

Re-scheduling of Codeine formulations

Dr Michael Tedeschi MBBS FChAM(RACP FRACGP MASAM DipFM

Senior Staff Specialist, Alcohol and Drug Program ACT Health

Senior Lecturer, ANU Medical School

TGA Rescheduling Decision

- Over the counter codeine containing compound analgesics (OTC CACCs) will become prescription only from 1 Feb 2018
 - Analgesics e.g. Panadeine & Nurofen Plus
 - Cold & flu meds e.g. Codral
- Rationale based on high quality evidence
 1. Lack of additional effectiveness
 2. Associated harms
 3. Extent of misuse & harms in community
 4. Availability of safer effective management

Minimal Analgesic Benefit

- Combination analgesics containing codeine plus paracetamol or plus ibuprofen provide minimal analgesic benefit c.f. simple analgesia (paracetamol or ibuprofen) alone
 - Moore & McQuay, 2011
- The apparent modest benefits of 10-15% are outweighed by the adverse events



CCCA Related Deaths

- Mortality associated with OTC CACC has not always been reliably identified
- Increasing codeine related deaths in Australia have been primarily driven by an increase in accidental deaths
 - They have now reached around half the number of deaths attributed to heroin & Schedule 8 opioids
- A recent study described that the overall rate of codeine-related overdose deaths more than doubled in the ten years to 2009, & OTC CACC contributed to a substantial proportion of these deaths

➤ Pilgrim et al, 2013; Roxburgh et al, 2015

- While noting deaths are not the only harm we ought to be concerned about
 - Renal, hepatic, GIT, metabolic, opioid addiction, medications focus for wrong reasons, ineffective treatment while declining or failing to access more effective Rx
- Also noting case finding rates are low & substance use data vastly under-captures the size of the problem

In Australia, the rate of deaths due to codeine – the most popular opioid – between 2001 and 2009 increased from 3.5 to 8.7 per million population. This increase may have been contributed to by the introduction of more potent over-the-counter (OTC) products including those that combined codeine with ibuprofen.³

The TGA noted that codeine toxicity was a factor in 1,437 deaths between 2001 and 2013, and both OTC and prescription sources were implicated. The National Opioid Pharmacotherapy Statistics show that in 2013 codeine was the opioid drug of dependence for 1038 clients receiving opioid substitution pharmacotherapy.⁵

- Final decision on re-scheduling of codeine: frequently asked question 20 December 2016 Media release. Australian Government Department of Health Therapeutic Goods Administration <http://www.tga.gov.au/final-decision-re-scheduling-codeine-frequently-asked-questions>

CACCs are a Problem

- This evidence indicates that codeine is a weak analgesic & that it appears to add little if anything to the analgesic efficacy of ibuprofen or paracetamol combination analgesics, while at the same time creating a risk of many serious adverse effects, including the risk of addiction & all of the life constraining consequences that brings with it

➤ Dobbin, 2015

How Safe & Effective are OTC CACCs?

- 3-methylmorphine (codeine) has very little inherent analgesic effect &...
 - Unpredictable individual response...
- Codeine is a prodrug metabolised via the cytochrome P450 (CYP2D6) pathway to the active agent morphine

Genetic Polymorphism

- Due to genetic polymorphism & variation in metabolism, in an evidence based world, codeine would only be contemplated when the patient's P450 (CYP2D6) status has been confirmed
- Genetic polymorphism of P450 status in patients can only be confirmed via a blood test & this is not readily accessible (one accredited lab in AUS, ~\$200 per test)
 - NPS MEDICINEWISE (2013) states before taking codeine, the patient should know their CYP2D6 status & codeine should never be available OTC
 - Very few people would know their status

Highly Variable Codeine Metabolism

Three Groups Identified

1. *Poor metabolisers* (low activity variants) – are unable to convert codeine to morphine efficiently and as a consequence may experience little or no analgesic effect
2. *Extensive metabolisers* (high or normal activity variants) – analgesic effect with 200-240mg oral codeine equal to OMEDD of morphine 30mg (approx. 8:1 ratio)
3. *Ultrarapid metabolisers* (multiple gene copy variants) – may metabolize codeine too efficiently leading to morphine intoxication given the analgesic effect of codeine in these individuals is equal to that of morphine (approx. ratio 1:1)

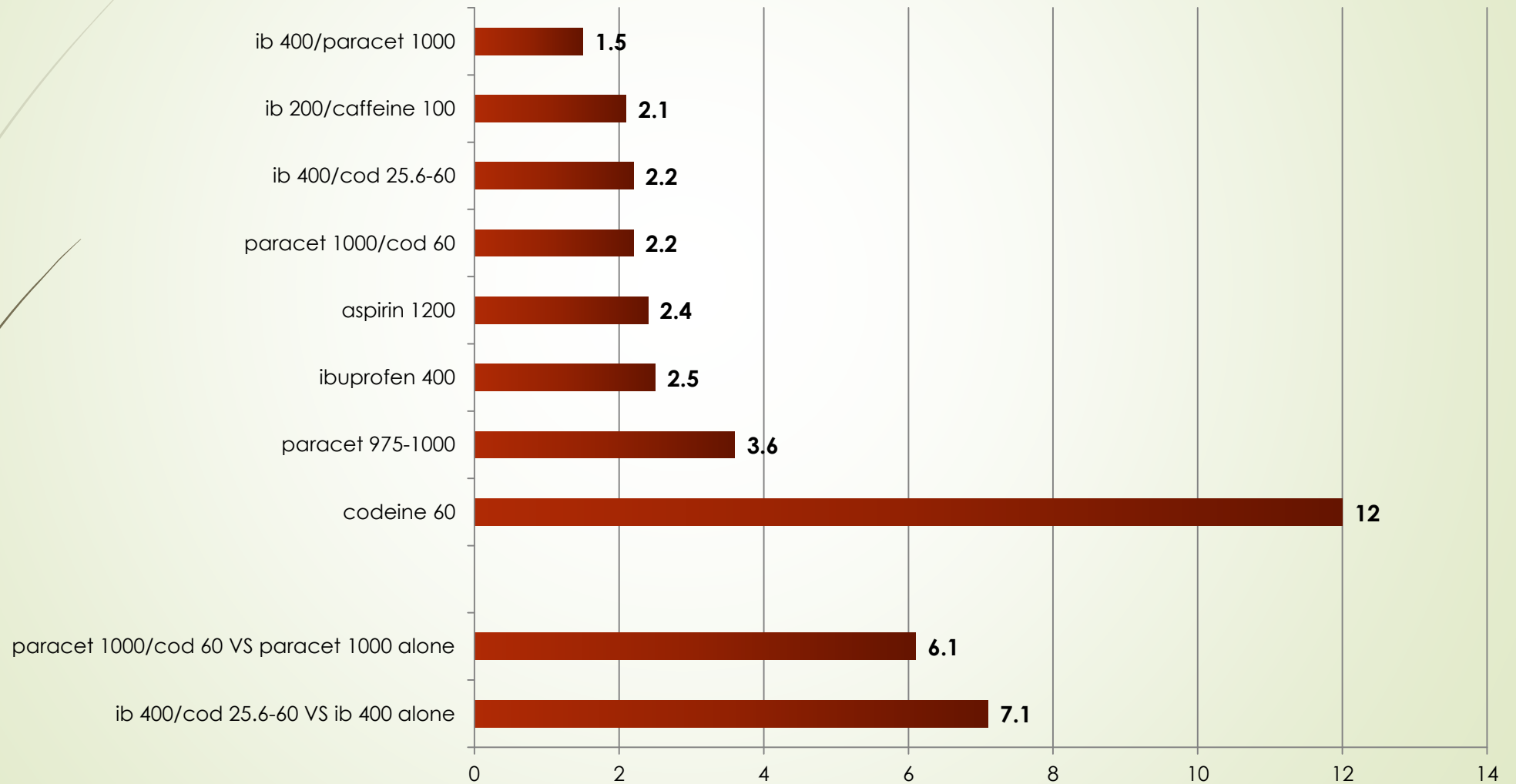
How Safe & Effective are OTC CACCs?

- Up to 10% of the Australian population are poor metabolisers of 3-methylmorphine
 - Leading to poor analgesic response whilst retaining the potential for harmful effects
- Up to 4-10% of the Australian population are ultra-fast metabolisers of 3-methylmorphine & are high risk of harm due to overdose from normal therapeutic doses

Low Efficacy at a Population Level

- Codeine in low (OTC) doses does not add additional analgesic benefit over & above analgesia provided by optimal dosing of other OTC agents such as ibuprofen & paracetamol, while at the same time presenting substantial risk
- A Cochrane review indicates the Number Needed to Treat (NNT) with a dose of **codeine** 30mg /**paracetamol** 1000mg for a 50% reduction in acute pain intensity is **7.1**
 - The NNT for **paracetamol** 1000mg alone is **3.5**
- The NNT for **ibuprofen** 400mg/ **codeine** 25.6-60mg is **2.2**
 - The NNT for **ibuprofen** 400mg **alone** is **2.5**
- The NNT for **ibuprofen** 400mg/ **paracetamol** 1000mg is **1.5**
- Summary of Cochrane reviews of RCTs evaluating efficacy of oral analgesics in different dose/drug combination in Rx of acute postoperative pain (Moore et al, 2011; Derry et al, 2013; Derry et al, 2015)
 - With the confidence interval almost overlapping , the authors commented that the difference barely reached statistical significance

Numbers Needed to Treat



Serious & Often Life Threatening Harm

- Serious harm arises from high dose exposure to supra-therapeutic doses of ibuprofen or paracetamol in CACC secondary to codeine addiction (Dobbin, 2016)
 - Gastric & duodenal ulcer with complications (haemorrhage & perforation, gastric outlet obstruction, chronic occult blood loss)
 - NSAID enteropathy with diaphragm disease, strictures, bowel obstruction, & small bowel ulceration & perforation
 - Hypoalbuminaemia
 - Renal tubular acidosis
 - Life-threatening hypokalaemia
 - Rhabdomyolysis
 - Iron deficiency anaemia
 - Paracetamol hepatotoxicity

Long term Opioid therapy is Not Indicated in the Treatment of PNMP Based on Evidence

Clinical Landscape is changing dramatically

Opioid therapy is not indicated for the long term management of chronic non-cancer pain based on current evidence. The limited evidence supporting long term efficacy is weak and based on non-blinded, industry-sponsored trials with significant potential for reporting bias. This is outweighed by a consistent body of evidence demonstrating lack of long term analgesic efficacy, lack of improvement in function or quality of life and greater risk of harm to both individuals and society than previously recognised.



2000-03



2012



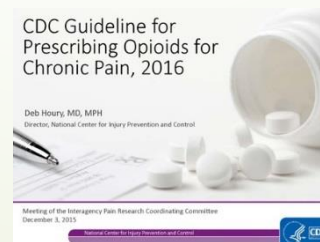
2015



2015



2014



2016

Clinical Management Pathways

A. Low Level & Uncomplicated Codeine Use

- Low level use & *absence* of *inappropriate* reasons for use & absence of *aberrant* drug use behaviours may be associated with some symptoms of opioid withdrawal but these patients won't require a medication management intervention (majority of persons taking OTC CACC)
 - Pharmacist &/or GP can provide information, normalise & promote confidence in the patient to self-manage any mild withdrawal symptoms that may arise (i.e. time limited sleeping difficulty, mild flu like symptoms or increased craving for codeine medications)
 - Advise that it will be short-term & manageable
 - Advise that alternative (& more effective) analgesia is available in paracetamol/ibuprofen combinations (e.g. Maxigesic®) or simply continuing with the paracetamol or ibuprofen alone, when no evidence of medical harm, as appropriate to the patient & medical history & presentation

Clinical Management Pathways

B. Moderate Level Use (& Minimally Complicated)

For moderate doses (> 120 mg per day or slightly more daily for more than a month), uncomplicated or minimally complicated use, or where patient reports or demonstrates minor withdrawal symptoms or some psychosocial or medical complexity) & the patient is motivated to cease codeine use, opioid withdrawal symptoms may create a specific challenge separate from any associated underlying pain issues

- Weaning codeine (by gradually tapering the codeine dose) is generally an ineffective strategy & cannot be recommended
- However, medication assistance may be required & helpful

Clinical Management Pathways

B. Moderate Level Use (& Minimally Complicated)...cont.

- These patients may benefit from symptomatic medications to alleviate the most worrisome withdrawal symptoms (while carefully considering any contraindications, especially with NSAIDs**)
- Cease codeine on pre-determined day (could be very soon if no supplies)
 - Simple analgesia using ibuprofen or paracetamol (whichever not used in excess in OTC)
 - Loperamide
 - Hyoscine butylbromide
 - Metoclopramide
- **Don't prescribe benzodiazepine medication, quetiapine or other sedative medication! Don't prescribe CACCs, Panadeine Forte, strong opioids or Tramadol which are also 'low value' & present unacceptable risks**
- Withdrawal may amplify existing pain, so explain this to your patient
- If this approach fails, consider buprenorphine assisted withdrawal management (next slide)
- If that fails, follow the high dose/ high complexity pathway


Classic “4Cs” of Addiction – Key Indicators


1. Loss of **control**
2. **C**raving
3. **C**ompulsive use
4. **C**ontinued use despite harm

5. **S**alience

- **Tolerance** & a **withdrawal** syndrome on cessation of use or sudden significant reduction of dose may be observed but are not necessary to diagnose dependence (‘addiction’)

Translating Degree of Dependence to Intervention

No dependence  Stop Codeine and use alternative analgesia (if at all)

Mild Physical Dependence but no psychological dependence (“addiction”) -
 Withdraw over 7 days

Dependence -  Consider referral for maintenance opioid replacement

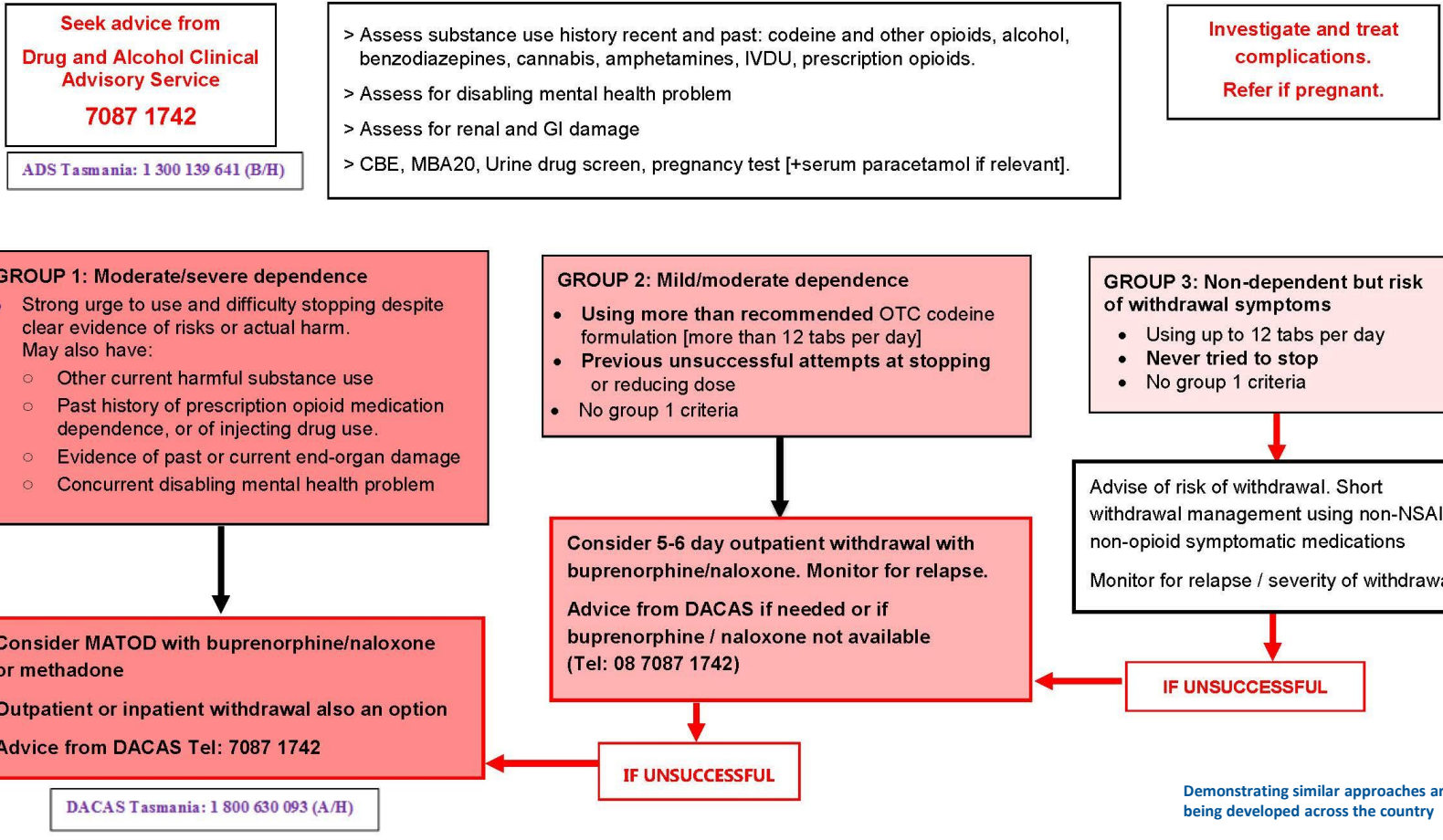
Clinical Management Pathways

C. High Level Use &/or Use Associated with Psychosocial Complexity & Opioid Dependence

- At high levels of codeine intake (i.e. daily use of $\geq 2X$ max rec. daily dose over months to years, (360 mg/24 hours), biopsychosocial complexity, opioid withdrawal Sy & Sx, (+/-) medical harms, psychosocial dysfunction & distress, (+/-) Hx of relapse - patient warrants definitive Rx of dependence
 - Consider referral to your Addiction Medicine service or other medical practitioner who is experienced & authorised to prescribe Methadone and Suboxone or (even better!), request support to become an authorised prescriber & continue to Rx the patient
 - Consider referring to multi-disciplinary pain management service &/or mental health services when this expertise is indicated
 - But Multidisciplinary Pain Services may advise referral only if & when the patient is willing to engage & motivated to adhere to a new approach to their pain management, given their limited resources

DASSA Pathway (SA)

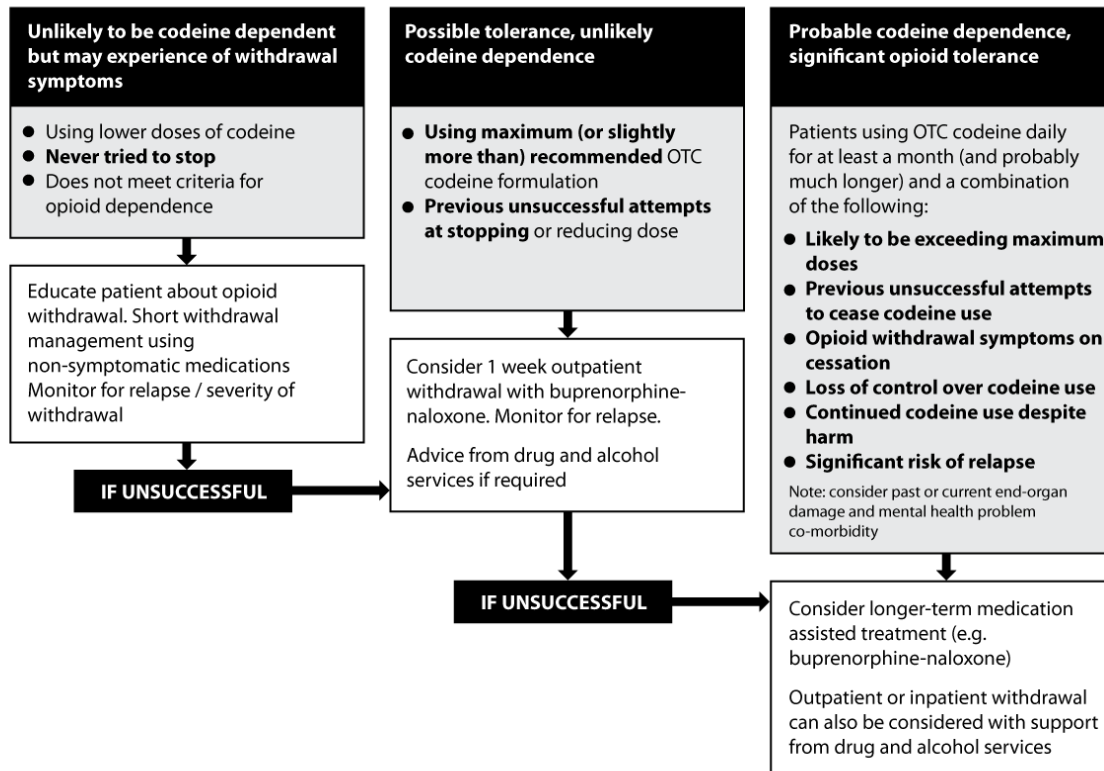
QUICK GUIDE TO MANAGING PATIENTS WITH REGULAR OTC CODEINE USE (i.e. history of daily or almost daily for at least one month)



Clinical Management Pathways

QUICK GUIDE TO MANAGING PATIENTS WITH REGULAR OTC CODEINE USE (i.e. history of daily or almost daily for at least one month)

- ➔ Assess substance use history recent and past: codeine and other opioids, alcohol, benzodiazepines and any other substance use
- ➔ Assess for mental health problems
- ➔ Assess for gastrointestinal bleeding or ulcers with ibuprofen use
- ➔ Full blood count, liver and kidney function, urine drug screen, pregnancy test (+serum paracetamol if relevant).



- Dr. Suzanne Nielsen, NDARC, UNSW work in progress, Dec, 2017

Where to get help if you're in trouble!!

ACT Health Intake - 02 6207 9977

A&D Specialists

A&D Liaison



Via TCH Switchboard