 VAS Single dose	5hr
Heidrich 1985	US	Post ortho surgery	I Para 300 + C30 placebo	31 31	40 40	0-100mm VAS	6hr
Quiding 1983	Sweden	Post meniscectomy	I P1000 + C60 Placebo	16 10	33 38	0-10 Pain intensity difference Single dose	6hr

Efficacy in Acute Pain

- It is believed that a dose of at least 30mg is required
- …current data suggests that paracetamol alone has greater efficacy than paracetamol with codeine at doses <30mg
- Current evidence shows improved analgesia with codeine 60mg and ibuprofen 400mg compared to ibuprofen 400mg alone
- Minimal data at lower doses

Efficacy in Chronic Pain

- The efficacy of opioids in chronic non-malignant pain limited by
  - Development of tolerance
  - AE pattern
  - Dependence potential
- Little role for IR opioids in persistent pain
- Codeine (morphine) produces analgesia for 3-4 hours only
- There are no CR formulations of codeine available

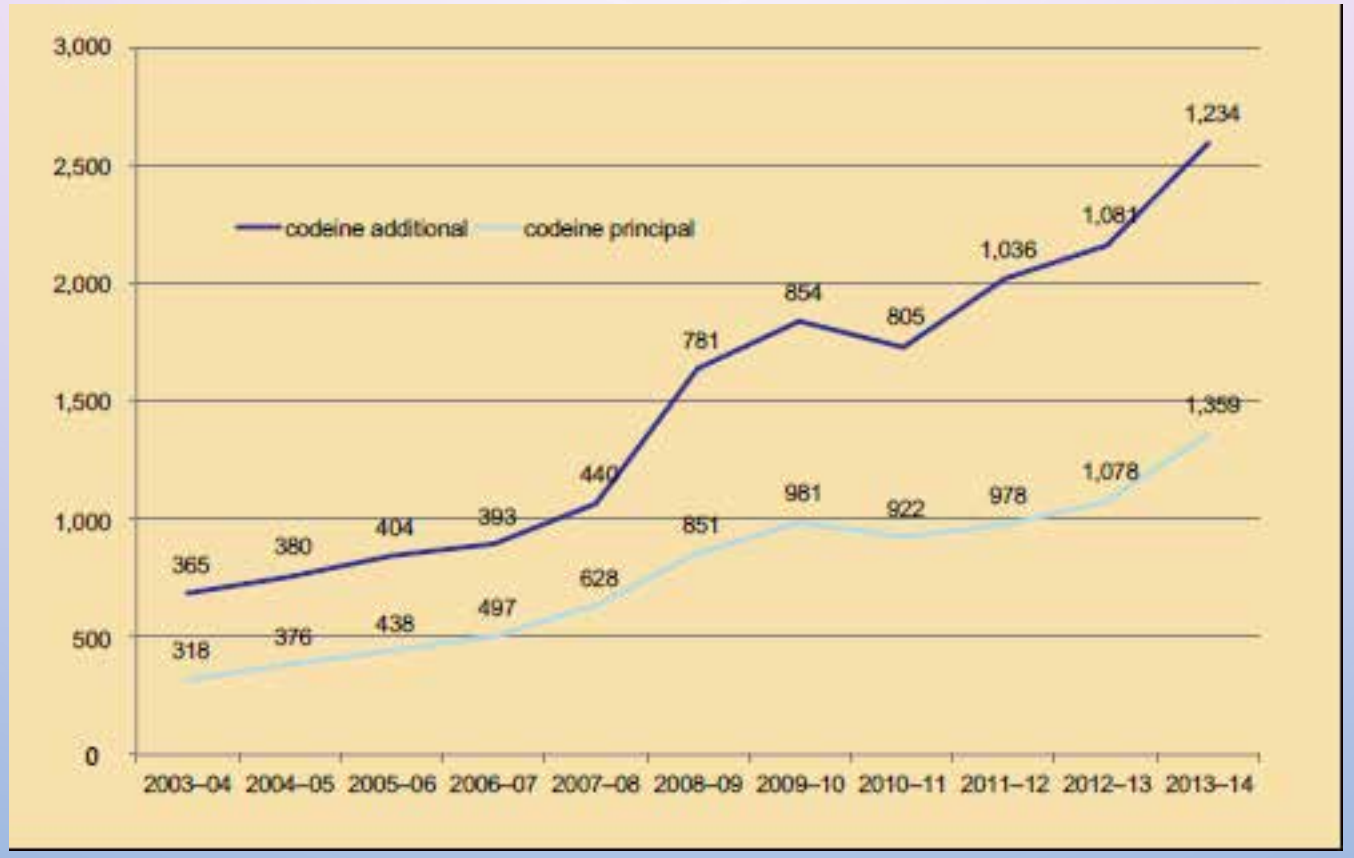
Harm

Codeine described as a ‘Weak’ Opioid

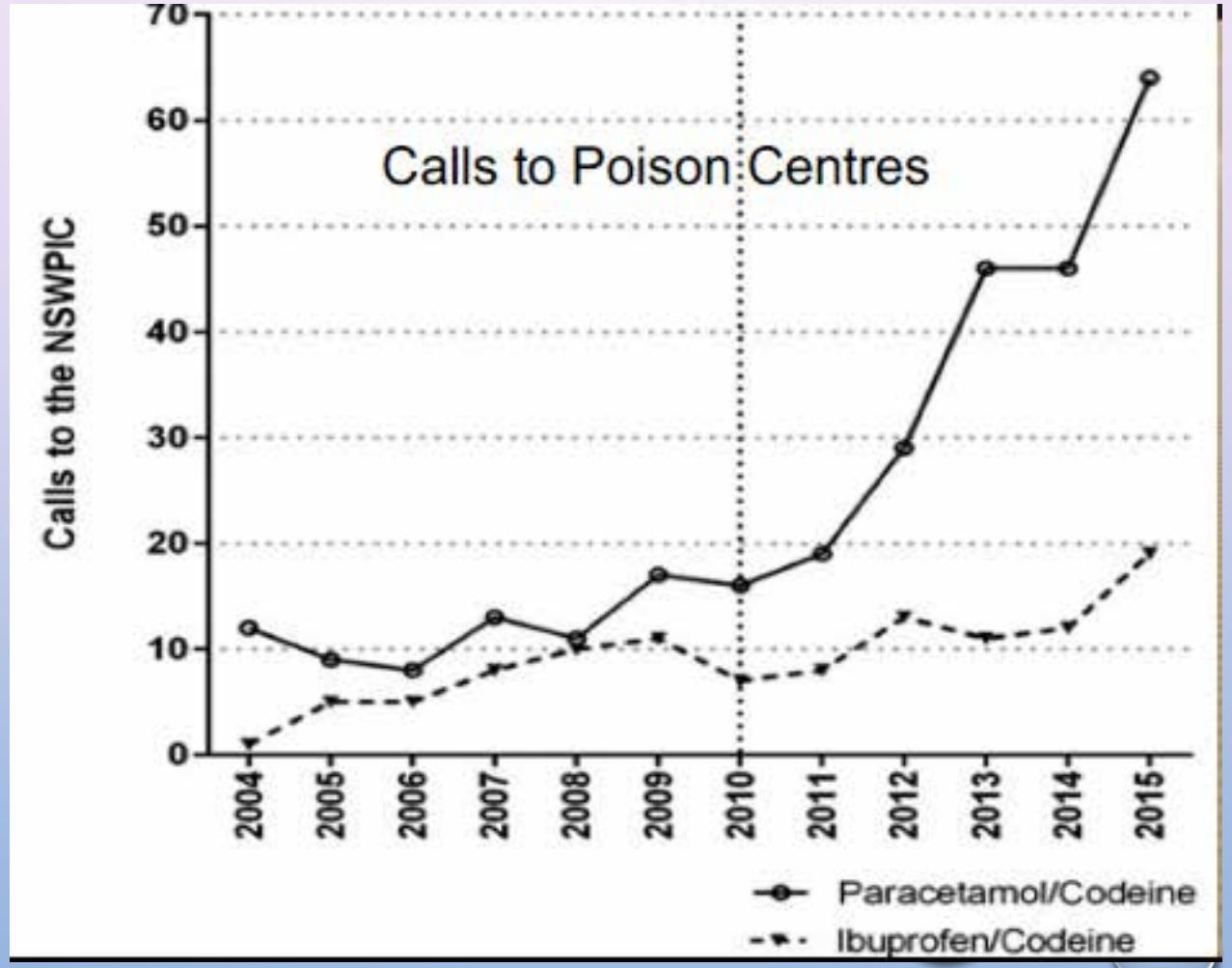
- The WHO described codeine, dihydrocodeine, dextropropoxyphene and tramadol as ‘weak’ opioids for use in their ‘Pain Ladder’
- The potency of codeine and tramadol influenced by CYP2D6
- All opioids display similar dose-dependent adverse effects
- Require the same vigilance in use as morphine despite differences in reputation and regulation.

Prescrire International 2016

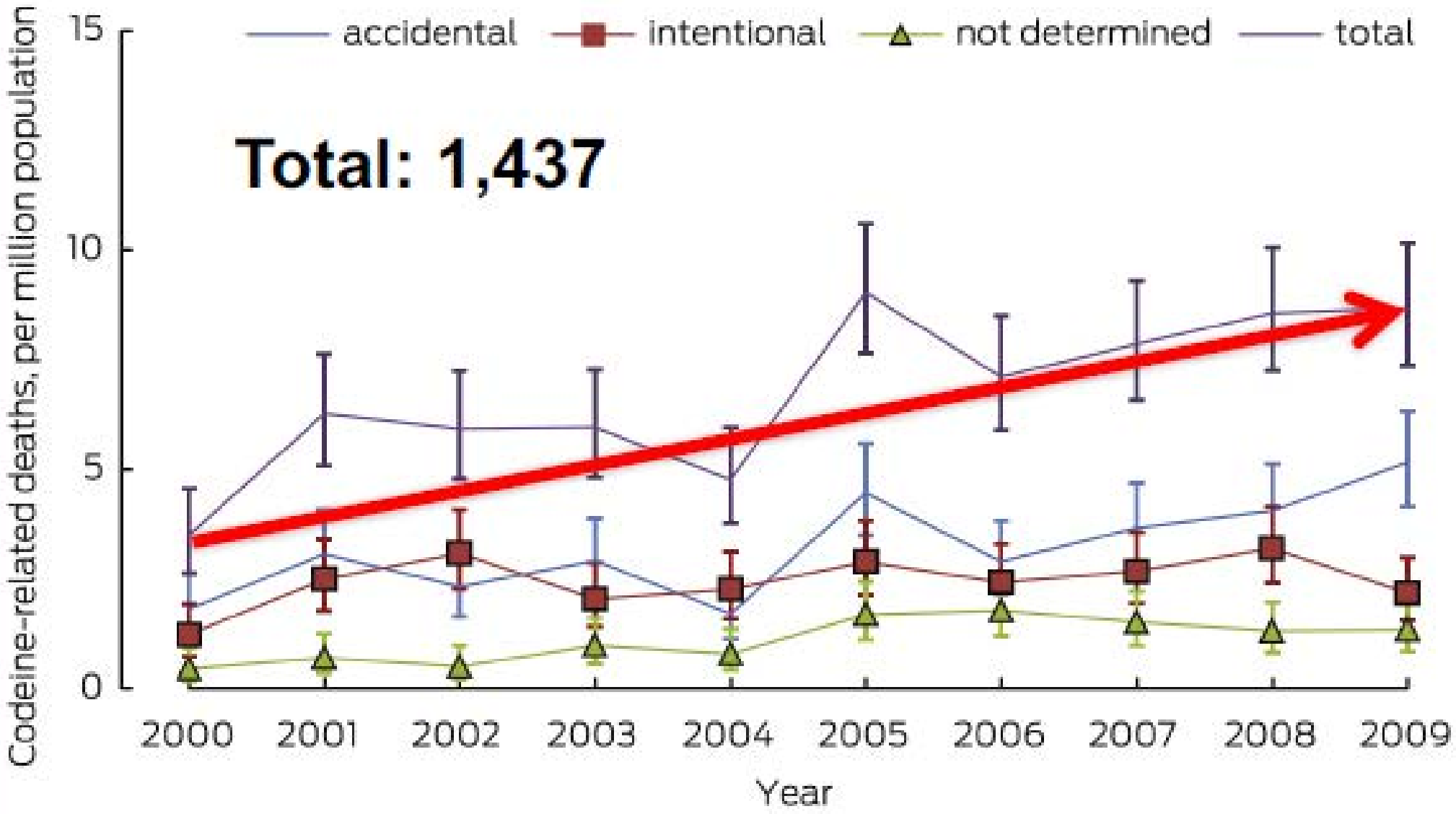
Codeine as a reason for Drug Abuse Treatment



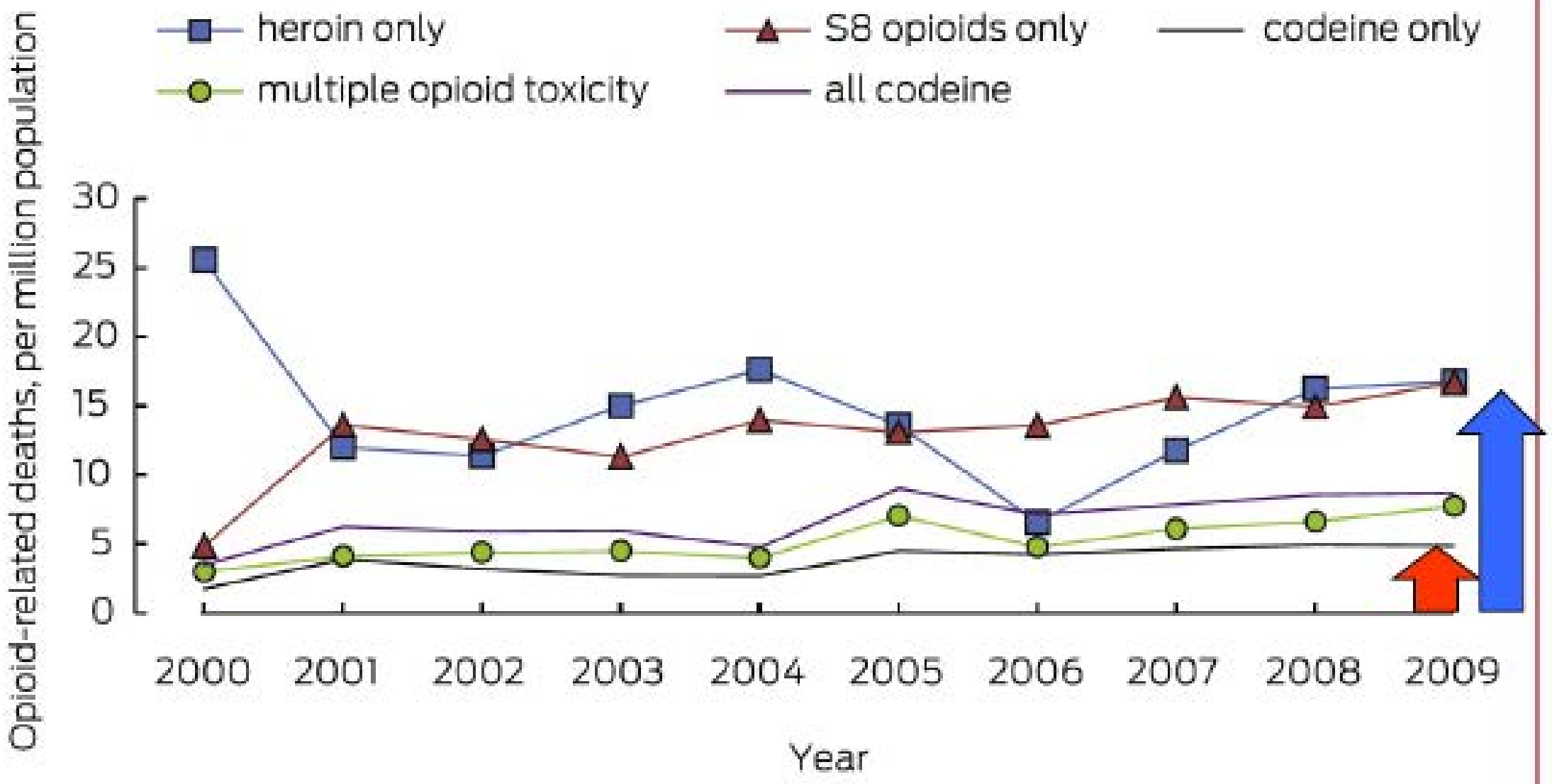
Codeine – Poison Centre calls



1 Rates of codeine-related death by intent, per million population, 2000–2009



2 Rates of codeine-related death, per million population, compared with other opioid-related deaths, 2000–2009



Australian Government

Australian Institute of Health and Welfare

National Drug Strategy Household Survey 2016

Detailed findings

- 1 in 8 Australians have used an illegal substance in the last 12 months
  - Cannabis 10.4%
  - Cocaine 2.5%
  - MDMA 2.2%
  - Methamphetamine 1.4%
- 1 in 20 have misused a pharmaceutical drug
  - of which 75% contained Codeine

Risk of Overdoses of combination Codeine products

- Amounts taken in range of 80-100 tablets/day
  - Liver toxicity due to XS paracetamol
  - XS ibuprofen associated with
    - Acute kidney failure
    - Life threatening hypokalaemia from renal tubular acidosis
    - Non healing GI ulceration with significant risks of perforation and gastrointestinal haemorrhage

Drug and Alcohol REVIEW

APSAD

Drug and Alcohol Review (2017)
DOI: 10.1111/dar.12595

Counting the cost of over-the-counter codeine containing analgesic misuse: A retrospective review of hospital admissions over a 5 year period

DEANNA MILL[1], JACINTA L. JOHNSON[1,2], VICTORIA COCK[3], EMILY MONAGHAN[3] & ELIZABETH D. HOTHAM[2]

[1]SA Pharmacy, SA Health, Government of South Australia, Adelaide, Australia, [2]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia, and [3]Drug and Alcohol Services of South Australia, SA Health, Government of South Australia, Adelaide, Australia

Admission characteristic	*Mean (range)*
Daily OTC-CACC use[g,h]	
OTC-CACC (tablets/day)	28 (2–90)
Duration of use (days)	606 (3–3960)
Codeine phosphate intake (mg/patient/day)	327 (25.6–1152)
Ibuprofen intake (mg/patient/day)	5586 (400–18 000)
Paracetamol intake (mg/patient/day)	10 200 (1000–20000)
Admission and separation	
Length of stay (days)	5.9 (0–64)
Intensive Critical Care Unit length of stay (days)	0.4 (0–8)
Amount of admissions requiring intensive critical care unit stay, count (%)	10 (10.1%)

- 99 admissions over 5 year period with estimated costs to health system of $1.008 M
- Mean cost/admission $10,183

So if codeine-containing products aren’t effective what can you use?

A ‘new’ pain paradigm

- Instead of focusing on how **much** pain an individual is experiencing (mild, moderate, severe) we should now focus on how **long** they have been in pain and what the patient believes the cause to be
- Acute pain describes pain experienced over a short period of time 0-3 months.
  - Correlates with expected healing of an injury
  - Acute pain trajectory is always to ‘no pain’
  - May require short term management of pain using non-pharmacological and simple pharmacological means
- Chronic or Persistent pain is pain that has been experienced, although not necessarily continually, for more than 3 months.
  - Does not correlate with healing but more with an increase in neural sensitivity
  - Appropriate management aimed a biological, psychological and social issues - more COMPLEX
  - No analgesic will ‘cure’ persistent pain and the objective is not to reduce pain to zero but to manage severity and stabilise the pain experience at levels consistent to a return of function.
  - Pharmacological analgesics can actually make persistent pain worse and become part of the problem rather than the solution
- Acute on chronic pain
  - Management of chronic pain should identify appropriate strategies to manage acute flares.
  - What has been incorporated into this individual’s pain management plan? Has it been implemented?

So what can we use?

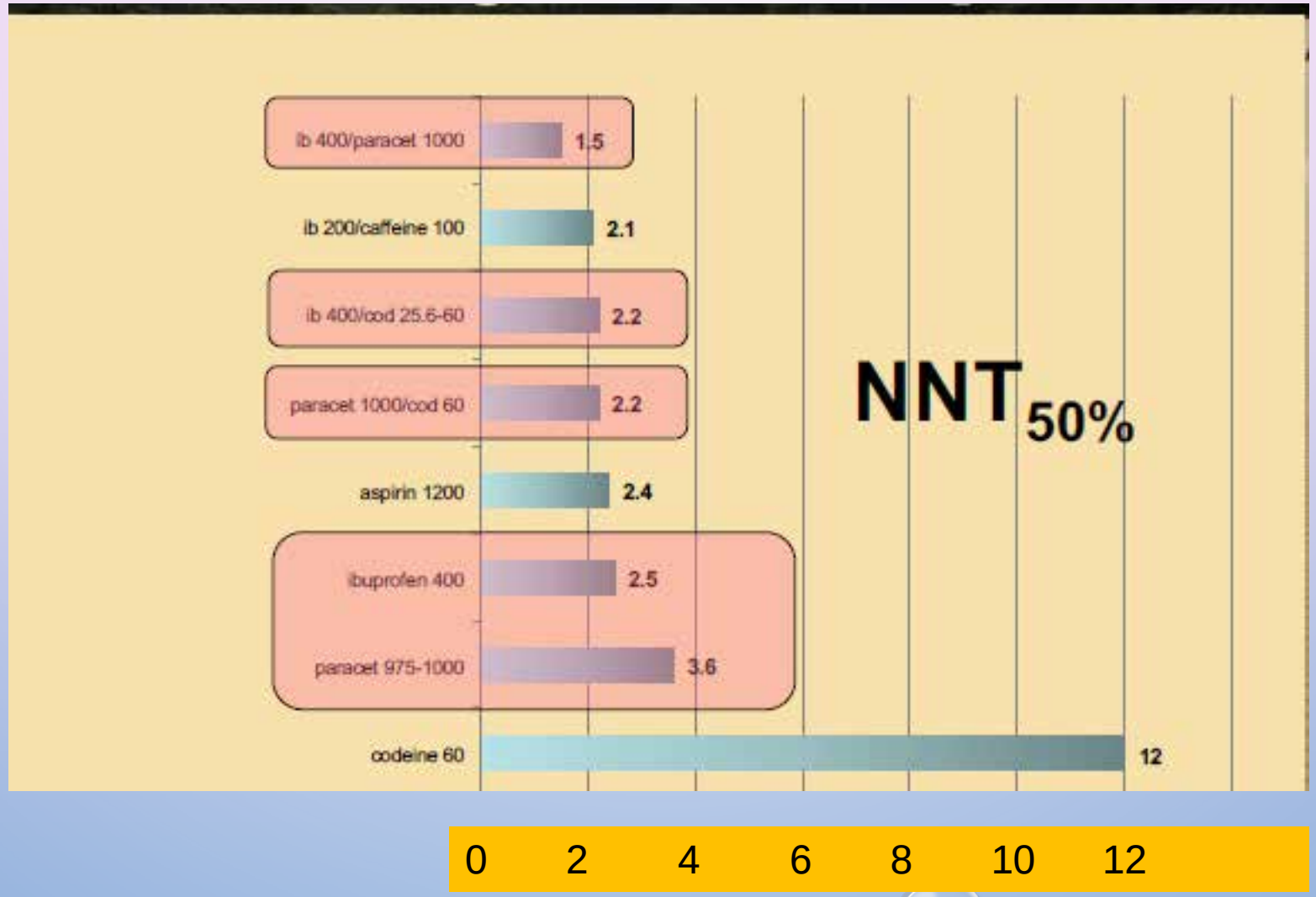
- Dependent upon the nature and type of pain being experienced.
- Acute Pain
  - Treatment dependent upon cause
    - Tooth ache - see a Dentist
    - Fractured wrist - needs immobilisation
    - Soft tissue injury - Rest, Ice, Compression, Elevation
- Chronic or Persistent Pain
  - Complexity of issues requires medical input and a management plan like all chronic health conditions e.g. asthma
- Acute on Chronic Pain
  - Treatment dependent upon cause of flare
  - Similar to Acute Pain

Simple analgesics

- Two major groups of simple analgesic
  - Paracetamol (Acetaminophen)
    - Not very potent even for acute pain
    - Generally considered safe in recommended doses
      - currently 4g/day in divided doses but some suggestions that should be reduced to maximum 3g/d
      - Well recognised risk groups for toxicity at low doses e.g. glutamine deficiency
  - Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)
      - Weak to moderate analgesic potency
      - Well recognised gastrointestinal toxicity, especially on regular long-term use
      - Relatively recent recognition of cardiovascular toxicity
      - Known interaction with some antihypertensive medications (ACEi, ARBs, Betablockers and diuretics) and risk of aggravating bronchoconstriction in 10% asthmatics with aspirin-exacerbated respiratory disease (AERD or Samter's triad :-asthma, NSAID-induced bronchospasm and nasal/ethmoidal polyposis)

Efficacy of simple analgesics

NNT for 50% pain reduction

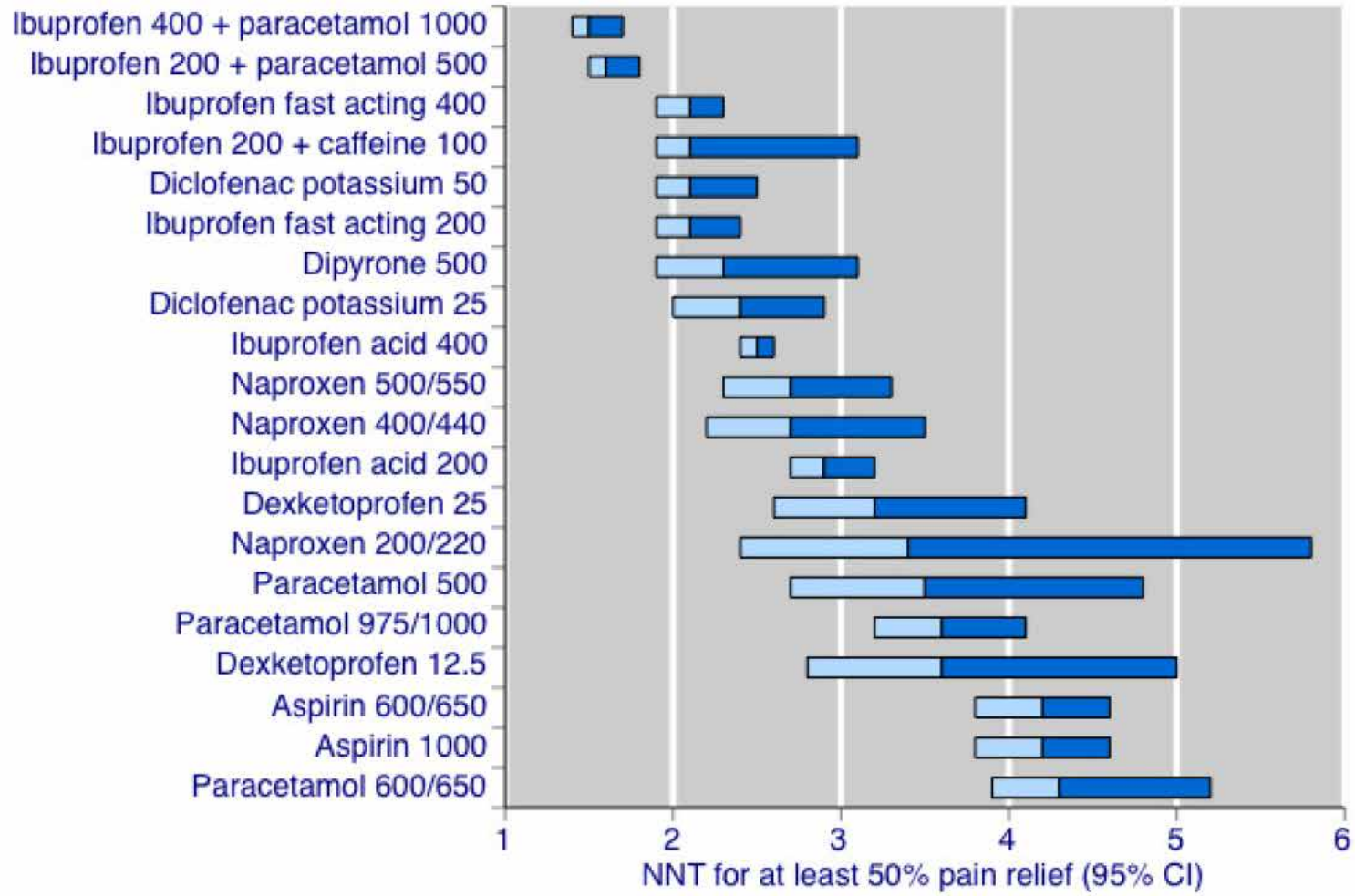


Non-prescription OTC analgesics for Acute pain

Moore Cochrane 2015

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

Single dose studies



Maxigesic vs Nuromol

- Maxigesic® (ibuprofen 150mg + paracetamol 500mg)
- Rec dose 2 tabs q6hr
- Maximum **8**/24 hrs
- Merry 2010 -
- Excluded patients <16yrs, taking warfarin, ACEi, corticosteroids, immune suppressants, having severe local infections, Hx of PUD, asthma, haemopoetic, renal or hepatic disease

- Nuromol® (ibuprofen 200mg + paracetamol 500mg)
- Rec dose 1 tablet q8hrs
- Maximum **3**/24 hrs
- Daniels 2011 – patients scoring mod to severe (score >50mm on 0-100mm VAS) post operative pain (within 6hrs of surgery)
- Excluded patients <16yrs, Hx of hepatic or renal disease, any other painful condition, recurrent Hx of PUD or GI bleed, concomitant meds)

Maxigesic®

Study	Country	Indication	Intervention	Mean Age yrs	Number	Outcome	Follow up
Merry 2010	NZ	Wisdom tooth extraction	A Ibu 150 +P 500 (Maxigesic®) B Ibu 150 C P 500 Fentanyl IV for BT in hospital Codeine po for BT at home 2 tabs preop then q6hr for 48hrs	25 23.7 2.5	40 39 43	0-100mm VAS AUC/t (rest +active) Maxigesic® superior to paracetamol or ibuprofen alone	48 hrs

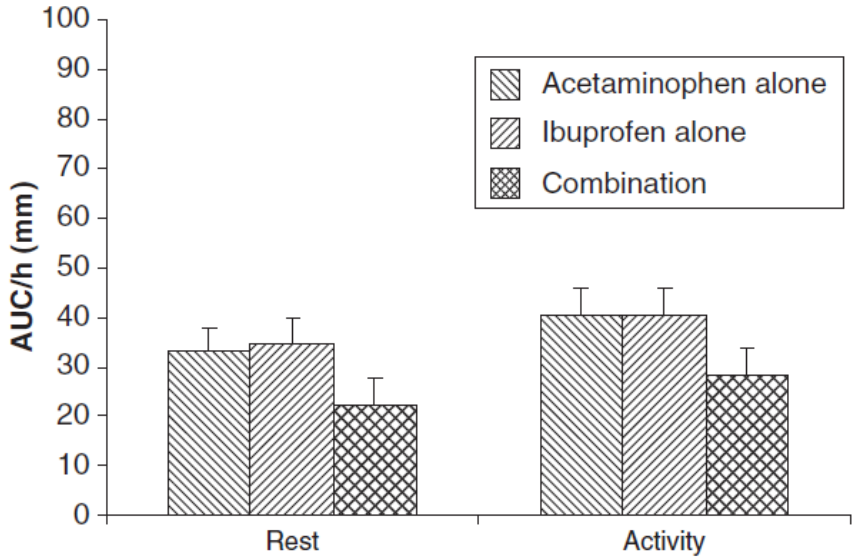
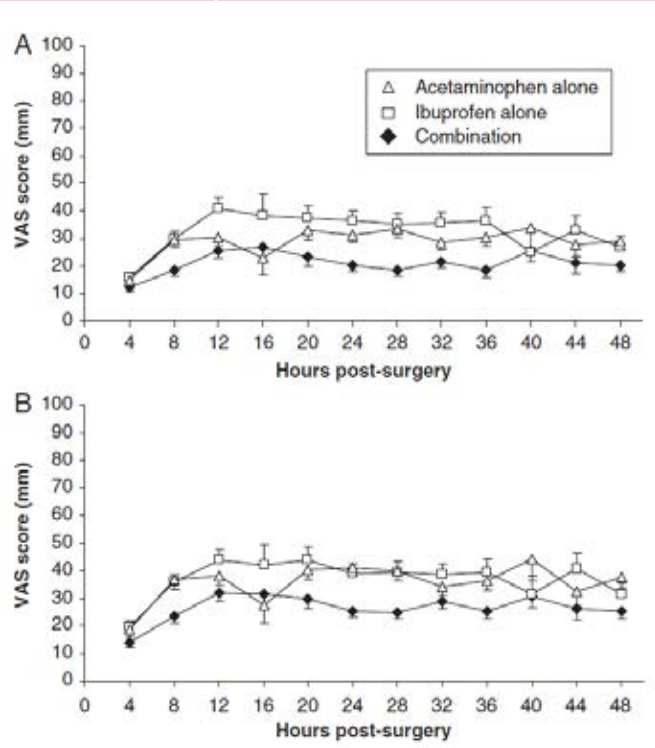


Fig 2 Mean (+95% CI) mm of time-adjusted AUC (AUC/time) for VAS at rest and on activity by treatment group.

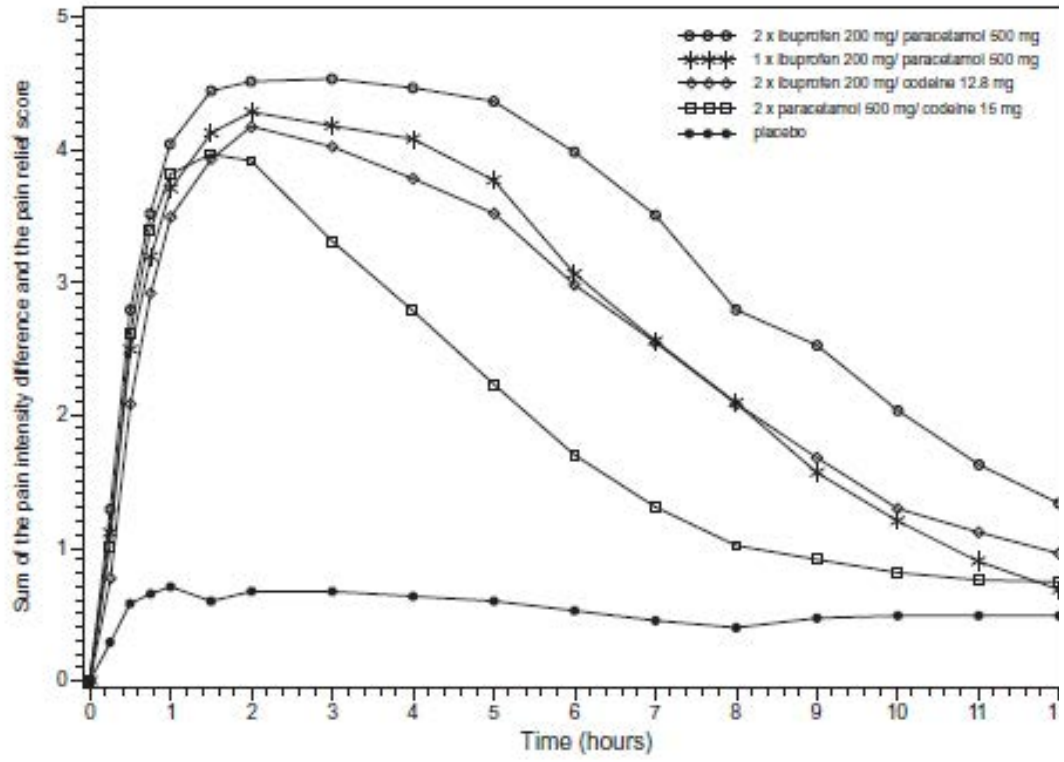


at rest

on activity

Nuromol®

Study	Country	Indication	Intervention	Mean Age yrs	Number	Outcome	Follow up
Daniels 2010 Mehlisch 2010	US	Impacted molar tooth extraction	• Ibu200 +P500 o Ibu400+P1000 (Nuromol ®) ◇ Ibu400+C25.6 ▯ Para1000+C30 ● Placebo Tramadol 100mg XR x 1 then ketorolac 30mg IV/IM for BT in 1st 4 hrs then oral hydrocodone/para 10/325mg	20.2 19.8 20.1 19.7	172 164 167 112	0-100mm VAS Sum of mean Pain Relief and Pain Intensity Differences (SPRID) Total Pain Relief (TOTPAR) at 0-4, 0-6, 0-8, 0-12hrs Patient Global Impression of Change Randomised 5 arm parallel group placebo controlled	12 hrs



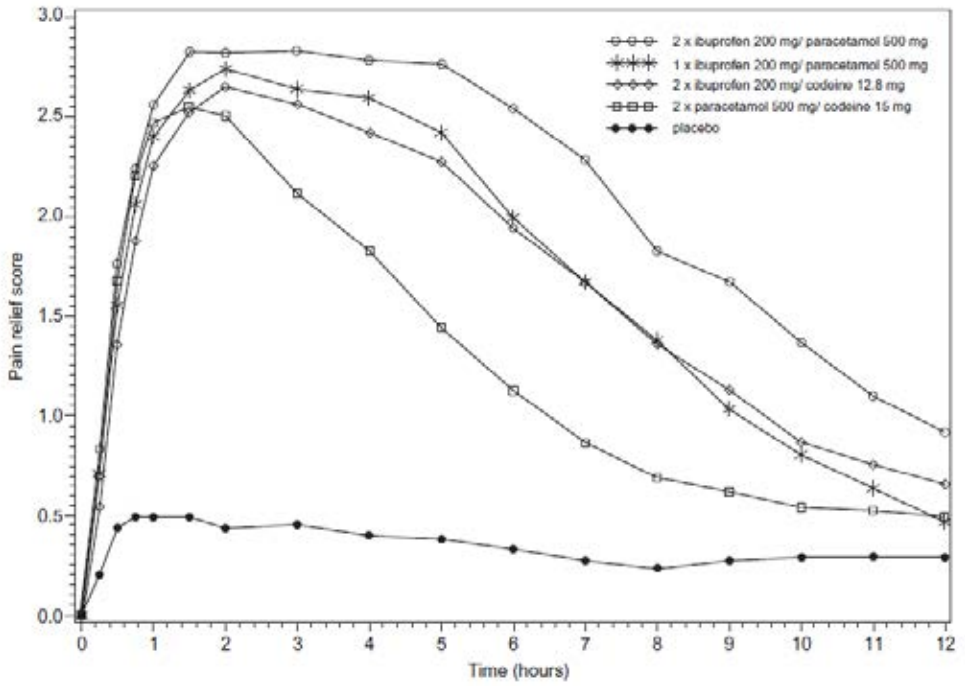
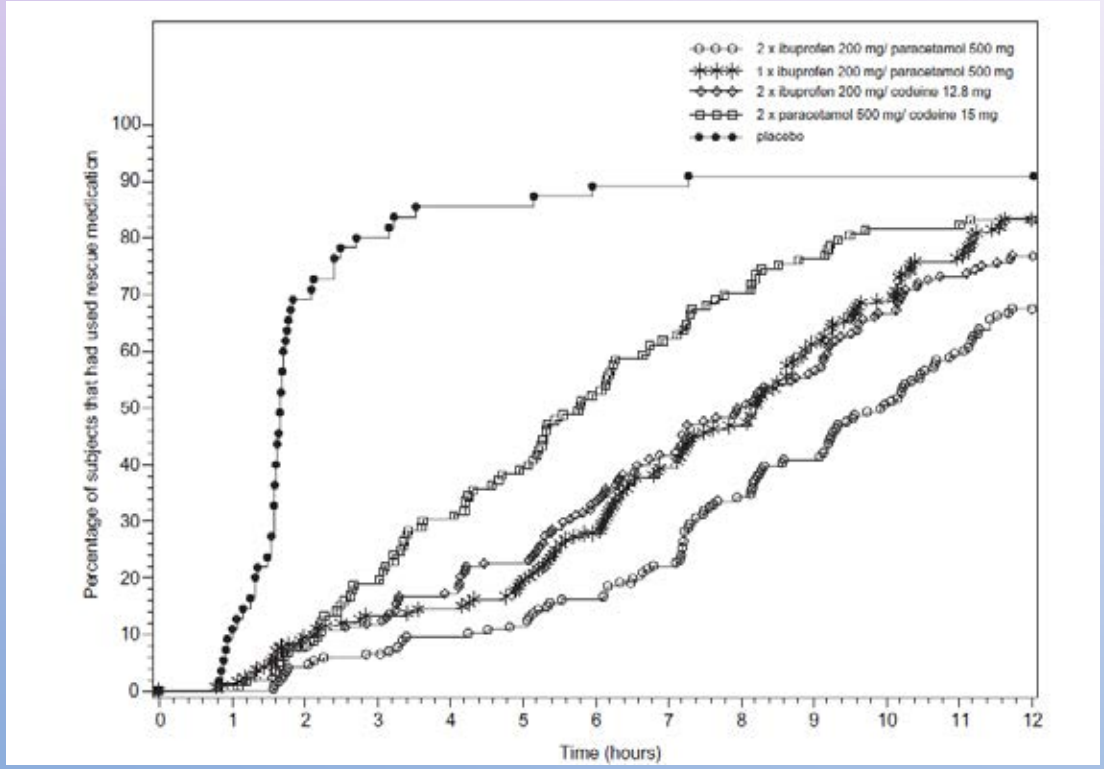


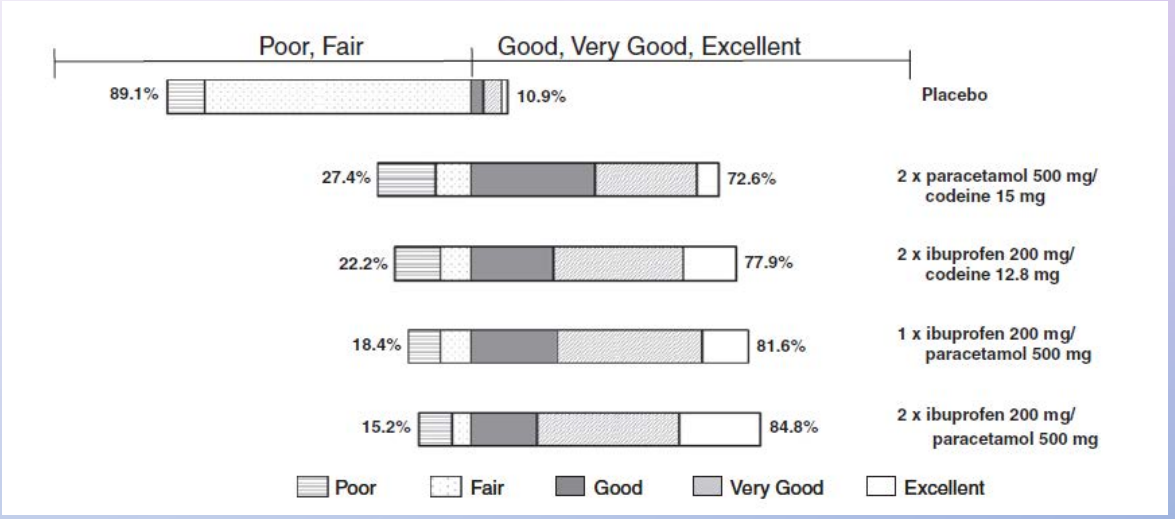
Fig. 3. Mean pain relief at each time point (intention-to-treat population).

Daniel, + Mehlisch 2010

Time to 1st administration of rescue medication



Patient Global Impression of Change



Moore et al. 2017

- Multicriteria Decision Analysis for Risks and benefits of OTC analgesics

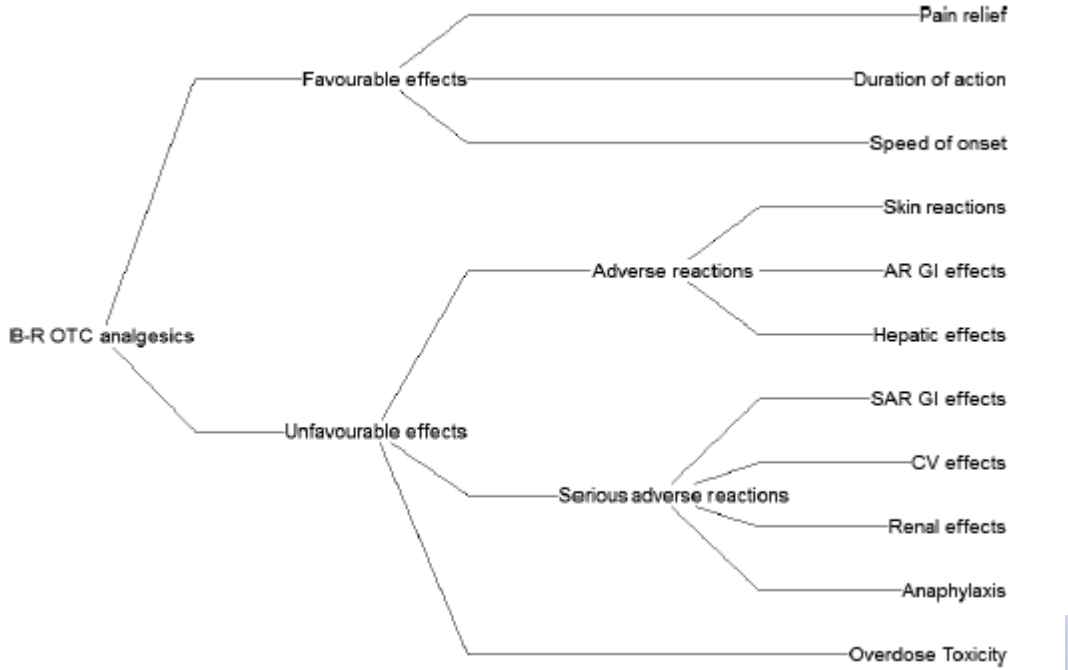
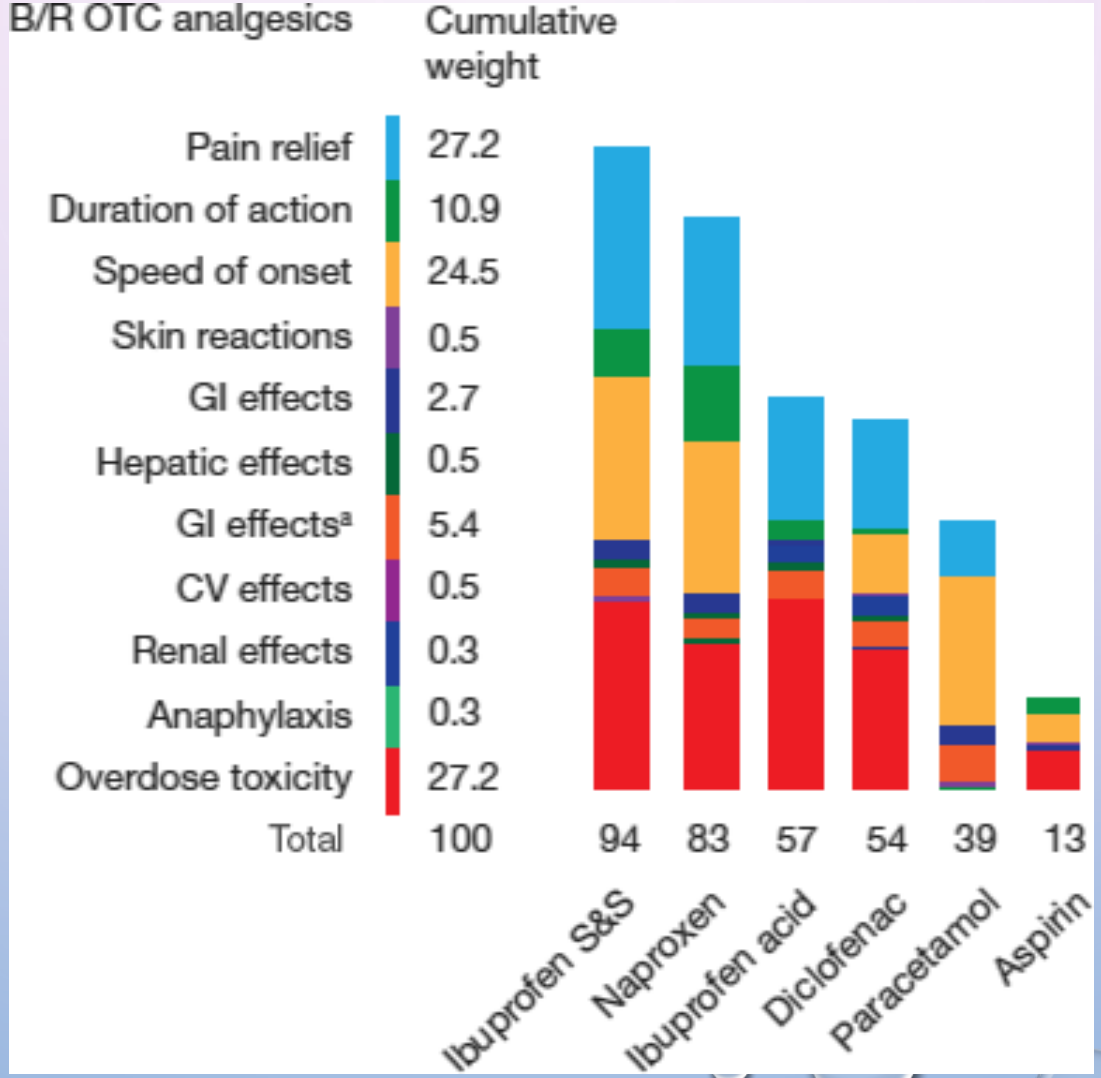


Table 1 Effects table highlighting the data inputs into the model. The first four rows are measured data, and the remaining rows are preference judgements

Effects	Units	Ibuprofen acid	Ibuprofen S&S	Paracetamol	Diclofenac	Aspirin	Naproxen sodium
Favourable effects							
Pain relief	%	48	63	33	45	20	55
Duration of action	h	5.5	7	4	4.5	5	9
Speed of onset	min	55	27	30	45	50	30
Unfavourable effects							
Adverse reactions							
Skin reactions	No.	24	24	77	41	124	26
GI safety	Pref.	100	100	100	100	0	100
Hepatic safety	Pref.	100	100	0	100	30	50
Serious adverse reactions							
GI safety	Pref.	40	50	100	30	0	20
CV safety	Pref.	75	75	75	0	100	80
Renal safety	Pref.	100	100	100	100	100	0
Anaphylaxis	Pref.	50	50	100	50	0	50
Overdose Toxicity	Pref.	100	100	0	0	75	75

These are as presented in clinical studies. Some as percentages and others as actual numbers of incidents. Times as h (hours) or min (minutes) are mean times.

Moore et al. 2017



CONCLUSIONS

- Rescheduling OTC codeine to s4 is the correct decision - even the PSA + Pharmacy Guild agree with that!
  - Should there be exemptions – I think not! My view is that the pharmacy profession has demonstrated that they don't take their medicines custodianship seriously enough and don't deserve this capacity – much to the possible detriment of our patients.
  - What next ? - PPIs, NSAIDs, Salbutamol inhalers
- I would argue that we should not stop at S4 but reschedule to S8
  - Risks due to pharmacogenetics differences in metabolism
  - Lack of efficacy at OTC doses
  - Evidence of significant harm
    - Abuse
    - Mortality
    - Overdose of non-opioids in combination products

Major question remains

- What to use for patients presenting with acute pain to ED?
- What to use for patients presenting with acute pain to GP?
- What to use for patients presenting with acute pain with conditions where NSAIDs contraindicated?

- Do NOT want to encourage use of Oxycodone IR

‘Hot off the Press!’

- Chang et al. “Effect of a Single Dose of Oral Opioid and Non-opioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial.” JAMA 2017
- Four arms 104 patients/arm aged 21-64 years – mod to severe acute extremity pain
  - 400mg Ibuprofen + 1000mg paracetamol
  - Oxycodone 5mg + paracetamol 325mg
  - Hydrocodone 5mg + paracetamol 300mg
  - Codeine 30mg + paracetamol 300mg
  - 11 point NRS (0-10)
  - Predefined that a change of 1.3 on the NRS was clinically important
- No statistically significant or clinically important differences at 2hrs
- For ED patients with acute extremity pain (e.g. sprains, strains, contusions and fractures) any of the paracetamol/ibuprofen or opioid/paracetamol combinations above were equally effective
- Need for rescue analgesia (13.5% oxycodone/paracetamol, 17.8% ibuprofen/paracetamol, 22.3% codeine/paracetamol)

CONCLUSIONS

- Rescheduling OTC codeine to S4 was the correct decision
- I would argue that we should not stop there but reschedule to S8
- Risks due to pharmacogenetics differences in metabolism
- Lack of efficacy at OTC doses
- Evidence of significant harm
  - Abuse
  - Mortality
  - Overdose of non-opioids in combination products
  - More effective OTC combinations without codeine are now available

Outstanding questions

- What is the most appropriate way to manage Acute Pain presentations in situations where paracetamol and NSAIDs are contraindicated, especially where medical input not available
- First line should always be non-pharmacological measures
- Single doses of paracetamol, NSAIDs or combination unlikely to be harmful except in AERD