Managing patients with regular OTC codeine use

Background

On 1 February 2018, all medicines containing codeine will require a prescription; there will no longer be access to over-the-counter codeine containing medicines without a prescription. These changes are based on clear evidence that over-the-counter codeine (OTC) containing preparations offer very little additional benefit when compared to similar medicines without codeine, and are susceptible to misuse, resulting in significant death and disability in the Australian community, in part due to ingestion of supra-therapeutic doses of NSAIDS and paracetamol.

The metabolism of codeine is highly variable due to dependence on cytochrome p450 enzymes to convert it to morphine. Genetic variation in CYP450 result in some people experiencing very little opioid effect from codeine and others experiencing close to 1:1 conversion to morphine.

People taking codeine daily for more than one month can experience withdrawal symptoms when they stop taking codeine. This document outlines an approach to the management of such patients in primary care. Given the lack of controlled trials for the management of codeine withdrawal and dependence, the following recommendations are adapted from the experience of treating dependence on other opioids. The majority of patients using codeine intermittently will stop their OTC codeine use and will not need any specific treatment other than explanation and re-assurance.

Some patients with ongoing pain issues will need alternative pain management strategies. These will include non-pharmacological interventions, as well as medication based and may include (non-opioid) adjuvants.

There is another more severely affected group who are primarily codeine dependent. This group may require support to cease their codeine use and prevent relapse or alternatively they may need ongoing Medication Assisted Treatment for Opioid Dependence using Suboxone or methadone.

For those codeine dependent people who undertake a quick (i.e. 1-2 week) withdrawal, either symptomatic medications or Suboxone [for which an authority from the Drugs of Dependence Unit is needed] are recommended (see flow chart FIGURE 1).

Where buprenorphine/naloxone treatment is not possible, consult with a Drug and Alcohol Clinical Advisory Service [DACAS - SA 08 7087 1742] for other options. Other medications (such as codeine, clonidine, tramadol, and buprenorphine patches) can be used with caution in outpatient opioid withdrawal, however each has specific risks, dosing, and regulatory considerations and it is recommended they only be used in consultation with an Addiction Medicine Specialist.
Assessment

> If the person is not using OTC codeine every day or almost every day, for at least 1 month, they are unlikely to have developed tolerance or dependence.

> Is the person experiencing physical harm from their OTC combination product?

- Ibuprofen-codeine: Peptic ulceration, renal tubular acidosis, [eg unexplained low K⁺], unexplained anaemia, “histology negative” Crohn’s disease, NSAID enteropathy.
- Paracetamol-codeine: Hepatic failure, acute drug induced hepatitis

> Is the person codeine dependent?

Irene age 28 attends her GP asking for assistance with her OTC codeine problem. She was recently in hospital with severe iron deficiency anemia and was given an iron infusion, booked for an outpatient endoscopy, and advised to see her GP because of her use of codeine-ibuprofen. Irene has been using between 20 and 40 tablets per day for about 12 months.

Initially she started to use them because of intermittent pelvic pain, but found that they also helped her relax when she was feeling stressed. She has tried to stop at least twice but she experiences diarrhoea, nausea, muscle pains and aches and she has strong intrusive thoughts about using the tablets which are difficult to resist.

> Some questions to ask:

- Quantity and frequency of codeine used currently?
- Past history of prescription opioid dependence?
- Past history of injecting drug use?
- Physical complications?
- Disabling mental health problem?

> Responding to evidence of physical complications:

- If anemia, GI symptoms, low albumin, monitor for improvement after cessation of medications likely to cause complications; if persistent abnormalities then consider further investigation and referral.
- If paracetamol has been consumed in supra-therapeutic amounts then refer to the Consensus Guidelines on Management of Paracetamol Poisoning in Australia and New Zealand.
- If ALT is ≥ 50IU/L, OR serum paracetamol is ≥ 20 mg/L (132μmol/L) consider N-acetyl-cysteine treatment and discuss with specialist gastroenterologist.

> Psychological problems

- Anxiety disorders and depression are common in people who have developed problems with OTC codeine containing analgesics.

> Other substance use

- People using OTC codeine preparations frequently use other substances; in particular alcohol and benzodiazepines. Assess their recent use of alcohol, benzodiazepines, cannabis, other opioids, and stimulants such as methamphetamine. If problematic use is identified then work with the patient to address this use and seek advice from an Addiction Medicine Specialist DACAS (08 7087 1742)

> Investigations to consider

- CBE
- MBA 20
- Urine drug screen request screen for drugs of dependence including methadone, buprenorphine, oxycodone and fentanyl
- Serum paracetamol if relevant
- Urine pregnancy test.
Management of codeine use disorder

- **GROUP 1: Moderate/severe opioid dependence group**
  A minority of patients will be clearly opioid dependent. Typically such patients are using OTC codeine multiple times daily for more than a month and have been unable to stop taking the codeine containing medications despite concerns about the risks of doing so. They may also have other elements more typically seen in drug dependence such as:
  - A past history of other harmful substance use, including prescription opioid use
  - Evidence of past or current end-organ damage
  - Significant concurrent disabling mental health problems
  - A past history of prescription opioid dependence or injecting drug use

  In these situations consumption has typically escalated over time out of proportion to any underlying medical condition. There have usually been unsuccessful attempts to stop, and they feel a strong desire to take codeine medication.

  Simple medication assisted (i.e. non-opioid) withdrawal management is NOT recommended in this group. They are not likely to tolerate sudden cessation of opioids and may be exposed to significant risk from other sources of opioids.

  These patients will probably require ongoing Medication Assisted Treatment for Opioid Dependence (MATOD) with Suboxone [buprenorphine/naloxone], or alternatively with methadone. See below for details. However some of these patients may not wish to embark on a MATOD program due to its restrictive nature and may elect for a simple withdrawal. [see below]

  Seek advice from the Drug and Alcohol Clinical Advisory Service (08 7087 1742) if unclear about management. Patients may be able to be managed in general practice setting or may need to be referred to specialist addiction service, depending on individual circumstances.

- **GROUP 2: Mild / moderate dependence group**
  Patients using OTC codeine daily or almost daily for more than a month:
  - using more than recommended (more than 12 tabs per day)
  - without features of severe dependence as listed above,
  - with previous unsuccessful attempts at stopping or reducing their use.

  Opioids should not be used for ongoing management of chronic non-malignant pain.

  Supported withdrawal over a 1-2 week period is recommended using a short course of buprenorphine/naloxone (Suboxone) treatment. See below.

  Seek advice from DACAS (08 7087 1742) if unsure.

  Use other non-opioid analgesics such as paracetamol or NSAIDs as per guidelines.

  Counsel patient (or refer) for non-pharmacological approaches such as aerobic exercise, psychological approaches such as guided imagery, meditation, cognitive therapy.

- **GROUP 3: Not opioid dependent but at risk of mild opioid withdrawal group**
  Patients using OTC codeine daily or almost daily for more than a month,
  - using up to recommended doses (up to 12 tabs per day)
  - without characteristics of dependence
  - previously never having tried to stop unsuccessfully.

  A trial of symptomatic treatment for opioid withdrawal is indicated. (see below).

  If this is unsuccessful then it is likely that the person in fact has at least mild/moderate opioid dependence and a short course of Suboxone for opioid withdrawal would be the next step.
Opioid withdrawal

**Symptoms of withdrawal** are similar for all opioids, but are of varying severity and duration depending on opioid taken. For example, physical symptoms of codeine withdrawal commence six to 12 hours after last use and last for approximately five days. Symptoms can range from mild to very unpleasant, but are rarely life-threatening (providing adequate hydration and electrolyte balance is maintained) and include:

- lacrimation, rhinorrhea and sneezing
- dilated pupils > 4mm
- yawning
- hot and cold flushes, sweating and pilo-erection
- craving
- anxiety, restlessness and irritability
- disturbed sleep
- gastrointestinal tract symptoms (for example anorexia, abdominal pain, nausea, vomiting and diarrhoea)
- muscle, bone and joint aches and pains,
- headache, muscle cramps
- tremor

Opioid withdrawal management

1. **Symptomatic** for mild withdrawal
   - Metoclopramide 10-20mg 8 hourly PO for nausea
   - Simple analgesia using ibuprofen or paracetamol (whichever was not used in excess in OTC)
   - Loperamide 4mg stat then 2mg PRN up to 16mg per 24hours total.

   If the patient is not coping with this treatment then consider using Suboxone [buprenorphine/naloxone]

2. **With Suboxone** (Buprenorphine/naloxone) for moderate to severe withdrawal

   Buprenorphine is ideal for opioid withdrawal management as it is a partial agonist and can be administered with once daily supervised dosing. Any doctor in South Australia can prescribe buprenorphine for opioid dependence for up to 5 patients simultaneously but will need to apply for a permit.

   Prior to commencing treatment, an authority is required from Drugs of Dependence Unit [DDU] Suboxone is only dispensed by specific pharmacies, who need to agree to accept the patient.

   Identify a dispensing pharmacy. ADIS 1300 13 1340 can identify the nearest MATOD dispensing pharmacy.

   Complete the authority application form, then fax or email to DDU, then ring 1300 652 584 or HealthDrugsofDependenceUnit@sa.gov.au for authority number.

   Commence Suboxone (buprenorphine/naloxone) only when objective signs of withdrawal are present. This confirms that there is significant opioid tolerance and reduces the possibility of buprenorphine induced withdrawal*. Objective signs include dilated pupils 5mm +, piloerection, yawning, sniffling, restlessness, HR>100.

   Buprenorphine/naloxone withdrawal regimen:

   **Day 1**
   - 2 mg at onset of withdrawal as pharmacist supervised dose. Assess tolerance 2 hours later. Give an additional 2 to 4mg as a supervised dose two to four hours later prn if severe withdrawal

   **Day 2**
   - 4 – 8 mg mane supervised.

   **Day 3**
   - 4 -6 mg mane supervised.

   **Day 4**
   - 2 – 4 mg mane supervised.

   **Day 5 and 6**
   - 2mg mane supervised then cease

   If the situation is unclear or **withdrawal seems to be persisting** then ring DACAS (Drug and Alcohol Clinical Advisory Service) 08 7087 1742 for advice.

   Withdrawal symptoms from long-term codeine use can persist for a few days longer than the duration of the 5 – 6 day Suboxone regimen but can then usually be managed with non-opioid medications (see above). If this is not sufficient, consider a period of maintenance treatment with buprenorphine/naloxone or methadone.

   Inpatient withdrawal may be indicated if the person has been using multiple substances, or if the codeine intake has been very high, or if the severity of withdrawal is high despite buprenorphine/naloxone treatment.
Medication Assisted Treatment for Opioid Dependence (MATOD)

For some people with codeine dependence, treatment on an ongoing basis with buprenorphine/naloxone (Suboxone) or methadone has been a lifesaving intervention. Although codeine dependence is less risky than dependence on injectable opioids such as heroin, it can still be debilitating and risky for some individuals and maintenance treatment with supervised buprenorphine/naloxone or methadone is an appropriate treatment response.

MATOD should be considered for moderate to severe dependence, for example when there is:

- A past history of other harmful substance use, OR
- A past history of Injecting OR
- A past history of prescription opioid medication dependence OR
- Evidence of past or current end-organ damage OR
- Significant concurrent disabling mental health problems

For more detailed information on MATOD with Suboxone see the following SA Health factsheet.

Prior to commencing treatment, an authority is required from Drugs of Dependence Unit. Complete form, fax or email, then ring 1300 652 584 or HealthDrugsofDependenceUnit@sa.gov.au for authority number. If an authority has already been obtained for a Suboxone medicated withdrawal, then this authority remains current for ongoing MATOD.

If the situation is unclear then ring DACAS (Drug and Alcohol Clinical Advisory Service) 08 7087 1742 for advice.

- Patients can access help directly from the Alcohol and Drug Information Service 1300 13 1340
  7 days per week, 0830 to 2200hrs.
- Information on Referrals to DASSA Community Clinics can be obtained from the SA Health website
  Open the tab ‘for health professionals’.
- Clinicians can seek advice from the Drug and Alcohol Clinical Advisory Service on (08 7087 1742)
  7 days per week, 0830 to 2200hrs.

Alcohol and Drug Information Services (ADIS)
Phone: 1300 13 1340
Confidential telephone counselling and information available between 8.30am and 10pm every day.
Revised April 2018. DASSA.00546
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, cannabis, amphetamines, IVDU, prescription opioids.

> Assess for disabling mental health problem

> Assess for renal and GI damage

> CBE, MBA20, Urine drug screen, pregnancy test [+serum paracetamol if relevant].

GROUP 1: Moderate/severe dependence
- Strong urge to use and difficulty stopping despite clear evidence of risks or actual harm.
  - Other current harmful substance use
  - Past history of prescription opioid medication dependence, or of injecting drug use.
  - Evidence of past or current end-organ damage
  - Concurrent disabling mental health problem

Consider MATOD with buprenorphine/naloxone or methadone
Outpatient or inpatient withdrawal also an option
Advice from DACAS Tel: 7087 1742

GROUP 2: Mild/moderate dependence
- Using more than recommended OTC codeine formulation [more than 12 tabs per day]
- Previous unsuccessful attempts at stopping or reducing dose
- No group 1 criteria

Consider 5-6 day outpatient withdrawal with buprenorphine/naloxone. Monitor for relapse.
Advice from DACAS if needed or if buprenorphine / naloxone not available (Tel: 08 7087 1742)

GROUP 3: Non-dependent but risk of withdrawal symptoms
- Using up to 12 tabs per day
- Never tried to stop
- No group 1 criteria

Advise of risk of withdrawal. Short withdrawal management using non-NSAID non-opioid symptomatic medications
Monitor for relapse / severity of withdrawal

IF UNSUCCESSFUL

Investigate and treat complications. Refer if pregnant.