Responding To Pharmaceutical Opioid-Related Problems

A Resource For Prescribers

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NCETA
Australia's National Research Centre on AOD Workforce Development

Flinders UNIVERSITY

NCETA

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NCETA is located at Flinders University and is a collaboration between the University and the Australian Government Department of Health.

Suggested citation: Nicholas, R. (2018). *Responding to problems related to pharmaceutical opioids: A resource for prescribers.* National Centre for Education and Training on Addiction (NCETA), Flinders University, Adelaide.

ISBN: 13: 978-1-876897-66-6

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Published by the National Centre for Education and Training on Addiction (NCETA).
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Design and layout by Blend Creative
www.blendcreative.com.au

Foreword

This booklet stems from a literature review undertaken by the National Centre for Education and Training on Addiction, Flinders University and funded by Indivior Pty. Ltd. The literature review informed the development of this resource and is available at nceta.edu.au. The literature review provides substantially more detail on the issues covered in this booklet and includes a comprehensive list of references. Indivior played no part in the literature review or the development of this resource.

The central focus of this resource is assessing and responding to patients with pharmaceutical opioid-related problems. It touches briefly on the issue of managing persistent non-cancer pain (PNCP) [i] noting that there is already a wealth of evidence-based guidelines on this topic available elsewhere. More information about the role of opioids (if any) in managing PNCP is available at the following links:

- NSW (New South Wales Therapeutic Advisory Group Inc.)
- South Australia (Drug and Alcohol Services, SA)
- Victoria (NPS Medicinewise / Victorian Government)
- Western Australia (Government of Western Australia, Department of Health)
- Queensland (Queensland Drugs of Dependence Unit)
- The Royal Australian College of General Practitioners
- The Royal Australasian College of Physicians
- Canada (National Pain Centre)
- The United States (Centers for Disease Control and Prevention)

Acknowledgements

The author would like to thank the following for their assistance in the development of, and feedback on, this resource:

- Dr Penny Briscoe: Director, Pain Management Unit, Royal Adelaide Hospital
- Dr Nico Clark: Former Clinical Director, Drug and Alcohol Services SA
- Dr Meredith Craigie: Pain Medicine Specialist, Royal Adelaide Hospital, Dean, Faculty of Pain Management, ANZCA
- Associate Professor Suzanne Nielsen: Deputy Director, Monash Addiction Research Centre
- Professor Ann Roche: Director, National Centre for Education and Training on Addiction
- Dr Tim Semple: Deputy Head, Pain Management Unit, Royal Adelaide Hospital.

[i] In this context persistent non-cancer pain includes cancer survivor pain.

List of Acronyms

ANZCA:	Australian and New Zealand College of Anaesthetists
CNS:	Central nervous system
COX-2:	Cyclooxygenase-2
DASSA:	Drug and Alcohol Services South Australia
FBC:	Full blood count
ICD:	International Classification of Diseases
LFT:	Liver function test
MATOD:	Medication assisted treatment of opioid dependence
MBA:	Multiple Biochemical Analysis
oMEDD:	Oral morphine equivalent daily dose
OTC:	Over-the-counter
NSAID:	Non-steroidal anti-inflammatory drug
PNCP:	Persistent non-cancer pain
QR:	Quick response
SUD:	Substance use disorder
TENS:	Transcutaneous electric nerve stimulation
TGA:	Therapeutic Goods Administration
UEC:	Urea, electrolytes and creatinine

Contents

1 WHY THE FOCUS ON PHARMACEUTICAL OPIOIDS?

In recent years, there have been increasing concerns about the burgeoning harms associated with the use of pharmaceutical opioids in Australia. These harms include hospitalisations, iatrogenic dependence, adverse physical effects and deaths.

In Australia, more than twice as many people die from pharmaceutical opioid overdose than from heroin overdose. Between 2001 and 2012, rates of fentanyl, oxycodone, and methadone deaths all increased significantly, by an average annual rate of approximately 40%, 16% and 3% respectively. [1]

Much of the increase in opioid use has been for persistent non-cancer pain (PNCP). Increased use for PNCP has occurred despite evidence of:

- A lack of long-term benefits
- Poorer outcomes, particularly in terms of function and mental health
- Dose-related risks. [2]

As of February 2018, medicines containing low-dose codeine (most importantly compound analgesics) were no longer available from pharmacies in Australia without a prescription.

These over-the-counter (OTC) analgesics offer little additional benefit over non-codeine analgesics but are associated with increased harms, such as overdose. [3, 4]

When taken in excess, high levels of paracetamol, ibuprofen or aspirin can lead to:

- Renal and hepatic impairment
- Gastrointestinal bleeding
- Electrolyte imbalances
- Collapse
- Rhabdomyolysis
- Death. [5-8]

Codeine metabolism is also highly variable. Some patients derive no benefit from the drug, while others are at risk of overdose. [3]

Consumers may also incorrectly interpret the symptoms of codeine withdrawal, and/or hyperalgesia, as a worsening of their pain condition.

The regulatory change limiting the availability of codeine-containing medicines, along with increased awareness of lack of effectiveness of opioids for PNCP, means many people may need support to adopt alternative non-pharmacological or non-opioid pain relief modalities.

Others may find it difficult to stop their opioid use and may need more complex treatment that will require careful consideration, planning and dialogue.

2 PROBLEMS WITH LONGER-TERM OPIOID USE

OPIOIDS: INCREDIBLY USEFUL MEDICINES BUT...

Opium and its derivatives have been amongst humanity's most useful medicines. Fossilised opium poppy seeds dating as far back as 30,000 years suggest the use of opium by neanderthals. [9]

The use of opioids for acute and palliative care pain and the treatment of opioid dependence is uncontroversial.

More recently, opioids have increasingly been used to treat PNCP, despite a lack of evidence concerning efficacy. Multidisciplinary treatment approaches for PNCP that emphasise non-pharmacological over pharmacological treatment and promote self-management are generally recommended. [10]

However, opioids can play a role in certain situations, such as short-term use while non-pharmacological approaches are introduced.

Once these approaches are established, best practice regimes indicate gradual opioid withdrawal.

There is mounting evidence of harms associated with longer-term opioid use.

Harms include:

- Opioid endocrinopathies [ii]
- Increased prevalence of fractures
- Opioid-induced hyperalgesia
- Decreased natural and acquired immunity
- Respiratory depression (including sleep apnoea)
- Sleep disturbance
- Depression
- Nausea, vomiting and constipation
- Adverse effects on driving. [2]

[ii] For example, reduced levels of gonadotropin-releasing hormone with subsequent reductions in testosterone, estrogen and adrenal androgens.

3 EFFECTIVE MANAGEMENT OF PERSISTENT NON-CANCER PAIN

While a 'cure' for PNCP may not be possible, it is generally feasible to reduce pain and achieve and maintain an acceptable level of function in personal, social and occupational life if patients adopt active self-management measures.

It is critical to adopt multidisciplinary and multidimensional approaches to PNCP that do not rely on drug therapy. If drug therapy is required, non-opioid therapies are preferred.

Opioid treatment can have a role in the management of PNCP but should be regarded as a treatment of last resort given its limitations and potential harms.

Great caution is required in the use of opioids for PNCP if a patient has an active or past substance use disorder (SUD) or unstable psychiatric disorders. [10] Such conditions do not necessarily preclude opioid therapy, but flag the need for close monitoring. [10, 11]

While evidence does not support routine use of opioids in the management of PNCP, if opioids are selected as part of a management plan the following steps are recommended.

1. Seek specialist advice if uncertain about the advisability or conduct of a trial of opioids
2. Negotiate an opioid therapy trial that explicitly identifies goals and duration
3. Closely monitor oral morphine equivalent daily dose (oMEDD) and keep below 40mg and then only for up to 90 days. If doses are escalating seek assistance well before 100mg is reached
4. Where existing patients are on >100mg oMEDD, attempt to taper this dose to more appropriate levels
5. Undertake intermittent planned reductions of opioid dosage
6. Avoid fentanyl patches
7. Monitor the effectiveness of opioid therapy, for example using the 5As opioid therapy monitoring tool. [10,12]

Opioids should be discontinued if:

- Pain has resolved
- There is no improvement in function during the trial period
- Adverse effects, or other risks, outweigh any benefit
- Aberrant behaviours develop.

A successful trial of opioid therapy is indicated by improved function and quality of life. Thereafter, ongoing treatment should be renegotiated to include goals, duration and lowering of dose.

[iii] If opioids are required for patients with a SUD, evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with other therapies) is recommended. Referral to specialist substance use services is advised. It is also important to be mindful of regulatory restrictions concerning the prescribing of opioids to patients with opioid dependence.

4 OPIOIDS: TOLERANCE, PHYSICAL DEPENDENCE, WITHDRAWAL, SUBSTANCE DEPENDENCE [iv]

Long-term opioid use can lead to tolerance, meaning that patients may need larger doses to obtain the same effect. Patients who are tolerant to one opioid will generally be tolerant to other opioids, however the degree of cross-tolerance is unpredictable.

Physical dependence on opioids means that if the opioid is antagonised, suddenly stopped, or abruptly reduced in dose, a withdrawal (or abstinence) syndrome can develop. This is most likely if the patient has been taking opioids for >1 month (or possibly less with short-acting opioids).

Opioid withdrawal syndrome symptoms include:

- Tachycardia
- Hypertension
- Mydriasis
- Lacrimation
- Gastrointestinal upsets
- Anxiety, irritability or restlessness
- Perspiration
- Bone or joint aches
- Tremor
- Goosebumps
- Rhinorrhoea
- Yawning.

Opioid withdrawal can be assessed and recorded using tools such as the Clinical Opioid Withdrawal Scale (see Appendix 2 of the National Guidelines for Medication-Assisted Treatment of Opioid Dependence).

Some patients may be using multiple substances and may experience withdrawals from each substance.

[iv] To meet the diagnostic criteria for Substance Dependence in the ICD 11, an individual must have two or more of the following features: Impaired control over substance use; substance use becoming an increasing priority such that it takes precedence over other interests or enjoyment; and physiologic features indicative of neuroadaptation to the substance, such as tolerance, withdrawal or use of the substance to prevent and alleviate withdrawal. This definition aligns more closely with the medico-legal definitions contained in Australian legislation concerning the prescribing of controlled drugs to dependent people, than does the DSM-5 diagnostic criteria for Substance Use Disorder.

Tolerance and physical dependence are natural biological consequences of repeated opioid use. The existence of tolerance or physical dependence in a patient do not imply misuse, or align with the International Classification of Diseases (ICD) diagnostic criteria for *Substance Dependence.*

Some patients may not be aware that they are physically dependent.

The revised definition of *Substance Dependence* in the ICD 11 refers to a pattern of drug taking behaviours and compulsive drug use despite evidence of physical, psychological, or social harm.

Among people who use opioids for pain-related problems, some will experience *Substance Dependence* (see Figure 1).

IT IS IMPORTANT TO BE MINDFUL THAT SOME PATIENTS WITH PAIN, WHO APPEAR TO BE EXHIBITING DRUG-SEEKING BEHAVIOURS, MAY SIMPLY BE SEEKING BETTER PAIN RELIEF.

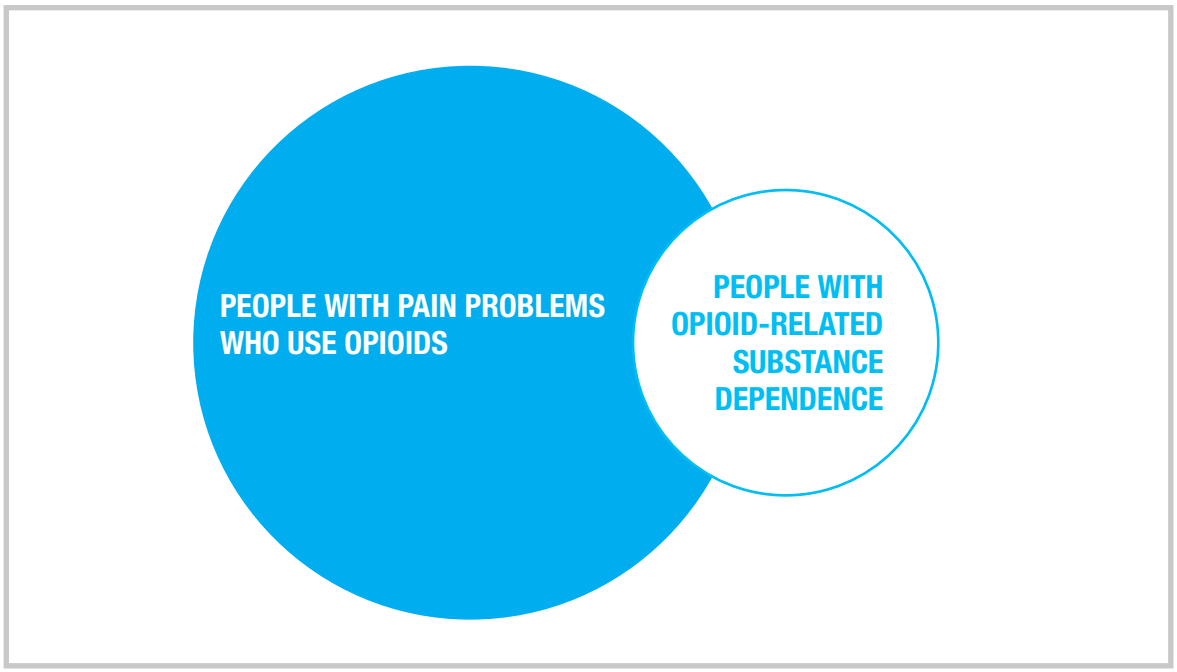


Figure 1: The overlap between people with pain problems who use opioids and people with opioid-related substance dependence (schematic representation only).

5 PREPARING MEDICAL PRACTICES FOR PATIENTS WITH PRESCRIBED OPIOID PROBLEMS

The rescheduling of codeine in February 2018 increased the likelihood that medical practices in Australia would see more patients with difficulties related to codeine or other pharmaceutical opioids.

It is important for practices to have a range of response measures in place, including:

- Assessment approaches
- Consistent policies and approaches regarding opioid prescribing applied by all practitioners
- Written resources about codeine and other opioids readily available to provide to patients
- Referral information available for relevant alcohol and other drug and pain services.

6 ASSESSING OPIOID USE

Assessing patients with opioid use-related problems is an important part of patient-doctor engagement. A comprehensive biopsychosocial assessment is necessary. Assessment of potential opioid problems and a patient's willingness to change their opioid use is also central.

It is important to assess the use of pharmaceutical opioids in terms of:

1. Amount and pattern of use
2. Social consequences of use
3. Experience of compulsion/craving/loss of control. [13, 14]

Do not assume that what is being prescribed is what is being taken – patients may be using greater or lesser amounts than those prescribed.

Check if the patient has been hoarding or diverting opioids (e.g., giving, selling, bartering or stealing opioids), or if using other than as prescribed (e.g., in response to stressful situations or for emotional escape). This may include over- or under-consumption, topping up with other drugs or pills, or tampering with tablets or patches.

Tampering can turn slow release formulations into ones with immediate actions if smoked, swallowed or taken via intranasal or intravenous consumption. [12, 13]

Careful assessment will assist clinical treatment decisions, such as the need for opioid pharmacotherapy. Physical signs of opioid intoxication or withdrawal, as well as biochemical testing (such as urine drug screens), may also help to formulate management plans. [14]

Excess consumption of combination OTC products containing paracetamol or NSAIDs may place the patient at risk of hepatic, gastric or renal damage. Consider urgent assessment of FBC, UECs, LFTs and screening for blood borne viruses (if there is a history of drug injection).

Problematic use of opioids may progress to dependence. The ICD11 defines opioid dependence as a disorder of regulation of opioid use arising from repeated or continuous use of opioids. The characteristic feature is a strong internal drive to use opioids, which is manifested by impaired ability to control use, increasing priority given to use over other activities, and persistence of use despite harm or negative consequences. These experiences are often accompanied by a subjective sensation of urge or craving to use opioids. Physiological features of dependence may also be present, including tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of dependence are usually evident over a period of at least 12 months, but the diagnosis may be made if opioid use is continuous (daily or almost daily) for at least 1 month.

7 NON-OPIOID SYMPTOMATIC APPROACHES TO PHARMACEUTICAL OPIOID CESSATION OR REDUCTION

For most patients, abrupt withdrawal from opioids is uncomplicated. They may benefit from a range of medications for common symptoms (see Table 1).

Table 1: Recommended medications for opioid withdrawal symptoms.
Source: DASSA (2018).

SYMPTOMS	MEDICATION
Nausea and vomiting	Anti-emetics
Gut cramps	Hyoscine butybromide
Diarrhoea	Loperamide
Headaches, muscle aches and pains	Paracetemol and/or NSAIDs
General withdrawal symptoms	Clonidine/Lofexidine
Insomnia, anxiety/agitation	Benzodiazepines (short-term only and caution is required when also prescribing another CNS depressant)

After opioid cessation or reduction, patients may require support with pain management. Recommended non-pharmacological approaches include:

- Planned daily walks or exercise
- Physiotherapy/hydrotherapy
- Heat or ice packs
- Transcutaneous Electrical Nerve Stimulation (TENS) machines
- Counselling (e.g., cognitive behavioural therapy in person, online or via telephone)
- Relaxation therapy/mindfulness/yoga
- Nutritional change with support from a dietitian
- Attending a group pain management program
- Enhancing social connection.

Non-opioid pharmacological options may include:

- Paracetamol, non-steroidal anti-inflammatory drugs (either non-selective or COX-2 inhibitors)
- Adjuvant drugs (e.g., antidepressants or anti-neuropathic agents [for neuropathic pain only]).

8 USING OPIOIDS FOR PHARMACEUTICAL OPIOID MAINTENANCE, REDUCTION OR CESSATION [v]

OPIOID MAINTENANCE

While non-pharmacological and non-opioid approaches will be sufficient for most patients, there is a group for whom opioids, such as methadone or buprenorphine/naloxone, will be required.

If opioids are used to treat pharmaceutical opioid dependence via maintenance, reduction or cessation, compliance with relevant regulatory requirements regarding the prescribing of these drugs for this patient group is essential.

For such patients, an opioid dose equivalence calculator is an important starting point to calculate equi-analgesic doses. Note that these calculators are not totally reliable for guiding dose transfers onto buprenorphine/naloxone or methadone, as the calculators:

- Generally relate to short-term, not chronic, pharmaceutical opioid use
- Have usually been determined with relatively low levels of opioid use (e.g., 20 or 30mg oMEDD). [15]

Opioid dose equivalence calculators can be particularly problematic in relation to codeine (see Table 2).

The Opioid Dose Equivalence Table (Table 2) was developed by the Faculty of Pain Management, ANZCA and is available here, along with a list of practical considerations and references that provide guidance in establishing your patient's opioid dose equivalence.

An Opioid Calculator App is also available free of charge for both iPhone and Android versions. It is available from the App Store or Google Play by searching for ANZCA Opioid Calculator.

Alternatively, the app can be downloaded using the QR code below.

[v] More detail is provided in Sections 9 & 10 concerning ways to respond to codeine-related problems.

Table 2: Opioid dose equivalence. Calculation of oral morphine equivalent daily dose oMEDD (mg) = Current opioid dose x Conversion factor.
Source: Faculty of Pain Management, Australian and New Zealand College of Anaesthetists (2015). [16]

OPIOID	DOSAGE	CONVERSION FACTOR	PROPRIETARY NAMES
ORAL (SWALLOWED) PREPARATIONS Note: Modified release formulations are marked as MR			
Morphine	mg/day	1	Anamorph, Kapanol (MR) MS Contin (MR) MS Mono (MR), Ordine, Sevredol
Oxycodone	mg/day	1.5	Endone, OxyContin (MR), OxyNorm, Targin (MR)
Hydromorphone	mg/day	5	Dilaudid, Jurnista (MR)
Codeine	mg/day	0.13	Aspalgin, Codalgin, Panadeine, Panadeine Forte, Mersyndol, Nurofen Plus, others
Dextropropoxyphene	mg/day	0.1	Di-Gesic, Doloxene
Tramadol	mg/day	0.2	Durotram-XR (MR), Tramal, Tramadol SR (MR), Zydol, Zydol SR (MR), others
Tapentadol	mg/day	0.4	Palexia-SR (MR)
SUBLINGUAL PREPARATIONS			
Buprenorphine	mg/day	40	Suboxone, Subutex, Temgesic
RECTAL PREPARATIONS Note: Absorption from rectal administration is highly variable			
Oxycodone	mg/day	1.5	Proladone
TRANSDERMAL PREPARATIONS			
Buprenorphine	mcg/hr	2	Norspan
Fentanyl	mcg/hr	3	Denpax, Durogesic, Dutran, Fenpatch, Fentanyl Sandoz
PARENTERAL PREPARATIONS			
Morphine	mg/day	3	DBL morphine sulphate injection, DBL morphine tartrate injection
Oxycodone	mg/day	3	OxyNorm FI
Hydromorphone	mg/day	15	Dilaudid FI, Dilaudid-HP FI
Codeine	mg/day	0.25	Codeine phosphate injection USP
Pethidine	mg/day	0.4	Pethidine injection BP
Fentanyl	mcg/day	0.2	DBL fentanyl injection, Sublimaze
Sufentanil	mcg/day	2	–

Buprenorphine/naloxone appears to be safe and well-tolerated by pharmaceutical opioid dependent patients. [17] Opioid substitution dosages should be titrated according to patient responses.

Careful consideration should also be given to dose titration goals. Some clinicians provide dosages that are intended to simply ensure that withdrawal does not occur. Others aim to titrate the dose to reduce the risk of cravings.

A short-term taper is, in general, not effective for opioid dependence. Longer term maintenance treatment is the recommended option (see the National Guidelines for Medication Assisted Treatment of Opioid Dependence).

REDUCING / TAPERING OPIOIDS

Buprenorphine/naloxone is an excellent opioid for tapering/withdrawal, as buprenorphine is a partial agonist and can be administered with once daily dosing.

Buprenorphine/naloxone can be used for a withdrawal regime for the treatment of opioid dependence after appropriate regulatory authorisation has been obtained.

Buprenorphine/naloxone should only be commenced when objective signs of opioid withdrawal are present e.g.:

- Pupils dilated 5mm
- Goose bumps
- Yawning
- Sniffling
- Tachycardia. [17]

Opioid dosage reductions can be fast (10-25% of daily dose per week), or slow (10-25% of the daily dose per month) if a patient has been using opioids for some years.

Discontinuing or tapering opioid therapy is often hindered by problems such as patients' psychiatric comorbidities, under-developed coping skills or an unsupportive home environment.

If previous attempts at opioid weaning have proven unsuccessful, then the rate of tapering can be slowed.

The goal of tapering is to improve or maintain patient wellbeing while opioids are being withdrawn.

Schedule frequent consultations and ask about, and emphasise, the benefits of tapering (e.g., improved pain, mood, alertness) at each appointment.

Referral for counselling or other support during the tapering process is recommended, especially if there are other significant issues.

If a patient is not successfully reducing their dose, or there is an escalation in use beyond prescription, involve other practitioners such as pain or addiction specialists. [15]

REDUCING RISK

It is important to remain vigilant to the possibility of opioid-related overdose and death. Naloxone is an essential tool to mitigate this risk.

Consideration should be given to the co-prescribing of naloxone for patients on higher doses of opioids or those who are also using other sedatives.

9 SCREENING FOR CODEINE-RELATED PROBLEMS

Restrictions on over-the-counter supply of codeine implemented in February 2018 may result in requests for prescribers to provide this medicine. It is estimated that approximately 20% of users of OTC codeine are codeine dependent. [18]

See the TGA's Codeine Information Hub for tips on talking to patients about codeine and resources for patients.

Patients with codeine-related problems may not self-identify as 'people who use drugs'. They may be socially advantaged with high achievements in education and work roles, strong social supports and good incomes.

To determine if a patient is having difficulties with their use of codeine (or are likely to experience codeine withdrawal) first establish:

1. Quantity, frequency and duration of codeine use (unless using OTC codeine most days, for at least 1 month, major tolerance or dependence is unlikely)
2. If the dose has increased over time
3. Any past history of prescription opioid dependence/injecting drug use/other substance use problems
4. Mental health problems (such as anxiety and depression) or physical complications are present (e.g., from excessive exposure to paracetamol or NSAIDs)
5. Issues with other substances (such as alcohol, benzodiazepines, cannabis, stimulants)
6. If codeine has been used for conditions for which there is no indication
7. Whether the patient experiences symptoms if a dose is missed. [16]

Relevant investigations could include:

- FBC
- MBA 20
- Urine drug screen for drugs of dependence (e.g., methadone, buprenorphine, oxycodone and fentanyl)
- Serum paracetamol if relevant
- Urine pregnancy test. [16]

The screening tool in Figure 2 can help establish whether patients are likely to be dependent on codeine and require more intensive treatment.

Figure 2: Codeine Screening Tool.
Source: McCoy, Nielsen & Bruno (2015). [19]

OTC CODEINE SCREENING TOOL:

1A How often do you take OTC codeine? (Choose one of the following)

Everyday ☐	Most Days ☐			*Proceed to question 1B*
Once a week or more ☐	About once a month ☐	Every few months ☐	Once or twice a year ☐	*Proceed to question 2*

1B How long have you been using OTC codeine with this frequency?

Last week ☐	Last four weeks ☐		1 Point
Last year ☐	Longer than one year ☐	Longer than three years ☐	2 Points

2 What was the main reason OTC codeine was taken the last occasion it was used? (Choose one of the following)

Headache ☐	Back pain ☐	Dental pain ☐	Migraine ☐	Period pain ☐	Any other physical pain ☐	0 Points
To relax ☐	To feel better ☐	To sleep ☐	Other _____ ☐			1 Point

3 In the past 12 months, how difficult did you find it to sleep or go without OTC codeine? (Choose one of the following)

Not difficult ☐	0 Points
Quite difficult ☐	1 Point
Very difficult ☐	1 Point
Impossible ☐	1 Point

A score of ≥ 2 on the OTC Codeine Screening Tool indicates a high likelihood that the patient will probably fall into one of the 3 groups described in Section 10.

The version of the Tool in Figure 2 is to be used by practitioners to obtain the patient's score. A slightly different version of the Tool to be provided to patients appears in Appendix 1.

10 RESPONDING TO CODEINE-RELATED PROBLEMS [VI]

Patients who require assistance from prescribers for problems related to their codeine use fall into 3 groups:

- **Group 1:** Those who are not codeine dependent but are at risk of mild opioid withdrawal symptoms
- **Group 2:** Those with mild to moderate dependence
- **Group 3:** Those with moderate/severe codeine dependence.

Most patients experiencing difficulties with their codeine use will be in Group 1, with decreasing proportions in Groups 2 and 3 (see Figure 3).

Approaches for each of the three groups are displayed in the flow chart on Page 17 (Figure 4). The clinical management of each group is discussed below.

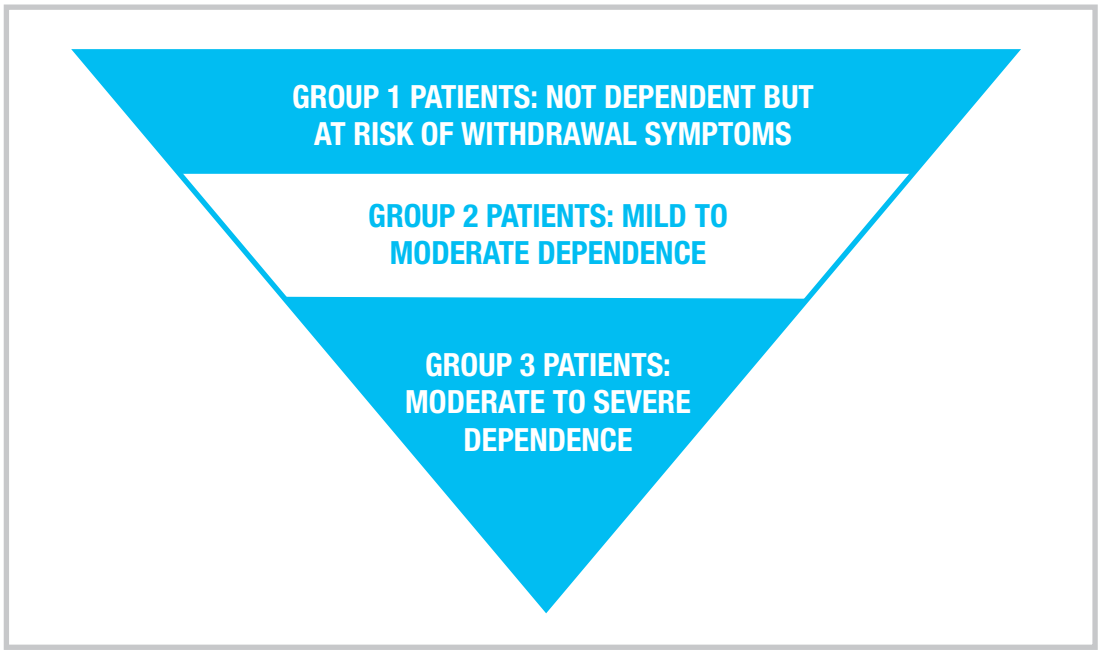


Figure 3: Typology of patient experiences of codeine use-related difficulties.

[vi] The content of this section is adapted from Managing Patients with Regular OTC Codeine Use (DASSA, 2018).

GROUP 1: THOSE WHO ARE *NOT* CODEINE DEPENDENT BUT AT RISK OF MILD OPIOID WITHDRAWAL SYMPTOMS

These are patients who have been using codeine daily or almost daily for more than a month:

- Using up to the recommended doses
- Without characteristics of dependence
- Without having tried to stop their codeine use.

A trial of symptomatic treatment for opioid withdrawal (see page 8) is indicated for this group. These patients would also benefit from education about opioid withdrawal and the importance of not confusing opioid withdrawal with worsening pain or other symptoms.

If a patient cannot cope with this approach then it is likely that at least mild/moderate opioid dependence is present and a short course of buprenorphine/naloxone is indicated.

GROUP 2: THOSE WITH MILD TO MODERATE DEPENDENCE

These are patients who have been using codeine daily or almost daily for more than a month:

- At doses higher than recommended
- Without features of severe dependence/withdrawal
- With previous unsuccessful attempts at stopping or reducing their use.

These patients are most likely to benefit from:

- A supported withdrawal regime using a short course of buprenorphine/naloxone (see Table 3)
- Use of other non-opioid analgesics such as paracetamol or NSAIDs
- Non-pharmacological treatments such as psychological approaches including cognitive behaviour therapy, guided imagery, meditation, and aerobic exercise.

When considering buprenorphine dosages it is important to note that equi-analgesic opioid dosage calculators can underestimate the dose of buprenorphine required to replace codeine. This can result in buprenorphine doses that are too low, which has potential to contribute to poor clinical outcomes.

There is also considerable individual variability in the doses of buprenorphine required to replace codeine, which highlights the importance of individual dose titration.

A sample buprenorphine/naloxone withdrawal protocol is shown in Table 3. If the dosing levels in this protocol are insufficient, a period of maintenance with buprenorphine/naloxone may be required.

Withdrawal symptoms from long-term codeine use can persist for longer than the duration of the 5-6 day buprenorphine/naloxone regime. These symptoms can usually be managed with non-opioid medications.

However, inpatient withdrawal may be required if:

- The patient has been using multiple substances
- The codeine intake has been very high
- The withdrawal is severe despite buprenorphine/naloxone treatment.

Table 3: Supported withdrawal protocol.
Source: DASSA (2018). [17]

SUPPORTED WITHDRAWAL PROTOCOL	
BUPRENORPHINE/NALXONE TREATMENT	
Day 1	2mg at onset of withdrawal as a supervised dose. Assess tolerance 2 hours later. Give an additional 2 to 4mg as a supervised dose 2 to 4 hours later prn if in severe withdrawal.
Day 2	4-8mg mane supervised.
Day 3	4-6mg mane supervised.
Day 4	2-4mg mane supervised.
Days 5 and 6	2mg mane supervised then cease.

GROUP 3: THOSE WITH MODERATE/ SEVERE CODEINE DEPENDENCE

This group have used codeine multiple times daily for more than a month (and probably much longer), exceeded recommended dosages, and are probably unable to stop doing so despite being concerned about and experiencing harm from their use of the drug.

They are also likely to be highly tolerant to the effects of codeine, experience withdrawal symptoms on cessation and have made unsuccessful attempts to stop in the past. They may also have:

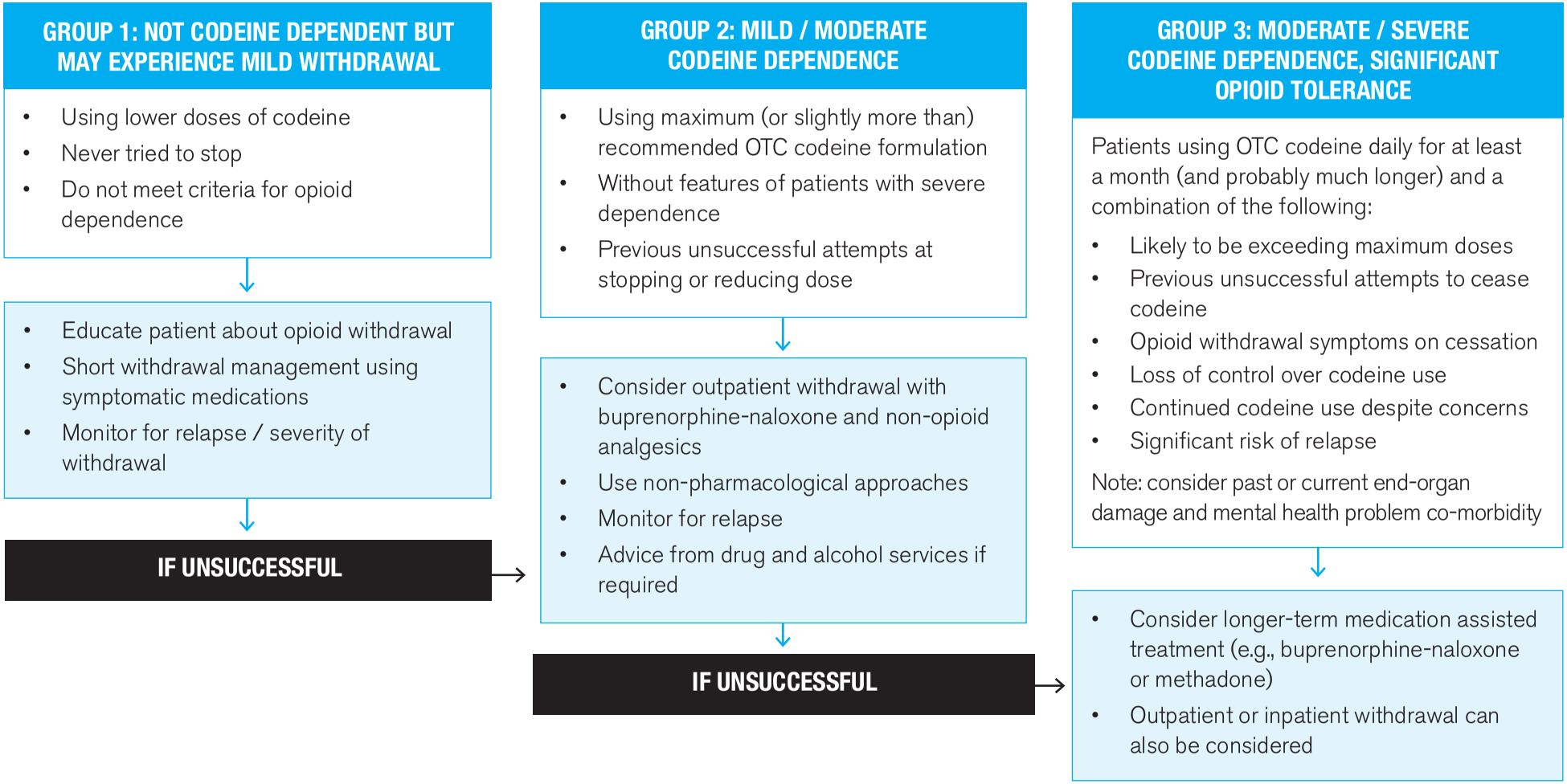
- A history of other harmful substance use (such as prescription opioid use or injecting drug use)
- End organ damage
- Disabling mental health problems.

These patients are at significant risk of relapse. They are unlikely to respond to non-opioid withdrawal management and are not likely to cope with sudden cessation of opioids. They may also try to obtain prescribed or illicit opioids in lieu of OTC codeine, thereby exposing them to significant risks. They will probably require ongoing medication assisted treatment for opioid dependence (MATOD) with buprenorphine/naloxone or methadone (see National Guidelines for Medication-Assisted Treatment of Opioid Dependence).

Some of these patients may not wish to enter a MATOD program due to its restrictive nature. These restrictions include the need for daily or almost daily dispensing of their opioids from pharmacies or other settings. As a result, they may elect to undertake a Supported Withdrawal Protocol (see Table 3) or an inpatient detoxification.

Figure 4: Quick Guide to Managing Patients with Regular OTC Codeine Use Problems.
Source: Dr Suzanne Nielsen personal communication.

- Assess recent and past substance use history including codeine and other opioids, alcohol, benzodiazepines and any other substance use, and 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).



Links to further resources

- Information about codeine for health professionals and consumers. (Therapeutic Goods Administration: Codeine Information Hub).
  https://www.tga.gov.au/codeine-info-hub

- National guidelines for medication-assisted treatment of opioid dependence (Department of Health Canberra)
  http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/AD14DA97D8EE00E8CA257CD1001E0E5D/$File/National_Guidelines_2014.pdf

- Prescribing drugs of dependence in general practice (RACGP Clinical Guidelines)
  https://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-c/

- Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain. (Faculty of Pain Management, ANZCA)
  http://fpm.anzca.edu.au/documents/pm1-2010

- Managing patients with regular codeine use (Drug and Alcohol Services SA)
  https://www.sahealth.sa.gov.au/wps/wcm/connect/ce32e126-276e-42fb-a0a2-2358ff9a8e41/OTC+GP+management+factsheet+-+CEC+approved+05+04+18+FINAL.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-ce32e126-276e-42fb-a0a2-2358ff9a8e41-mbMmLIX

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Appendix 1

PATIENT VERSION OF THE OTC CODEINE SCREENING TOOL

Figure 5: Codeine Screening Tool.
Source: McCoy, Nielsen & Bruno (2015). [19]

OTC CODEINE SCREENING TOOL:						
1A How often do you take OTC codeine? (Choose one of the following)						
Everyday ☐	Most Days ☐					*Proceed to question 1B*
Once a week or more ☐	About once a month ☐	Every few months ☐	Once or twice a year ☐			*Proceed to question 2*
1B How long have you been using OTC codeine with this frequency?						
Last week ☐	Last four weeks ☐					
Last year ☐	Longer than one year ☐	Longer than three years ☐				
2 What was the main reason OTC codeine was taken the last occasion it was used? (Choose one of the following)						
Headache ☐	Back pain ☐	Dental pain ☐	Migraine ☐	Period pain ☐	Any other physical pain ☐	
To relax ☐	To feel better ☐	To sleep ☐	Other _____ ☐			
3 In the past 12 months, how difficult did you find it to sleep or go without OTC codeine? (Choose one of the following)						
Not difficult ☐						
Quite difficult ☐						
Very difficult ☐						
Impossible ☐