19 May 2009

Secretary, National Drugs and Poisons Schedule Committee
GPO Box 9848
Canberra
ACT 2601

Dear Sir,

As Dean of the Faculty of Pain Medicine I would like to put in a submission regarding the proposed up scheduling of over the counter (OTC) Codeine combinations.

My understanding is that NDPSC's proposed changes include:

- Deletion of Schedule Two codeine entries and amending this to Schedule Three codeine entry
- Limiting the recommended daily dose to a maximum of 100mg of codeine base
- Limiting a pack size to a maximum of five days supply
- Restricting divided preparations to a maximum 12mg codeine base per dosage unit
- Restricting undivided preparations to a maximum concentration of 0.25% codeine base.

I have discussed these proposed changes with a number of colleagues who represent Acute Pain Management Physicians, Chronic Pain Management Physicians and representatives from Drugs and Alcohol Services, and the feedback I have had supports the NDPSC in their endeavours.

We particularly support the changing of the scheduling to schedule three such that a patient will need to be provided the medication by a pharmacist who can make a professional assessment of pain and the risk of misuse and supply more informed recommendations about the management of pain.

We strongly the support the deletion of Schedule two entry for codeine.

However, we feel that with the further recommendations, the NDPSC may not have gone far enough:

a) We are not aware of any evidence of analgesic benefit in the literature for preparations with fewer than 30mg of codeine (see the Oxford Analgesic League Table). Therefore, as the codeine in these low dose preparations has no analgesic purpose, but potentially increases the risk of physiological and psychological dependence and therefore substantial physical morbidity, our recommendation in the longer term would be that the low dose combination preparations containing codeine should be withdrawn.

b) We are aware that 8-10% of our population do not metabolise codeine to morphine, which is the required step for the analgesic properties of codeine in the body. However, we are also aware that approximately 7% of our population are “ultra rapid metabolisers” who would therefore get a “hit” of morphine when they take the codeine preparation. These individuals maybe the individuals who potentially develop dependency on these low dose codeine preparations.

c) As practising clinicians, we are aware of sporadic reports in the literature of individuals developing dependency upon the OTC preparations and who take far in excess of the recommended doses with significant co-morbidities. I will outline such a case that we have been treating in Adelaide at the end of this letter.

d) Limiting the recommended daily dose of codeine base to 100mg, will in fact equates to approximately 140mg of codeine phosphate per day.

Allowing140mg codeine phosphate daily, would mean that patients taking Panadeine 15 (containing 15 mg of codeine phosphate) could take up to 9 tablets per day, which of course would exceed the recommended dose of paracetamol.

If this same rule was applied to Panadeine (containing 8mg of codeine phosphate) patients could potentially take 16 tablets per day providing 8g of paracetamol. The hepatotoxic dose is between 7-10g. Theoretically unless spelled out, a 5 day supply of panadeine (at 16 tablets per day) would be 80 tablets in the packet.

Nurofen Plus (which in our experience seems to be the most problematic OTC codeine analgesic) contains 12.8mg of codeine phosphate; hence your changes would allow a daily dose of 10.6 tablets per day (say 10 tablets), which would enable a supply of 50 tablets for the proposed limit of 5 days.

e) With the above outlined, we believe that the NDPSC should consider recommending that the daily dose of codeine base should be limited to 60mg. If that was the case, we would then support limiting the pack size to 5 days and strongly recommend maintaining a current maximum of 10mg of codeine base per dosage unit. This would limit all the OTC codeine / ibuprofen analgesic products (including Nurofen Plus but excluding Panadeine 15) to 6 tablets per day and a maximum pack size of 30 tablets.

f) We would strongly advocate that an *addiction warning* be placed on all packs of OTC codeine containing preparations.

We understand this is done voluntarily in the United Kingdom by the pharmaceutical industry, and the packs have a warning about the risk of addiction.

Panadeine packs contain a warning to keep to the recommended dose and warn of the risk of serious liver damage if an excessive dose or an overdose is taken. However, currently there are no warnings on the ibuprofen packs with a serious risk of injury if the daily dose recommended is exceded.

We would strongly recommend there be a warning on the packs of the OTC codeine/ibuprofen analgesic:

“Keep to the recommended dose”.

“You may be at serious risk of stomach perforation, bleeding, liver / kidney failure or death if you exceed the recommended dose”.

In summary, I will present a brief outline of the case of a young girl (University Student) who we have been managing in Adelaide for a number of years.

She has become addicted to Nurofen Plus and as a result of her misuse, has undergone a number of procedures, a number of complications and has been near death on a number of occasions. I believe she is currently doing reasonably well, but it has been a very long battle.

Related to her Nurofen Plus abuse she has undergone:

- a cholecystectomy (for vague upper quadrant abdominal pain)
- a partial gastrectomy (for suspected gastric crohns)
- Peritonitis following that procedure
- a deep vein thrombosis complicated by a pulmonary embolus
- Protein loosing enteropathy with a plasma albumin of 5gm per litre
- E coli septicaemia
- Hypogammaglobulinemia
- Anaemia of chronic disease
- Vitamin B12 deficiency
- Neuropathy of chronic disease (similar to Guillain Barre syndrome)

We are also aware of reports in the literature of people dying from hypokalemia with cardiac arrhythmias, secondary to Nurofen Plus abuse.

Unfortunately, many of the public are aware of the concerns with excess paracetamol but are totally unaware that there are any problems with taking excess ibuprofen in the form of a nurofen plus.

I would also like to recommend as a reference:

- Ferner R: Beard K: Over the counter medicines proceed with caution: BMJ: 2008: 336: 694- 696.

I thank you for the ability to make a submission on behalf of the Faculty of Pain Medicine and I congratulate the NDPSC on the steps that they are taking to limit the availability of OTC codeine but would in fact like you to go further.

Yours sincerely,

Penelope Briscoe
Dean, FPM

Figure 1: WARINILLA ADMISSIONS (DASSA) 2002 -2014

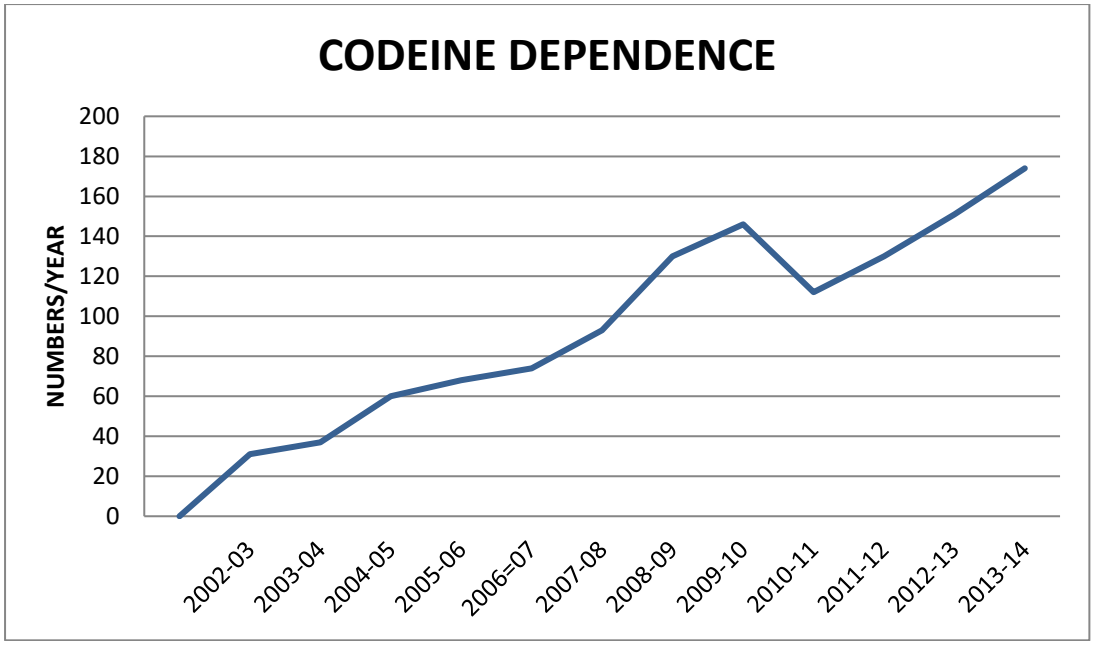
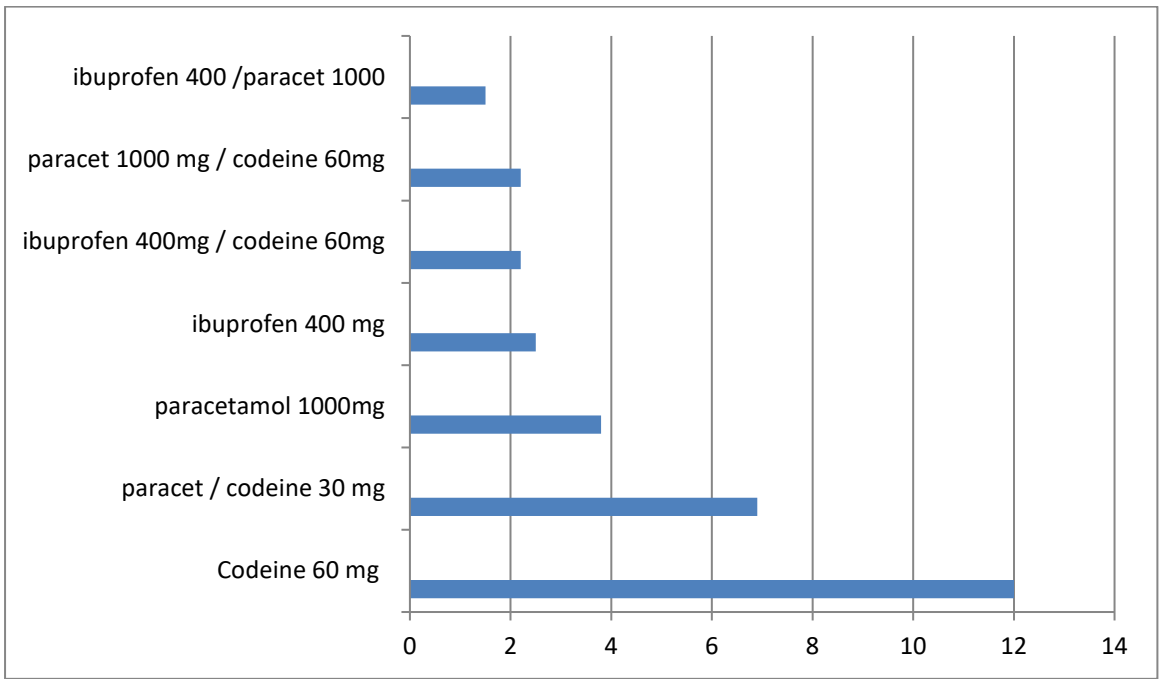


Figure 2:

Numbers needed to treat (NNT) for one patient to obtain 50% analgesia.

Figures extrapolated from reference 8: Moore et al, and 2007 Oxford league table of analgesic efficacy.



23rd February 2015

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TO WHOM IT MAY CONCERN

RE: Rescheduling Of Codeine-Containing Medications from Schedule 3 To Schedule 4

Medicine Details:

1. The medications needing to be Rescheduled include all the available "over-the-counter" medications containing codeine available at pharmacies as a Schedule 3 drug. We believe they should be rescheduled as Schedule 4. The medications include Panadeine®, Panadeine Extra®, Nurofen Plus®, Aspalgin® and Mersyndol® (plus other brands).

2. Active ingredient: Codeine
   Codeine is sold "over-the-counter" in combinations with other medications including paracetamol, aspirin, and ibuprofen.

3. Dosage form:
   Codeine preparation varies from 8mg to 15mg per tablet.

4. Indication for Medication:
   Analgesics containing codeine are sold for the "effective temporary relief of strong pain and discomfort associated with a number of different medical conditions". They are said to provide effective temporary relief from pain, and the advantages stated is that the patient does not need to see a General Practitioner.

5. Codeine containing preparations were switched in 2010 from Schedule 2 to Schedule 3. This aimed to provide increased surveillance of the medication usage by a Pharmacist to ensure quality use of medicines. This rescheduling occurred as it was recognised there is potential for harm if used inappropriately.

6. We, the undersigned, believe that all codeine preparations should now be switched to Schedule 4 because we are of the opinion codeine fits the factors required for Schedule 4, as outlined in the Australian National Consultative

Committee on Therapeutic Goods (NCCTG) scheduling, factors for prescription only medicines (Schedule 4) which include:

- **The use of the substance (codeine) at established therapeutic dosage levels may produce dependency, but has a moderate propensity for misuse, abuse, or illicit use.** Control of access and duration of therapy by a medical, veterinary or dental practitioner is required
- **The seriousness, severity, and frequency of adverse effects are such that monitoring or intervention by a medical practitioner is required to minimise the risk of using this substance (codeine).**

APPLICANT DETAILS

- Dr Penelope Anne Briscoe, Head of the Pain Management Unit, Royal Adelaide Hospital.
- Associate Professor Pamela Macintyre, Director of the Acute Pain Service, Royal Adelaide Hospital
- Professor Jane Andrews, Head IBD Service + Education, Department of Gastroenterology, Royal Adelaide Hospital
- Dr Tim Semple, Deputy Director of the RAH Pain Management Unit, and Immediate Past President of the Australian Pain Society.
- Prof David Watson, Head, Flinders University Department of Surgery, Flinders Medical Centre.
- Date of Submission 2015.
- Contact email address penny.briscoe@health.sa.gov.au
- Postal address: C/- of the Royal Adelaide Hospital Pain Management Unit, Level 6, Emergency Block, North Terrace, Adelaide 5000.
- Ph No: 08 8222 5403
- Fax No: 08 8222 5904

Declaration:

I, Penelope Anne Briscoe, declare that the information provided in this application is true and current. Undertake to treat as confidential information and not publically disclose the notice of interim decision in respect to this application until the interim decision is reached pursuant to subsection 42ZCZP of the Therapeutic Goods Regulation 1990 or the final decision is published pursuant to subsection 42ZCZS of the Therapeutic Goods Regulation 1990.

We, the undersigned, believe that the risk for individuals who are “ultra-rapid metabolisers”, requires that for societal “duty of care”, we need to reschedule these potentially lethal medications (in otherwise ”normal” people), to Schedule 4 (ie under Medical Supervision).

In *“Rescheduling of codeine containing medications from Schedule 3 to Schedule 4”* (see document attached) we have concluded:

- Codeine is ineffective as an analgesic (NNT 12).
- In up to 10% of our population (poor metabolisers), it is ineffective but can still causes harmful effects.
- In up to 4 - 10% of our population (ultrarapid metabolisers), it can cause life threatening toxicity.
- *If it is to remain as an analgesic, then the metaboliser status of patients needs to be ascertained before it is prescribed or dispensed.*

Murnion [(1)] commented previously *“given the lack of documented analgesic efficacy of low dose codeine preparations, rescheduling is unlikely to impact significantly on analgesic options, but may reduce harms from overuse”.*

In Figure 2 attached, an attempt has been made to compare simple analgesics to OTC compound analgesics to “high dose” Schedule 8 codeine phosphate.

Studies are difficult to evaluate as the trials usually look at single dose studies in postoperative or dental pain.

The Numbers Needed to Treat (NNT) is calculated by seeing the number of individuals that needed to be treated, such that one will obtain 50% pain relief over 4-6 hours compared to placebo. However, up to 18% of patients treated with placebo alone will report adequate analgesia [(8)]

Codeine performs unfavourably compared with simple analgesics such as paracetamol and NSAID’s[(3)]. Codeine is a weak opioid analgesic, and it appears that it adds little to the analgesic efficacy of ibuprofen or paracetamol in combination.

There is now good evidence the alternative combination of the two non-opioid analgesics, ibuprofen plus paracetamol provides better analgesic efficacy with a NNT of 1.5. [(8)]

NPS MEDICINE WISE[(6)] advises in Practical Points:
“Do not use codeine in adults or children known to be ultra-rapid metabolisers”.
This **strong recommendation** is inconsistent with codeine being available “over-the-counter”.

Even in the 80% of Caucasians who metabolise their codeine as expected, codeine is a poor analgesic. The Cochrane Database 2011 (Figure 2) reports the NNT for codeine 60 mg alone is 12.

The OTC codeine preparations contain lower doses of codeine. Comparing them to the same dose of paracetamol alone the benefit was modest with only a further 10-15% of patients achieving adequate analgesia[3]. Recent Cochrane reviews have compared paracetamol plus codeine (60 mg) to paracetamol alone[14] and ibuprofen plus codeine 60 mg to ibuprofen alone[15], and the benefits for the addition of codeine to the simple analgesic is very small.

NNT paracetamol + codeine / paracetamol = 6.1[14].

NNT ibuprofen+ codeine / ibuprofen = 7.1[15].

Adding the codeine has minimal benefit, but increases adverse effects of CNS depression and constipation in particular.

Unfortunately, despite rescheduling in April 2010, we are still seeing a concerning number of patients who are admitted each year to the Royal Adelaide Hospital with complications from, and significant issues associated with, codeine misuse and abuse from OTC (Schedule 3) codeine. Our Colleagues at Flinders Medical Centre have written of their experience. [13]

Reports of harm from the inappropriate use of the OTC medications, is still being reported despite the rescheduling in 2010, in Australia and overseas.

Children and infants of breast feeding mothers can be at risk even with usual doses.

Rescheduling to Schedule 3 has *not achieved* the required reduction in harm to the individuals affected, and more needs to be done.

We are happy to provide more details if you require, but would very strongly advocate *that if* codeine continues to be available in Australia, combination products containing codeine should be transferred to Schedule 4, so that they require a prescription which can be monitored by their Medical Practitioner.

- Patients, Prescribers and Pharmacists should also be aware of our recommendation:
  If codeine is to remain as an analgesic, then the metaboliser status of patients needs to be ascertained before it is prescribed or dispensed.

Yours sincerely,

DR PENNY BRISCOE
DIRECTOR
PAIN MANAGEMENT UNIT

On behalf of:

- Associate Professor Pamela Macintyre, Director, Acute Pain Service, Royal Adelaide Hospital
- Professor Jane Andrews, Head IBD Service + Education, Department of Gastroenterology, Royal Adelaide Hospital
- Dr Tim Semple: Deputy Director Pain Management Unit, Royal Adelaide Hospital. Immediate Past President Australian Pain Society.
- Prof David Watson, Head, Flinders University Department of Surgery, Flinders Medical Centre.

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Application to Amend the Poisons Standard

Rescheduling of codeine containing medications from Schedule 3 to Schedule 4.

23rd February 2015

Dr Penelope Briscoe Head of Pain Management Unit,

Royal Adelaide Hospital North Tce Adelaide, 5000.

penny.briscoe@health.sa.gov.au

February 2015

Confidentiality
Please indicate if your application:

X contains no material supplied in confidence or

CONTENTS

RE: Rescheduling Of Compound Codeine Containing Medications From Schedule 3 To Schedule 4

Medicine Details:

1. **Codeine:** All the available Schedule 3 over the counter (OTC) compound medications containing codeine available at Pharmacies. The medications include Panadeine®, Panadeine Extra®, Nurofen Plus®, Aspalgin® and Mersyndol® (plus many other brands)(1).

2. **Active ingredient:** Codeine
   Codeine is sold in "over the counter" combinations with other medications including paracetamol, aspirin and ibuprofen.

3. **Dosage form:**
   Codeine varies from 8 mg to 15 mg per tablet.

4. **Indication for Medication:**
   Analgesics containing codeine are sold for the "effective temporary relief of strong pain and discomfort associated with a number of different medical conditions" (2).

5. **Current poisons schedule:** Codeine containing preparations were switched in 2010 to Schedule 3. This aimed to provide increased surveillance of the medication usage by a Pharmacist to ensure quality use of medicines. This rescheduling occurred as it was recognised there is potential for harm if used inappropriately. As will be seen (see Figure 1) although initially this may have reduced the exposure of the community to harm from these products, and thus decrease the incidence of abuse, since 2011 the numbers presenting to Waranilla, Drug & Alcohol Services SA (DASSA) for detoxification from codeine has continued to grow. We are unaware of any study that has investigated the *pros* and *cons* following the switch to Schedule 3.

6. **Proposed poisons schedule:** Schedule 4.
   Codeine fits the requirements for Schedule 4, as outlined in the Australian National Consultative Committee on Therapeutic Goods (NCCTG) scheduling, factors for prescription only medicines (Schedule 4) which include:
   - **The use of the substance (codeine) at established therapeutic dosage levels, may produce dependency but has a moderate propensity for misuse, abuse or illicit use.** Control of access and duration of therapy by a medical, veterinary or dental practitioner is required
   - **The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical practitioner is required to minimise the risk of using this substance (codeine).**

APPLICANT DETAILS

- Dr Penelope Briscoe, Head of the Pain Management Unit, Royal Adelaide Hospital.
- Associate Professor Pamela Macintyre, Director of the Acute Pain Service, Royal Adelaide Hospital
- Professor Jane Andrews, Head IBD Service + Education, Department of Gastroenterology, Royal Adelaide Hospital
- Dr Tim Semple, Deputy Director of the RAH Pain Management Unit, and Immediate Past President of the Australian Pain Society.
- Prof David Watson, Head, Flinders University Department of Surgery, Flinders Medical Centre.

- Date of Submission 2015.

- Contact email address penny.briscoe@health.sa.gov.au
- Postal address: C/- of the Royal Adelaide Hospital Pain Management Unit, Level 6, Emergency Block, North Terrace, Adelaide 5000.
- Ph No: 08 8222 5403
- Fax No: 08 8222 5904

Declaration:

I, Penelope Anne Briscoe, on behalf of and with the support of my colleagues, declare that the information provided in this application is true and current.

We undertake to treat as confidential information, and not publically disclose the notice of interim decision in respect to this application, until (if relevant) the interim decision is published pursuant to subsection 42ZCZP of the Therapeutic Goods Regulation 1990 or the final decision is published pursuant to subsection 42ZCZS of the Therapeutic Goods Regulation 1990.

Dr Penelope Briscoe

23rd February 2015

PART 1 – SUMMARY OF THE APPLICATION

PROPOSED SCHEDULING / RESCHEDULING OR OTHER CHANGE TO THE POISONS STANDARD

- Dr Penelope Briscoe and Colleagues request rescheduling of codeine containing compound analgesics from Schedule 3 to Schedule 4

SUGGESTED SCHEDULING

Schedule 4 – Proposed Amendment for compound codeine analgesics.

MEDICATION	CURRENT	PROPOSED
Panadeine® and other brands. Paracetamol 500mg / Codeine Phosphate 8mg.	Schedule 3	Schedule 4
Panadeine® Extra and other brands. Paracetamol 500mg / Codeine Phosphate 15mg.	Schedule 3	Schedule 4
Nurofen® Plus and other brands. Ibuprofen 200mg / Codeine Phosphate12.8mg.	Schedule 3	Schedule 4
Aspalgin® and other brands. Aspirin 300mg / Codeine Phosphate 8mg.	Schedule 3	Schedule 4
Mersyndol® and other brands. Paracetamol 450mg / Codeine Phosphate 9.75mg / Doxylamine.	Schedule 3	Schedule 4

There are over 40 different combination analgesic preparations available in Australia[(1)]. Most contain combinations of paracetamol 500 mg with codeine in doses from 8-30 mg. Some also contain doxylamine. Others are paracetamol/ dextropropoxyphene, aspirin / codeine, aspirin / dihydrocodeine, and ibuprofen / codeine[(1)]. This submission is in regard to *all* OTC codeine containing compound analgesics.

SUBSTANCE SUMMARY

Codeine is a prodrug requiring metabolism by the cytochrome P450 enzyme system to the active analgesic morphine. There is large individual variability in the ability to metabolise the codeine to morphine, due to the CYP2D6 enzyme genetic variants.

This genetic variability in metabolism *prevents* (up to) 10% of the Caucasian population of Australia from metabolising the prodrug codeine, to the active analgesic ingredient morphine, rendering it useless as an analgesic with no analgesic property, and with no benefit for these individuals[3]. These "poor metabolisers" of codeine receive no analgesic benefit but may still experience adverse effects[1,3].

A further proportion, (up to 4-10%) of the Australian population are "Ultra-rapid" metabolisers, and this is the group who may experience excessive and potentially dangerous (even lethal) toxicity[3].

With Australia becoming more multicultural we need to be aware that the percentage of "Ultra rapid" metabolisers, vary across ethnic groups (North African up to 30% and Middle Eastern up to 20%), increasing the risk for harm to individuals and increasing their risks of developing dependence on and abusing and misusing the codeine medications[3].

OVERVIEW

- Codeines analgesia is variable and unpredictable in up to 20% of the Australian population. This figure may be higher in people of North African or Middle Eastern descent.

- Patients who are "Ultra-rapid metabolisers" are at high risk of harm, with the compound codeine containing analgesics. They may develop dependence on the codeine and then over-use the compound analgesics and develop *all the sequelae* of high dose paracetamol or ibuprofen .

- High dose codeine (60 mg) alone is a poor analgesic with a NNT (one patient obtaining 50% pain relief) of 12[8].

- Compound analgesics containing codeine plus paracetamol or codeine plus ibuprofen, show minimal analgesic benefit compared to the simple analgesics (paracetamol or ibuprofen) alone[8].

PART 2 – BODY OF THE APPLICATION

BACKGROUND

Codeine could be classified as a “Heritage” drug. The current understanding of the unpredictable pharmacology of codeine would in our opinion prevent it from being a TGA approved analgesic if proposed today.

The level of analgesia from codeine varies considerably from person to person, from no analgesia to potentially toxic effects and this response is unpredictable, unless their cytochrome P450 2D6 (CYP2D6) status is known.

The “Ultra-rapid” metabolisers are the individuals who are at risk of significant harm associated with the use of the compound codeine analgesics. The effects of the augmented metabolism (opioid toxicity, including life threatening respiratory depression) can be seen at “usual” doses. There are many reports, over many years [3,4,5,6,7], of significant harms (including death) in these individuals, even with them using modest / usual dosages only, of the codeine combination medications.

PART 2.1 CRITERIA WHICH MUST BE ADDRESSED:

(A) RISKS & BENEFITS ASSOCIATED WITH THE USE OF A SUBSTANCE

- Combination codeine analgesics have been marketed to provide “temporary relief of pain and discomfort” associated with a number of pain conditions: headaches, Migraine headaches, Tension headaches, Period pain, Back pain etc[2].
- Codeine has been perceived as a safe and effective analgesic but increasing there are calls to withdraw codeine from the market[3].
- Having these analgesics available without prescription, means patients can access them without the cost and time required to see their General Practitioner.
- This does give the patient some autonomy and they are responsible for the cost of these medications.
- With mounting evidence of unpredictable analgesia and with low NNT’s, codeine’s “place in therapy is uncertain” [3].
- In a meta-analysis, codeine (60mg) as a single drug for postoperative pain, did not provide adequate analgesia in most patients (NNT 12). Codeine in fact performed unfavourably compared with the simple analgesics (paracetamol and ibuprofen) alone [8].
- Benefits of adding codeine to paracetamol, compared to the same dose of paracetamol alone was at best modest, with only a further 10-15% of patients achieving adequate analgesia[3,8].
- The modest benefits of codeine are outweighed by adverse events[3,9].
- Most of the preparations of OTC codeine preparations in Australia contain considerably less codeine than the doses studied in clinical trials. It is highly questionable whether the low dose codeine combination products can provide meaningful analgesia [1,3].

(B) THE PURPOSES FOR WHICH A SUBSTANCE IS TO BE USED AND THE EXTENT OF USE OF THAT SUBSTANCE

- OTC codeine analgesics allow more rapid access to these medications, (if deemed necessary), to temporarily treat mild pain.
- It allows patient autonomy and empowers them to self-manage minor conditions.
- Use of OTC codeine analgesics is widespread with reported sales of 16 million packs/ year [10].
- 33.3% Australians reported they had used OTC codeine analgesics in the Australian Institute of Health and Welfare 2014. National Drug Strategy Household Survey in the preceding twelve months.

(C) TOXICITY AND SAFETY OF THE SUBSTANCE

- Many individuals use this medication appropriately and safely.
- The "unknown" is – what is an individual's CYP2D6 metaboliser status?
- The prevalence of both poor and ultra-rapid CYP2D6 metaboliser phenotype in the population varies (2-20%), differing significantly with ethnic background[3].
- Both NPS MEDICINEWISE[6] and the Panadeine® product information[2] recommend *"Do not use codeine in adults or children known to be ultra-rapid metabolisers of codeine."* The Panadeine® product information in fact states "Ultra-rapid metabolism" is a CONTRAINDICATION to use.
- Most individuals DO NOT KNOW their CYP2D6 status. This suggests unless patients are aware of their CYP2D6 metaboliser status, *they should not be able to buy / access codeine.*
- There is only one laboratory in Australia "approved" to do this testing at the cost of approximately $200/ person[11].

(D) DOSAGE, FORMULATION, LABELLING, PACKAGING AND PRESENTATION OF A SUBSTANCE

- If combination codeine products are to remain available, it is essential that appropriate warning labels need to be added to the packaging.
  - Risks of addiction / dependence.
  - Risks of harm from the paracetamol / ibuprofen.
  - Risk of death.
- Access to codeine within Australia is inconsistent. Codeine 30 mg is classified as a Schedule 8 drug (with potential for abuse or addiction). Since rescheduling in 2010, up to 5 days' supply of the OTC analgesic is available in one pack. Thus Panadeine ® Extra, (8 tablets a day), has 40 tablets (600 mg codeine) / packet. This is the same dose of codeine only available as a S8 prescription (Codeine Phosphate 30 mg x 20) [3].

(E) POTENTIAL FOR MISUSE/ABUSE OF THE SUBSTANCE

For individuals who are "Ultra-rapid metabolisers", society has a "duty of care", to protect them from these potentially lethal medications, switching them to Schedule 4 (ie under Medical Supervision).

Ferner and Beard in the BMJ 2008 stated: "*there are also disadvantages when relatively safe and effective analgesics such as paracetamol and ibuprofen are combined with small doses of opioids that are likely to bring trivial therapeutic benefit but increase the risks of abuse, addiction and adverse effects".*[12]

If as has been stated, in both NPS MEDICINEWISE[6] and Panadeine® product information[2], that before taking codeine the patient should know their CYP2D6 metaboliser status, *codeine should never be available "over the counter".*

GP's prescribing Codeine Phosphate 30 mg, (Schedule 8) need to discuss with their patients the risks of 'Ultra-rapid" metabolism and warn them to seek help if they become excessively drowsy.

Codeine is a weak analgesic *per se*, and it appears that it adds little to the analgesic efficacy of ibuprofen or paracetamol in combination. In the 80% of Australians who metabolise their codeine as expected, evidence is mounting that codeine is a poor analgesic . The Cochrane Database 2011 has reviewed a number of analgesics and the NNT for codeine 60 mg is 12 (50% pain relief only). (Figure 2.)[8]

In May of 2009, as the Dean of the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists, I wrote to the Secretary of the National Drugs and Poison Federal committee requesting the "up-scheduling" of the "over the counter" (OTC) codeine combinations.

I acknowledged at that time that the National Drugs and Poison Schedule Committee proposed changes would include:

- Deletion of Schedule 2 codeine entries and amending this to Schedule 3 codeine entries.
- Limiting the recommended daily dose to a maximum of 100 mg of codeine base.
- Limiting pack size to a maximum of 5 day's supply.
- Restricting divided preparation to a maximum of 12 mg of codeine based per dosage unit.

I commented in my letter that I had discussed these proposed changes with a number of Colleagues who represented Acute Pain Medicine Physicians, Chronic Pain Management Physicians, and representatives from Drug and Alcohol Services, and we all supported the NDPSC in their endeavours.

Unfortunately, despite this rescheduling in April 2010, we are aware of, and are still seeing a concerning number of patients who are admitted each year

to the Royal Adelaide Hospital with complications from, and significant issues associated with, codeine misuse and abuse. Our Colleagues at Flinders Medical Centre have written of their experience. (13)

Warinilla (DASSA) monitor patients admitted and managed in their Service with Dependency problems. The number of patients treated for Codeine Dependency has risen from 31 a year in 2002-03 to 174 in 2013-14.(Figure 1). You will note (from the graph) there was a dip in 2009-2010 (codeine became Schedule 3 on 30th April 2010) however, since 2010 the number of patients affected each year has continued to rise.

Drug and Alcohol Specialists report the treatment of codeine dependency is often more difficult than for other opioids (including oxycodone), and the reasons for this remains uncertain(14).

Rescheduling to Schedule 3 has *not achieved* the required reduction in harm to the individuals affected, and more needs to be done. Indeed, we are unaware of any formal study that has examined the benefits and harms done by the switch to Schedule 3 and would recommend that such a study be conducted.

We have seen a number of patients admitted to the Royal Adelaide Hospital with a myriad of symptoms. Initially, these patients often present extremely well, and hide their codeine addiction (13). A higher proportion are female, they are often working and drug abuse is not suspected. They therefore undergo many investigations and even surgery until someone recognises that a lot of these symptoms may relate to their use of codeine containing preparations (we have most commonly seen this with Nurofen plus). Even when first asked the patients will usually initially deny there is a problem (13).

In my letter of May 2009 I presented the outline of a young woman (a University psychology student) who became addicted to Nurofen Plus and, as a result of her misuse, had undergone a number of surgical procedures, had a multiple of complications, and had been at or near death on a number of occasions.

In that letter I commented that I believed that she was currently doing reasonably well but it had been a long battle, and I outlined the complications she had had from her Nurofen plus abuse which included:

- A cholecystectomy (for vague upper quadrant abdominal pain).
- A partial gastrectomy for suspected gastric Crohn's.
- Peritonitis following that procedure.
- A deep vein thrombosis complicated by pulmonary embolus.
- Protein losing-enteropathy with a serum albumin of 5gms/L.
- E.coli septicaemia.
- Hypogammaglobulinaemia.
- Anaemia of chronic disease.
- Vitamin B12 deficiency.
- Neuropathy of chronic disease (similar to Guillain-Barre Syndrome).

I have had further information that in fact this young woman still continues to struggle and since then we have seen many others. We are also aware that our colleagues internationally are aware of this problem and, in fact, in Sweden, Germany and the United States, codeine is a prescription only medication.

(F) ANY OTHER MATTER THAT MAY BE RELEVANT TO THE SCHEDULING OF A SUBSTANCE

- As outlined, there is little evidence that codeine has much analgesic effect (NNT 12) but does cause harm.
- With is unpredictable metabolism, it is unlikely it would be approved by the TGA, today.
- The newly released alternative combination of non-opioid analgesics, ibuprofen plus paracetamol appears as though it may provide better analgesic efficacy with a NNT of 1.5. [8].

PART 2.2 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PARTS 1-3 OR PART 5 OF THE POISONS STANDARD

- Not applicable

CONCLUSION

- Codeine is ineffective as an analgesic (NNT 12).
- In up to 10% of our population (poor metabolisers), it is ineffective but can still causes harmful effects .
- In up to 4 - 10% of our population (ultrarapid metabolisers), it can cause life threatening toxicity
- *If it is to remain as an analgesic, then the metaboliser status of the patient needs to be ascertained before it is prescribed or dispensed.*

PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

- See my summary document (attached)

SUPPORTING DATA DETAILS

- See my summary document (attached)

COPIES OF PAPERS REFERENCED

- Attached

PART 4 – BIBLIOGRAPHY

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PART 5 – SUBMITTING THIS APPLICATION

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