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Upscheduling of codeine

An opportunity to better manage pain and dependence

Supplement

Farewell, over-the-counter codeine: the TGA's upscheduling of low-dose codeine

Does codeine have a future in pain management?

Codeine rescheduling and the GP

Tips for talking about codeine: guidance for health professionals with prescribing authority

Case studies in managing codeine tolerance and dependence

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SUPPLEMENT
UPSCHEDULING OF CODEINE: AN OPPORTUNITY TO BETTER MANAGE PAIN AND DEPENDENCE
MARCH 2018

ISSN 1443-430X

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Printed by Blue Star Web, Sydney.

The articles in this supplement have been specially commissioned for this publication. Each has been subjected to *Medicine Today's* usual rigorous peer review process. This supplement has been sponsored by an unrestricted educational grant from Indivior Pty Ltd. The opinions expressed in the articles are those of the authors and not necessarily those of Indivior. Some products and/or indications mentioned may not be approved for use in Australia. Please review Product Information, available from the manufacturer, before prescribing any agent mentioned in these articles.

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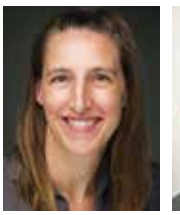
FOREWORD FROM THE SUPPLEMENT EDITORS



Codeine has been the most widely used opioid drug in Australia. The rescheduling of codeine promises to improve patient safety but also raises clinical challenges in the short term. With such a widely used medication, it is not surprising that the impact of the change has been significant. Pharmacists and doctors have been addressing queries from patients about the reasons for the change and advising those who have previously been able to self-medicate with codeine products. Given the limited evidence of efficacy of low-dose codeine and the growing evidence of harms, this may present an opportunity for better management of acute and chronic pain by healthcare professionals. Conversely, with the change in access to codeine, many who have been using codeine in higher doses for pain and other reasons may come to the attention of GPs, emergency departments and specialist services. This supplement outlines the background to the changes in access to codeine, provides perspectives on pain management and the treatment of dependence, and describes a series of case studies that reflect possible presentations and management approaches to pain, codeine tolerance and dependence. On behalf of all authors, we hope that these summaries are interesting, and relevant for the patients you see in your practices.

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Farewell, over-the-counter codeine

The TGA's upscheduling of low-dose codeine

JACINTA JOHNSON BPharm(Hons), PhD, MPS, MSHP

Low-dose codeine is now a prescription-only medication in Australia, as it already is in many other countries. The reasons – the what, when and why – for the TGA's decision to upschedule it are discussed.

Codeine is a low-potency opioid widely used for its analgesic, antitussive and antidiarrhoeal properties. In Australia, more packets of codeine are sold each year than of all other opioids, with data showing that packs of prescription and over-the-counter codeine accounted for two-thirds of all opioid packs sold in 2013.[1]

Codeine itself possesses little affinity for the mu-opioid receptor, and therefore relies upon conversion to morphine by the polymorphic cytochrome (CYP) 450 2D6 enzyme to exert is pain-relieving effects. As a result, the analgesic effects and safety of codeine are governed by the patient's CYP2D6 activity, with poor metabolisers experiencing virtually no appreciable analgesia, ultra-rapid metabolisers being at risk of opioid-related adverse effects and intermediate and extensive metabolisers falling between these two extremes.

KEY POINTS

- Over-the-counter analgesics and cold and flu preparations that contain low-dose codeine were upscheduled by the TGA to Schedule 4 'Prescription Only' from 1 February 2018.
- Codeine alone is a poor analgesic, and there is little evidence to show adding low-dose codeine (<30 mg) to nonopioid analgesics provides additional pain relief.
- Combining simple analgesics (e.g. paracetamol plus ibuprofen) may provide more effective pain relief than adding codeine at higher doses (30 to 60 mg) to paracetamol.
- Codeine dependence is a well-recognised problem in Australia, and can cause serious gastrointestinal, renal and hepatic problems, usually due to excessive intake of ibuprofen and paracetamol in codeine-containing combination analgesics.
- Codeine dependence can be identified by careful questioning regarding recent codeine use patterns, reasons for use and withdrawal symptoms on cessation, and surveillance for signs and symptoms of complications due to overuse of secondary nonopioid analgesics.
- The TGA resource 'Tips for talking about codeine: guidance for health professionals with prescribing authority' provides practical guidance for health professionals when talking to patients about codeine, including tips for discussing rescheduling, ongoing pain management options and codeine dependence (see page 24 in this supplement).

MedicineToday 2018; 19(3 Suppl): 3-7

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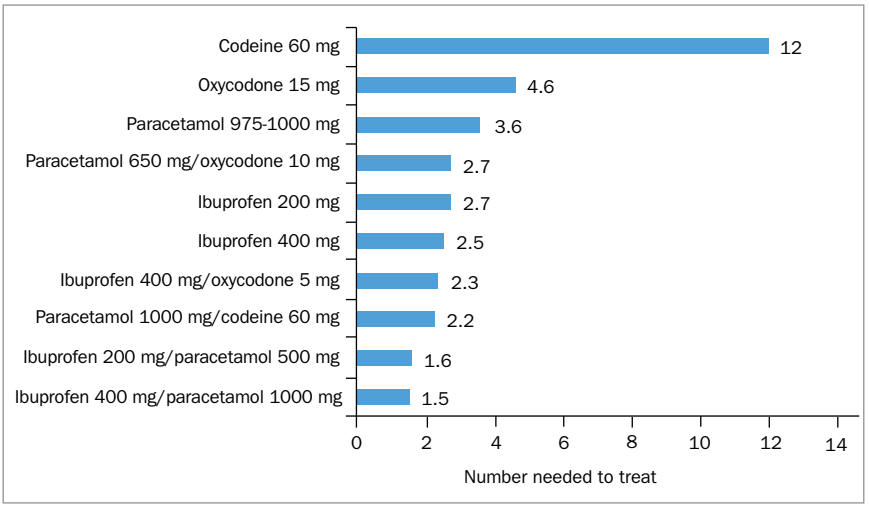

Figure 1. Comparison of number needed to treat to achieve at least 50% maximum pain relief over four to six years versus placebo in acute postoperative pain, collated from seven Cochrane reviews.[3,9,12-16]

Following a comprehensive review and consultation process, the Therapeutic Goods Administration (TGA) determined all combination analgesics that contain low-dose (8 to 15 mg) codeine would be removed from the Schedule 3 'Pharmacist Only' listing and would become Schedule 4 'Prescription Only' medicines from 1 February 2018. Similarly, over-the-counter cold and flu preparations containing codeine as a cough suppressant would be rescheduled from Schedule 2 'Pharmacy Only' to Schedule 4 'Prescription Only'.

How effective is codeine in providing pain relief?

Despite codeine being the most commonly consumed opioid globally,[2] interpatient variability in the conversion to morphine renders codeine an unreliable analgesic. As with more potent opioids, codeine has a limited role in managing chronic pain and is not recommended for managing migraine. In acute nociceptive pain, codeine as a single agent provides only a marginal benefit over placebo, and is less effective than nonopioid analgesics like NSAIDs.[3] The Australian therapeutic guidelines for analgesia suggest adding codeine 30 to 60 mg when moderate pain is not adequately relieved by paracetamol and/or an NSAID.[4]

The size of the benefit of adding codeine to nonopioid analgesic regimens containing paracetamol and/or anti-inflammatories such as ibuprofen is poorly defined. Evidence to support the incremental benefit of low-dose codeine (<30 mg) in particular is scarce. A recent systematic review commissioned by the TGA found only three randomised controlled trials have compared low-dose codeine in combination with nonopioid analgesics to the same doses of nonopioid analgesics alone, and of these two found no increase in analgesia with the addition of low-dose codeine.[5-8]

A 2009 Cochrane review reports a number needed to treat (NNT) of 2.2 for paracetamol (1 g) in combination with 60 mg of codeine versus placebo in pain due to inflammation following tissue injury; the addition of codeine increased the proportion of patients achieving at least 50% pain relief by 10 to 15%.[9] In contrast, recent studies have not detected such a benefit. In a 2017 trial, codeine 60 mg added to a regimen of paracetamol 1 g and ibuprofen 400 mg did not improve analgesia after third molar surgery, and in a 2016 study, adding either codeine 60 mg or oxycodone 10 mg to a combination of paracetamol 1 g and ibuprofen 400 mg provided no additional analgesia, compared with the addition of a nonopioid control (thiamine).[10,11]

The efficacy of analgesics in treating acute pain can be crudely compared by reviewing the NNT to achieve 50% maximum pain relief at four to six hours for each product. The NNT to achieve this pain reduction following one dose of a single-agent analgesic or a combination preparation, taken from seven separate Cochrane reviews, is shown in Figure 1.[3,9,12-16] Although these collated data do not derive from head-to-head studies, such comparisons highlight the relative efficacy of nonopioid analgesics, especially combination paracetamol plus ibuprofen products.

What problems are associated with codeine use?

Although codeine was once thought to pose a low abuse potential, codeine misuse and dependence have now been clearly documented in numerous case series and observational studies.[17] Such studies report patients taking excessive amounts of codeine, commonly consuming a packet each day and in some cases taking up to 10 times the recommended daily dose, for months or even years.[18,19]

Harms associated with codeine misuse may relate directly to acute opioid intoxication or prolonged high-dose opioid intake. However, many serious observed harms result from the overconsumption of ibuprofen or paracetamol found in codeine-containing combination products. Commonly reported consequences of primary codeine dependence with secondary nonopioid analgesic overuse include gastrointestinal ulceration and perforation with associated bleeding and anaemia, as well as renal and hepatic impairment (Box 1).[18,20,21] Codeine dependence can also have social and financial consequences on par with other forms of opioid dependence, impacting on relationships and employment.

1. COMPLICATIONS OF CODEINE DEPENDENCE WITH OR WITHOUT SECONDARY SIMPLE ANALGESIC OVERUSE

Ibuprofen-related complications

- Gastritis
- Gastrointestinal ulceration and perforation
- Gastrointestinal strictures
- Renal tubular acidosis
- Drug-induced liver injury

Paracetamol-related complications

- Drug-induced liver injury/failure

Codeine-related complications

- Opioid tolerance and withdrawal
- Medication overuse headache
- Bowel obstruction
- Respiratory depression

Additionally, some individuals, especially children and ultra-rapid metabolisers, are at risk of experiencing other serious adverse events when given codeine, such as difficulty breathing and death. National Coronial Information System data show increasing rates of fatal codeine-related overdoses in Australia, and that over a 13-year period codeine toxicity was a contributing factor in more than 1400 deaths and the attributed cause of death in 113 cases.[22]

Why has the TGA decided to upschedule low-dose codeine?

Access to codeine requires a prescription in the USA, Japan, Hong Kong, India, Russia and most European countries – few countries currently permit over-the-counter supply. Mounting evidence suggests that in countries with less strict regulations around codeine supply there is generally more abuse and misuse of low-dose codeine-containing medicines.

In Australia, discussions about rescheduling of over-the-counter codeine have spanned a decade. The National Drugs and Poisons Schedule Committee formed a Codeine Working Party in 2008, in response to increasing abuse of ibuprofen plus codeine products. In 2010, low-dose codeine-containing analgesics were moved from the Schedule 2 'Pharmacy Only' listing to Schedule 3 'Pharmacist Only', yet this change proved insufficient to limit medication misadventure. In 2015, codeine upscheduling was again on the agenda for the Advisory Committee on Medicines Scheduling, with the initial proposal, the interim decision and the final decision generating much controversy. The final decision to reschedule low-dose codeine products to Schedule 4 – requiring a prescription – was made in December 2016, to be implemented from 1 February 2018.

In view of the evidence, the risks associated with low-dose codeine supplied over the counter, including unpredictable morphine production, codeine dependence and death, were determined to outweigh any extra benefit for low-dose codeine over alternative medicines without codeine, to the extent that over-the-counter accessibility is undesirable. This change also aims to encourage patients with chronic pain in particular to see their GP for a comprehensive pain assessment and management plan, rather than self-managing with codeine.

How common is codeine dependence?

The prevalence of codeine dependence in Australia is unclear. In 2016, 1967 people across Australia reported entering opioid-substitution therapy specifically for codeine dependence. This is no doubt an underestimate of the codeine-dependent population in Australia, as the opioid of dependence was not reported for 36% of substitution therapy patients, and earlier data from an online survey indicate that only a quarter of codeine-dependent Australians have sought treatment.[23]

How can we recognise codeine dependence?

Detection of codeine dependence is often delayed, contributing to morbidity. Frequently, dependence is not recognised until after the patient presents with serious consequences of analgesic overuse.

2. INDICATORS OF OVERUSE OF CODEINE-CONTAINING COMBINATION ANALGESICS

Presenting signs and symptoms

- Abdominal pain
- Weight loss
- Constipation
- Muscle weakness

Possible associated laboratory findings

- Hypokalaemia
- Low bicarbonate
- Low haemoglobin
- Iron studies suggestive of iron deficiency anaemia
- Low albumin
- Abnormal liver function tests

In general practice, careful questioning is required when patients present requesting pain relief, to ascertain past use of over-the-counter codeine and identify when further assessment for dependence is necessary. To aid detection of problematic codeine use, a short four-item screening tool, the Codeine Dependence Scale, has been developed recently by the National Drug and Alcohol Research Centre (Figure 2).[24] This tool asks about duration and frequency of codeine use, the reasons for its use and difficulties experienced when stopping it.

Flags suggestive of the common complications of overuse of codeine-containing combination analgesics can also prompt further questioning regarding analgesic intake. Commonly reported presenting signs and symptoms and laboratory findings in patients with codeine dependence associated with combination analgesic overuse are listed in Box 2.[18,20]

How should we talk to patients about codeine dependence?

The TGA has published a useful resource providing guidance for health professionals when talking to patients about codeine, including tips for discussing rescheduling, ongoing pain management options and codeine dependence. This guidance

Screening Tool: OTC Codeine Assessment

1a **How often do you take over the counter (OTC) codeine?** (Choose one of the following)

Every day ☐ 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 stop 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 ☐

NDARC National Drug & Alcohol Research Centre

A score of **2 or more** indicates high likelihood of meeting criteria for dependence

Figure 2. Codeine Dependence Scale (CDS), healthcare professional version with scoring.[20,21] The CDS screens for risk of over-the-counter codeine dependence. Individuals who score 0 or 1 have a low likelihood of codeine dependence and are likely to be able to cease codeine; alternative nonopioid pain management approaches should be discussed. Individuals who score 2 or more possibly have codeine dependence and further assessment is recommended.

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document, titled 'Tips for talking about codeine: guidance for health professionals with prescribing authority' is available on the TGA website at https://www.tga.gov.au/tips-talking-about-codeine-guidance-health-professionals-prescribing-authority, and is included in this supplement (page 24).

Conclusion

On its own, codeine is a poor analgesic. Its clinical use is limited by low affinity for the mu-opioid receptor and its highly variable metabolism to morphine, which is dependent on an individual person's expression of the polymorphic CYP2D6 enzyme. Evidence for an incremental benefit when adding low-dose (below 30 mg) codeine to nonopioid analgesics is scarce. Even in higher doses (e.g. 60 mg), in many cases combination analgesics containing codeine appear to be no more effective than combinations of nonopioid analgesics such as paracetamol and ibuprofen.

As with all pharmaceutical opioids, codeine use has the propensity to cause opioid dependence, and codeine dependence is associated with serious and well-documented harms. Harms secondary to codeine dependence are increased beyond the consequences of opioid toxicity, as the vast majority of codeine-dependent individuals ingest combination analgesics and therefore receive supratherapeutic doses of nonopioid analgesics as well. Careful questioning regarding codeine use patterns, reason for codeine use and symptoms on codeine cessation, as outlined in the Codeine Dependence Scale, together with surveillance for the signs of nonopioid analgesic toxicity, can identify

patients with problematic codeine use for whom formal evaluation for opioid dependence is recommended. MT

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COMPETING INTERESTS: None.

Does codeine have a future in pain management?

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Now that codeine is available in Australia only on prescription, it is timely to consider how effective it is as an analgesic, both in acute pain and in chronic noncancer pain. What is codeine's future role in pain management? Are opioids ever indicated in patients with chronic noncancer pain?

KEY POINTS

- Codeine has 'had its day' in the management of pain, as the potential for adverse effects outweighs any efficacy.
- Viable alternatives to codeine are readily available, especially for the management of acute pain.
- Chronic noncancer pain is not a simple condition but rather a state of polysymptomatic distress influenced by social and psychological as well as biomedical factors.
- Opioids are not a core component of treatment of chronic noncancer pain; if a trial of opioid-responsiveness is indicated then other opioids are preferred to codeine.

MedicineToday 2018; 19(3 Suppl): 8-11

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The rescheduling of codeine to prescription-only (S4) in Australia on 1 February 2018 brought this country into alignment with most other developed countries. The main driver for this change in policy was the spectrum of adverse effects of codeine, especially dependence and addiction, often culminating in overdose, morbidity and mortality, which overshadowed its effectiveness as an analgesic.[1-3]

This raises the questions: how effective is codeine as an analgesic? and what role might it play in this new regulatory climate?

The harms of codeine are well documented elsewhere in this supplement, as are approaches to the assessment and management of people who have become dependent on it.[4,5] This article focuses on codeine's credentials as a tool for the management of pain, acute or chronic, and whether it should ever have had a seat at the therapeutic table.

Brief perspective on codeine pharmacology

Codeine (3-methyl-morphine) is classified as a weak mu-opioid receptor (MOR) agonist, with an affinity for the MOR one-200th that of morphine, for which it is in fact a prodrug. Morphine is classified as a strong MOR agonist and is the standard against which all opioids are assessed. (Codeine and morphine may

also be termed opiates, as both are alkaloids directly extractable from the plant *Papaver somniferum*, commonly called the opium poppy.)

In most individuals, up to 15% of codeine is O-demethylated by the cytochrome P450 2D6 (CYP2D6) enzyme in the liver to morphine, its most active metabolite. Codeine's other metabolites – codeine-6-glucuronide (60 to 70%) and norcodeine (10 to 15%) – have similar affinity to codeine for the MOR.[6] The pharmacogenetics of CYP2D6 may explain much of the heterogeneity of response to codeine, which is particularly relevant to arguments concerning its usefulness. The phenotype of poor metabolisers (5 to 10% of the populations studied, which were not stratified for race or ethnicity) experiences a poor analgesic effect from codeine. At the other end of the spectrum, ultra-rapid metabolisers (1 to 2%) have been shown to experience major adverse effects. The proportion of ultra-rapid metabolisers varies between ethnic groups and may be as high as 30% in people of Middle Eastern or North African descent. The most common phenotypes are intermediate metabolisers (2 to 11%) and extensive metabolisers (77 to 92%).[7,8]

Given the poor affinity of codeine and its main metabolites for the MOR, and the pharmacogenetic variability that characterises its conversion to the active drug, why would codeine – a weak agonist – be used in preference to morphine or indeed another strong agonist? This question is reinforced by codeine being produced commercially from the more abundant morphine back to which it is converted.

In this context, it may be worthwhile recalling the oral morphine equivalent (OME) dose for commonly used codeine doses. According to the Faculty of Pain Medicine 1 mg of oral codeine is equivalent to 0.13 mg oral morphine.[9] Applying this factor to the doses of codeine that were until recently available over the counter in Australia not only illuminates reports of its poor effectiveness but also puts into perspective the role of other opioids, should they be considered (see Table). A daily dose of six to eight analgesic tablets containing 8 mg codeine equates to 6 to 8 mg OME.

Effectiveness of codeine in acute pain

The effectiveness of codeine in acute pain – or more correctly, the pain of acute nociception (short-term tissue damage) – is discussed in this supplement and elsewhere.[5,10] In summary, the literature shows that the dose of codeine in combination preparations needs to be at least 30 mg (OME 4 mg) to achieve any analgesic benefit over and above that of paracetamol alone. By contrast, combinations of paracetamol and ibuprofen have been shown to be more effective than combinations of either with codeine in doses over 30 mg in acute pain (e.g. postoperative pain).

This conclusion needs to be tempered by clinical judgement of the degree of acute nociception incurred. There may be situations in which short-term use of an opioid may be considered desirable; in these cases low oral doses of a strong opioid agonist would be considered in preference to codeine.

Effectiveness of codeine in chronic noncancer pain

The role of opioids in chronic noncancer pain (CNCP) is currently subject to a robust debate, with a plethora of publications addressing the triple themes of increasing prescription, insufficient evidence of long-term effectiveness, and harms (adverse effects, addiction and overdose) outweighing benefits.[11]

The studies embraced in this and other reviews were of short duration (usually less than 16 weeks), conducted in heterogeneous populations often with stringent exclusion criteria, and many focused on pain as the sole outcome measure. The general conclusion is that the evidence is insufficient to determine the effectiveness of long-term opioid treatment in improving pain and function. A parallel conclusion is that there is an increased, dose-dependent risk of harms.

Although these studies did not specifically address codeine, they did include strong MOR agonists such as morphine, oxycodone, hydromorphone and fentanyl. There are no a priori reasons for expecting that studies on codeine would yield different results.

It can be concluded that, on pharmacological grounds alone,

TABLE. ORAL MORPHINE EQUIVALENT (OME) DOSES FOR COMMON OVER-THE-COUNTER ORAL CODEINE FORMULATIONS

Codeine dose per tablet (mg)	OME per tablet (mg)	Daily dose with 6 tablets per day		Daily dose with 8 tablets per day	
		Codeine (mg)	OME (mg)	Codeine (mg)	OME (mg)
8	1	48	6	64	8
10	1	60	8	80	10
12	2	72	9	96	12
15	2	90	12	120	16
30*	4	180	23	240	31

* Formulations containing 30 mg per tablet were not available over the counter.

codeine, as a weak, short-acting opioid agonist, would have no place in the management of patients with CNCP. The simple reason is that if an opioid analgesic were indicated then other drugs would be more efficacious.

Are opioids ever indicated in patients with CNCP?

This naturally leads to consideration of the current controversy of whether opioid analgesics are ever indicated in CNCP. No dogmatic answer can be given. However, the following points are relevant.

- The literature tends to bracket conditions as diverse as 'failed back surgery', so-called 'nonspecific' spinal pain and 'fibromyalgia' under the rubric 'chronic noncancer pain'. This is akin to saying that all forests are the same, no matter which trees they comprise.
- CNCP is not a simple condition with a discoverable, linear relationship to a state of underlying disease or damage. Rather it is a state of polysymptomatic distress in which social and psychological factors are as relevant to pathogenesis as biomedical factors.[12] The literature has simply not been able to dissect sufficiently these different factors in studies of drug efficacy.
- This understanding of CNCP underlies the sociopsychobiomedical framework used in the discipline of pain medicine to assess, treat and advise patients with CNCP about self-management, ideally tailored to the individual's circumstances.[13] Application of this approach is not easy and requires a changed frame of reference for both patient and physician, as well as time.
- Pharmacotherapy in general and opioid pharmacotherapy in particular cannot be considered a core component in the management of patients with CNCP.

Guidance in the Australian context

In the Australian literature, guidance regarding opioid prescription in CNCP has been available for almost a decade. Sources include:

- the Royal Australasian College of Physicians' *Prescription Opioid Policy* (2009)[14]
- the Faculty of Pain Medicine's *Recommendations Regarding the Use of Opioid Analgesics in Patients with Chronic Non-Cancer Pain* (2010, updated 2015)[15]
- the Royal Australian College of General Practitioners' *Prescribing Drugs of Dependence in General Practice, Part C2: the Role of Opioids in Pain Management* (2017)[16]
- the National Prescribing Service[17]
- publications in *Medicine Today* in 2010 and 2012.[18,19]

These publications enunciate the following consistent principles.

Comprehensive assessment

A comprehensive assessment occurs in a sociopsychobiomedical framework that identifies:

- factors in the patient's environment related to family and other relationships, work, life events, housing, sleep, activity and nutrition
- psychological factors, such as the patient's beliefs (including understanding of diagnosis and prognosis, expectations about treatment and willingness to be an active participant), mood state, behaviours and cognitive state
- biomedical contributors, including underlying disease, damage (including effects of surgery) and altered central nociceptive function.[20]

This comprehensive assessment also includes identifying polypharmacy and addressing the risk of opioid misuse.

Multimodal therapy

The aim of multimodal therapy is to support the transition from passive modalities, such as medication and procedures, to active self-management. Components of multimodal therapy include:

- nondrug therapies, such as education, pacing of activity (including use of the painful body part), addressing postural components, structured exercise programs, sleep hygiene and psychological therapies. Input is obtained, where required, from a nurse educator, physical therapist, psychologist, occupational therapist, social worker, rehabilitation counsellor or dietitian
- drug therapy used mainly for symptom control and only ever as a passport towards self-management; these medications should be prescribed on a time-limited basis.

Trial of opioid therapy

If, after comprehensive assessment, opioid therapy is thought to be warranted as part of a multimodal plan then it must be considered an ongoing trial of therapy to determine whether the individual patient's predicament is opioid-responsive. The main components of prescribing in this context are:

- agreement between the doctor and patient regarding an opioid trial, with frank articulation of negotiated goals of the trial that go beyond pain relief alone. Goals should emphasise improvement in physical, emotional and mental functioning, including an increase in activity. There should also be mutual recognition that if the goals are not met then the treatment will be discontinued
- conduct of an opioid trial that expressly avoids short-acting preparations in favour of controlled-release oral or transdermal products, thus excluding codeine
- a plan for response to difficulty in achieving or maintaining therapeutic goals; this usually requires comprehensive reassessment on the one hand and an array of actions on the other, such as recalibration of goals of therapy, reconsideration of other modes of treatment, consultation with colleagues, opioid reduction to the minimum effective dose, or cessation
- understanding of appropriate weaning strategies, which may reveal that the primary problem is opioid dependence rather than pain, which in turn may require specialist advice.

Conclusion

In retrospect, it is surprising that codeine, a weak opioid, was ever seen to have a role in the management of pain, especially CNCP. In the case of acute pain, nonopioid analgesics are just as, if not more, efficacious than codeine. If the degree of acute nociception demands an opioid analgesic then there are strong MOR agonists available. For CNCP, it can be confidently asserted that codeine has no place. If a trial of opioid treatment is considered to be indicated then modified-release preparations of strong MOR agonists can be used, according to published guidance. MT

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COMPETING INTERESTS: Professor Cohen has received personal fees from MundiPharma.

Codeine rescheduling and the GP

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With codeine becoming prescription-only from 1 February 2018, patients who have been taking over-the-counter codeine products are likely to present to their GPs. Recommended management ranges from advice about pain management through support for cessation to opioid maintenance treatment, depending on the patient's level of opioid tolerance or dependence.

On 1 February 2018, codeine became a prescription-only medication in Australia. Many patients who take codeine are likely to present to GPs and other healthcare providers in the next weeks to months asking for advice. Some patients may have been using codeine intermittently for acute pain in recommended doses, and others may have found themselves taking larger doses over a longer period (see the case of Julie in Box 1). This article outlines the recommended assessment and management strategies for patients who present with different levels of codeine use in general practice.

Why, how much, how often and how long?

The first step with patients presenting with over-the-counter (OTC) codeine use is to understand the underlying symptoms or conditions for which they are using codeine and to determine how likely they are to need help in stopping codeine. Are they taking codeine occasionally for acute pain or daily for chronic pain? Are they taking

KEY POINTS

- If a patient requests a codeine prescription, first establish the reason they take codeine and their pattern of use.
- If a patient has been using codeine regularly over a relatively long period (e.g. more than a month), assess for likely dependence.
- A taper from codeine (e.g. with symptomatic medication or a medication such as buprenorphine–naloxone) is a reasonable approach in the first instance where a diagnosis of codeine dependence is not established.
- When a patient clearly meets criteria for opioid dependence, with a well-established pattern of daily high-dose use, and taper approaches have failed, consider medication-assisted treatment for opioid dependence (e.g. with buprenorphine–naloxone), with the support of alcohol and drug services for nonaccredited prescribers.

MedicineToday 2018; 19(3 Suppl): 14-23

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1. A PATIENT WHO DOESN'T KNOW WHAT TO DO WITHOUT CODEINE

Julie, aged 52 years, presents to your general practice with intermittent diarrhoea and nausea. She has seen several other GPs previously and was investigated for a gastrointestinal infection and treated symptomatically with diphenoxylate hydrochloride plus atropine sulfate. The test results showed no evidence of infection.

You take a history, including asking whether she takes any over-the-counter (OTC) medications. She reports that she takes ibuprofen plus codeine phosphate (12.8 mg) for 'back pain and anxiety' and 'to help her sleep'. On further questioning, she says she takes 20 tablets a day and is worried about this. When she heard she will no longer be able to buy the medication OTC from the pharmacy, she stockpiled a few weeks' worth of tablets. Now she does not know what to do.

codeine for nonpain reasons, such as in response to stress, anxiety or insomnia?

The next step is to assess the pattern of codeine use and ask patients what happens when they do not take it. This information will help determine whether they have developed opioid tolerance and show signs of opioid withdrawal on cessation. These symptoms may be part of a pattern of opioid dependence. However, opioid dependence (as defined by the *International Classification of Diseases* [ICD-10]) goes beyond neuroadaptation to opioids (with tolerance and withdrawal) to include behavioural components such as craving, continued use despite ill health or other harm and loss of control over use.

Patient assessment

Assessment of patients taking codeine should cover:

- current codeine use (reason, dose, route of administration, duration and symptoms on cessation)
- other medication and alcohol, nicotine and substance use
- mental health and physical comorbidities
- social circumstances
- physical examination (including signs of opioid toxicity and withdrawal; see Box 2)
- investigations (e.g. urine drug screen, liver function tests, full blood count)
- how difficult the patient thinks it may be to go without codeine and whether they experience opioid withdrawal symptoms when they go without codeine
- whether the patient is exceeding maximum doses, buying codeine from multiple pharmacies, obtaining prescriptions for codeine or other opioids or hiding their use from others.

Identifying opioid dependence

The ICD-10 includes criteria to identify dependence. According to the ICD-10, opioid dependence is defined by the presence of three or more of the following features at any one time in the preceding year:

- a strong desire or sense of compulsion to take opioids
- difficulties in controlling opioid use
- a physiological withdrawal state
- tolerance
- progressive neglect of alternative interests or pleasures because of opioid use
- persisting with opioid use despite clear evidence of overtly harmful consequences.

There are other definitions of opioid dependence or 'use disorder' (e.g. the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, DSM-5), but the central features are the same: loss of control over use, continuing use despite harm, craving, compulsive use, physical tolerance and dependence remain key in identifying problems.

Is the patient experiencing pain or opioid withdrawal?

For a patient who takes codeine regularly, it can be difficult to differentiate between the re-emergence of pain and the emergence of opioid withdrawal symptoms. Pain symptoms often increase during opioid withdrawal. Some patients describe taking codeine as 'the only thing that works', for example in self-management of persistent or recurrent headaches. In some cases, a detailed assessment can reveal that opioid overuse or withdrawal itself may be the cause of the headaches (medication overuse headache, Box 3).[1] In other cases, patients have always used the 'strongest' product available and have never tried taking simple analgesics without codeine.

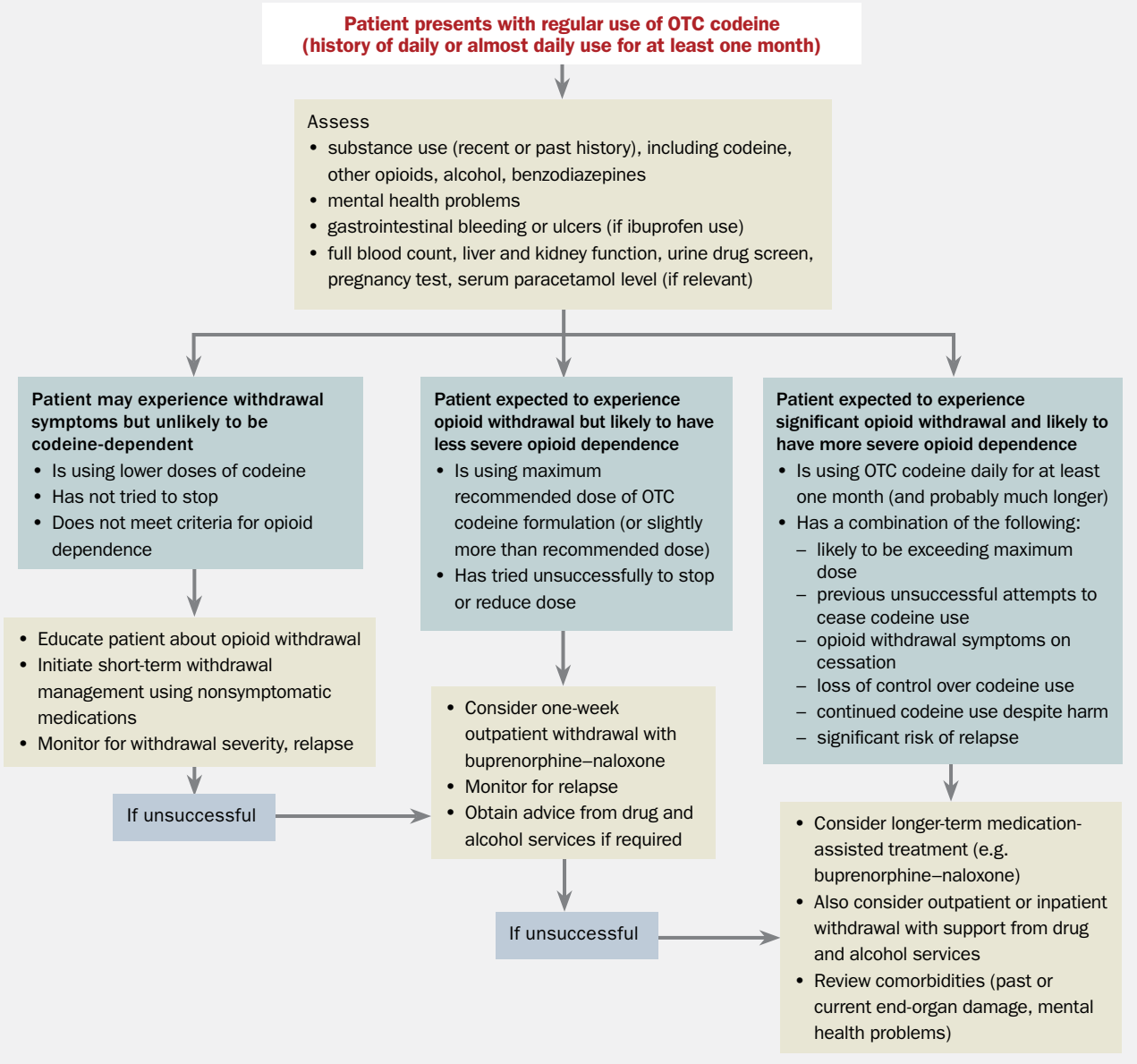
2. OPIOID WITHDRAWAL SYMPTOMS

- Symptoms of withdrawal are similar for all opioids but vary in severity and duration depending on the opioid
- Physical symptoms of codeine withdrawal commence six to 12 hours after last use and last for approximately five days
- Signs and symptoms of codeine withdrawal can range from mild to unpleasant but are rarely life-threatening (providing adequate hydration and electrolyte balance is maintained)
- Symptoms of opioid withdrawal include:
  - lacrimation, rhinorrhoea and sneezing
  - dilated pupils (>4 mm)
  - yawning
  - hot and cold flushes
  - sweating and piloerection
  - craving
  - anxiety, restlessness and irritability
  - tachycardia
  - disturbed sleep
  - gastrointestinal tract symptoms (e.g. anorexia, abdominal pain, nausea, vomiting and diarrhoea)
  - muscle, bone and joint pain
  - headache, muscle cramps
  - tremor

Is the patient likely to need help in stopping codeine?

The assessment and management of patients who present with regular OTC codeine use is summarised in the Flowchart. Management approaches depend on the likelihood of opioid tolerance and dependence.

SUGGESTED MANAGEMENT OF PATIENTS WITH REGULAR USE OF OVER-THE-COUNTER (OTC) CODEINE



Patients who are unlikely to be codeine tolerant or dependent

Patients who are unlikely to be opioid dependent include those who have taken codeine intermittently for relief of acute pain, for example once a week or less often. For most people, simple OTC analgesics are as effective as combination analgesics containing low-dose codeine. A typical example of such a patient, Tom, is described in Box 4.

Management principle: for patients who are unlikely to be opioid tolerant or dependent, give brief advice on the changes in codeine availability and other options for management of acute pain.

Patients with possible codeine tolerance and withdrawal but uncertain dependence

Some patients may have been taking codeine daily or on most days for at least a month, but do not have clear features of opioid dependence, as in the case of Harriet in Box 5. These patients describe codeine use only in the context of managing their pain. They take doses in the recommended range (albeit for a longer period than recommended), and they may not yet have tried to cease codeine.

These patients may need medical

3. MEDICATION OVERUSE HEADACHE

- Medication overuse headache is a common condition, affecting 1 to 2% of the population[1]
- Opioids are commonly implicated, although a wide range of other medicines can cause medication overuse headache
- This condition should be considered in patients who present complaining of chronic daily headache (headache occurring continuously or at least second daily on more than 14 days in a month)
- Most (50 to 70%) of patients respond well to withdrawal of the overused medication[1]

4. A MAN WHO USES CODEINE INTERMITTENTLY

Tom, aged 34 years, has been taking paracetamol plus codeine phosphate (8 mg) for a few days every couple of months for headaches. He attends your general practice asking for a prescription for paracetamol plus codeine as he cannot buy it OTC any more. You explain that, because of concerns about the lack of effectiveness of codeine and its associated risks, the decision was made to remove OTC codeine from sale. You tell him that, for most people, other OTC combinations that do not contain codeine are as effective as low-dose codeine products.

Tom presents several months later for another condition and incidentally reports that ibuprofen is adequately treating his occasional headaches.

5. A WOMAN WITH MILD CODEINE WITHDRAWAL

Harriet, aged 43 years, has a workplace injury to her hand and presents to you for an injury insurance review. She has been taking a strong pain tablet containing paracetamol 500 mg and codeine 15 mg. The pharmacy informed her that this is no longer available and suggested she see her GP.

Harriet has been taking six to eight codeine-containing tablets a day for the past four months. She is struggling with the work cover claim and is experiencing conflict with her employer, who is unable to provide suitable alternative duties. Her surgeon and physiotherapist are pleased with her progress. Harriet has noticed that she feels more anxious and experiences an upset stomach when she tries to go without codeine.

assistance in ceasing codeine use. Reasons not to prescribe codeine or another opioid are outlined in Box 6.[2] Depending on the patient's level of codeine use, opioid tolerance, self-efficacy and resilience, either a trial of cessation with no medication or a short opioid taper assisted by a nonopioid medication may be appropriate. Alternative (nonopioid) pain management approaches should also be discussed. ***Management principle: in the absence of a clear diagnosis of opioid dependence, support attempts at ceasing codeine.***

How useful is the codeine dose in diagnosing dependence?

The case of Harriet in Box 5 demonstrates that problems with codeine can emerge even at recommended doses. The dose of codeine taken may help indicate the degree of dependence and the likely severity of opioid withdrawal symptoms. However, codeine has variable metabolism. Around one in 10 people of Caucasian background are considered 'ultra-rapid metabolisers' of codeine, converting codeine into larger dose of morphine than usual and being at risk of toxicity. At the other end of the spectrum, 5 to 10% of the population are 'poor metabolisers' and cannot convert codeine into morphine, therefore experiencing little analgesia.[3,4]

Variation in metabolism is linked to genetics, with the reported prevalence of ultra-rapid metabolisers ranging from 1% to 25%, depending on genetic background.[3] Consequently, it is possible, albeit uncommon, to have a significant level of opioid tolerance while taking relatively low therapeutic doses of OTC codeine. For example, as few as eight tablets per day of OTC codeine has led to dependence requiring opioid agonist treatment. Similarly,

6. WHY NOT JUST PRESCRIBE CODEINE OR ANOTHER OPIOID?

Now that analgesics containing codeine are no longer available OTC, patients may request a prescription for codeine. It is important for GPs to explain that there is a lack of evidence demonstrating the long-term analgesic efficacy of codeine in treating chronic noncancer pain. Long-term use of opioids has not been associated with sustained improvement in function or quality of life, and there are increasing concerns about the risk of harm. Replacing low-dose codeine products with low doses of stronger opioids (such as low-dose oxycodone or oxycodone–naloxone combinations) is strongly recommended against for this reason.

GPs should explain that the risks associated with opioids include tolerance, leading to dose escalation, overdose, falls, accidents and death. It should be emphasised that OTC codeine-containing analgesics were only intended for short-term use (one to three days) and that longer-term pain management requires a more detailed assessment of the patient's medical condition and clinical management.

New trials have shown that for acute pain, nonopioid combinations can be as effective as combination analgesics containing opioids such as codeine and oxycodone.[2] If pain cannot be managed with nonpharmacological techniques and nonopioid medications then consider referring the patient to a pain specialist or pain clinic.

Patient resources for pain management are freely available online to all clinicians at websites such as:

- Pain Management Network in NSW – www.aci.health.nsw.gov.au/networks/pain-management
- Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine – fpm.anzca.edu.au
- Hunter Integrated Pain Service – www.hnehealth.nsw.gov.au/Pain/Pages/Pain.aspx

7. A WOMAN WITH SIGNIFICANT CODEINE DEPENDENCE

Ivana, aged 27 years, has been taking 20 to 30 ibuprofen plus codeine (12.8 mg) tablets daily for the past six months for recurrent lower back pain. She has been increasing the dose as the back pain is not responding. She finds that the tablets also help with her anxiety. She says she cannot stop because she feels terrible when she does: 'the pain is really bad, I feel sweaty, shivery, nauseous, with gut cramps and diarrhoea. My partner is very worried about me …'

She recently presented to the emergency department of the local hospital with acute abdominal pain, which was diagnosed as caused by an ulcer, and she was also told she has anaemia.

opioid toxicity has been reported in patients taking relatively low daily doses of codeine. The patient's symptoms on opioid cessation and assessment of other clinical indicators should drive the treatment approach as much as the codeine dose.

TABLE 1. SYMPTOMATIC MEDICATIONS TO TREAT OPIOID WITHDRAWAL SYMPTOMS

Withdrawal symptom	Symptomatic medication	Notes
Diarrhoea	Loperamide 4 mg as an initial dose then 2 mg as required	Maximum dose of 16 mg per 24 hours
Nausea or vomiting	Metoclopramide 10 mg every 4 to 6 hours (maximum 30 mg daily)	Prescription required, metoclopramide preferred as does not cross the blood–brain barrier and is not sedating
Muscle cramps or pain	Ibuprofen 400 mg three times a day or paracetamol (up to 1 g four times a day, no more than 4 g [eight tablets] in 24 hours) or hyoscine butylbromide 10 to 20 mg four times a day	Do not recommend ibuprofen for patients with a history or risk of peptic ulcer or gastritis, including a history of regular high-dose ibuprofen–codeine use; do not recommend paracetamol for those with a history or risk of hepatic problems
Insomnia	Symptomatic medications not recommended; provide psychological support and strategies for insomnia	
Agitation or anxiety	Symptomatic medications not recommended; provide psychological support and relaxation strategies for anxiety management	

Patients who are likely to be codeine dependent

Patients who have been taking codeine regularly (at least daily and probably multiple times a day for months or years) are likely to have developed tolerance to codeine and may have developed dependence, as in the case of Ivana (Box 7). These patients may take codeine for pain or for nonpain reasons such as insomnia and to help with psychological distress.

Other characteristics that are commonly associated with codeine dependence include:

- difficulty stopping or inability to imagine stopping codeine use
- emergence of withdrawal symptoms six to 12 hours after the last codeine dose
- self-medication with opioids for opioid withdrawal that has been self-diagnosed as re-emergence of pain (e.g. rebound headaches)
- other substance use disorders (more often alcohol, benzodiazepines, and less frequently other opioids or other illicit drugs)
- concurrent mental health conditions.

Management principle: advise patients with significant codeine dependence to consider maintenance treatment with buprenorphine–naloxone or methadone, following national guidelines.[5] Another option is detoxification. Address any concurrent mental health problems and investigate for possible adverse effects of high-dose ibuprofen or paracetamol, as relevant.

Management options for codeine dependence

Maintenance treatment with buprenorphine–naloxone or methadone (also termed substitution treatment) is indicated for the treatment of opioid dependence, including codeine dependence.[5] Other opioids, such as oxycodone–naloxone, are not indicated in the treatment of opioid dependence. Most state and jurisdictional regulations preclude the use of opioids other than methadone and buprenorphine (with or without naloxone) for the treatment of opioid dependence.

Detoxification is an alternative to maintenance treatment, particularly for patients who have less severe dependence and no medical problems such as liver, kidney and gastrointestinal complications due to the use of high doses of ibuprofen or paracetamol in codeine-containing products or other factors that increase the risk of relapse. For patients who have used larger doses of opioids and have established opioid dependence, short-term opioid tapering is associated with poorer treatment outcomes compared with maintenance treatment with opioid agonists.[6] The low rates of success for short-term withdrawal and risk of overdose with loss of tolerance should be discussed with the patient. The patient should be advised that if codeine withdrawal management is unsuccessful then maintenance treatment with supervised buprenorphine–naloxone or methadone is indicated.

Concurrent mental health problems such as anxiety should be addressed. Options include face-to-face psychological support (e.g. through a mental healthcare plan) or on-line support (e.g. through services such as beyondblue). During initial withdrawal, psychosocial approaches are recommended before psychotropic medications, as opioid withdrawal symptoms can contribute to diagnostic uncertainty.

When a patient is codeine dependent, longer-term prescribing of opioids should be under the framework of supervised medication-assisted treatment of opioid dependence (e.g. with buprenorphine–naloxone or methadone). Clinicians should contact the local health department to confirm requirements in their jurisdiction before prescribing pharmacotherapy, in addition to checking electronic medical records and prescription monitoring records where these are available.

When patients report taking large doses of ibuprofen plus codeine or paracetamol plus codeine combination products, relevant investigations should be considered, particularly to assess for renal and hepatic impairment and for anaemia. A range of serious and even fatal consequences have been reported with long-term high-dose use of codeine combination products, including perforated gastric ulcer, hypokalaemia and liver failure.[7]

Weaning off codeine in an outpatient setting

An opioid taper may be appropriate for patients who:

- show evidence of physiological dependence to codeine but no clear diagnosis of opioid dependence
- are otherwise in good health and do not have concurrent comorbidities that warrant specialist assessment or admission for inpatient treatment
- have no other concurrent substance use disorders and are not using other psychoactive substances of concern
- have home and social environments that are safe, supportive and free from other substance use.

An opioid taper can be considered as the first step in assessing opioid dependence when use has been in lower doses or over shorter periods, and other pharmacological approaches are not indicated.

Patients who have significant comorbidity or concurrent substance use disorder may be best managed in a specialist drug treatment setting, in an outpatient setting through a shared-care arrangement, or with the input and support of health care providers and services specialising in treatment of substance use disorders.

An opioid taper can be considered as the first step in assessing opioid dependence when use has been in lower doses or over shorter periods, and other pharmacological approaches are not indicated. For an opioid taper to be indicated, the patient should describe a pattern of daily or near daily codeine use for at least a month (it is likely it would be longer) and opioid withdrawal symptoms on codeine cessation (see Box 2). If the patient has not experienced opioid withdrawal symptoms on cessation then it is appropriate, before a medication-assisted taper is considered, to educate them about withdrawal symptoms and ask them to try ceasing codeine and record daily symptoms in a symptom diary.

Symptomatic medications (nonopioid medications that reduce the symptoms of opioid withdrawal) can be used by patients who wish to self-manage codeine cessation without an opioid being prescribed. Examples are listed in Table 1. Patients should be advised that these medications can reduce the discomfort but may not entirely relieve opioid withdrawal symptoms.

Medication options for managing codeine withdrawal symptoms

A range of medications have been proposed to help manage the temporary discomfort caused by codeine cessation, including the nonopioid symptomatic medications described above and opioids. These medications and their regulatory requirements, supporting evidence, advantages and disadvantages are summarised in Table 2.[8-16] This use is off-label for most; many have limited supporting evidence and not all can be recommended.

The largest body of evidence supports the use of sublingual buprenorphine (provided as buprenorphine–naloxone), followed by symptomatic medications. The latter nonopioid medications are an alternative that may be appropriate for patients with lower-level opioid neuroadaptation and are discussed above. Prescribed codeine, tramadol and buprenorphine patches have also been proposed to treat opioid withdrawal but their use is off label for this purpose and they have a limited evidence base. Tramadol and buprenorphine patches are indicated only to treat pain.

8. SAMPLE BUPRENORPHINE–NALOXONE WITHDRAWAL REGIMEN

Day 1: Administer 2 mg buprenorphine–naloxone at onset of withdrawal as a pharmacist-supervised dose. Assess tolerance two hours later. Give an additional 2 to 4 mg as a supervised dose four hours later, if required (depending on opioid withdrawal symptoms).

Day 2: Administer 4 to 8 mg buprenorphine–naloxone in the morning. Dose depends on total dose on day 1; assess whether any sedation occurred following the first dose, and if sedation is reported then reduce or do not exceed day 1 dose.

Day 3: Administer 4 to 6 mg buprenorphine–naloxone

Day 4: Administer 2 to 4 mg buprenorphine–naloxone

Days 5 and 6: Administer 2 mg buprenorphine–naloxone daily for two days, then cease.

TABLE 2. COMPARISON OF MEDICATION APPROACHES FOR SHORT-TERM MANAGEMENT OF OPIOID WITHDRAWAL (OVER SEVEN TO 10 DAYS)[8-16]

Medication	Regulatory requirements	Requires off-label use	Strength of evidence	Advantages	Disadvantages	Notes on dosage
Buprenorphine–naloxone (sublingual)	Permit before treatment; patient registered as drug dependent in some jurisdictions	Indicated for opioid dependence (off-label for pain)	Multiple well conducted RCTs demonstrate efficacy and safety[8]	• A large evidence base (e.g. Cochrane reviews) shows it is the most effective option for opioid taper[16]	• More restrictive than other options (regulatory requirements and supervised dosing) • Indicated only for opioid dependence, not for chronic pain in the absence of opioid dependence	• See sample withdrawal regimen (Box 8) or refer to state and national guidelines
Tramadol (oral)	Only those that apply to S4 medications	Yes (indicated for pain not opioid dependence)	Low – a small number of RCTs demonstrate efficacy and safety[9-12]	• A small number of studies examined a one-week tramadol taper, with outcomes comparable to those of other opioid tapers and superior to clonidine	• May produce serotonergic side effects, known drug interactions, use with caution in the elderly • Use is off label • Risk of seizures, even at usual doses • Variable metabolism through CYP P450, similar to codeine	• 100 to 300 mg sustained-release formulation twice a day for one week • Supervised dosing and daily dispensing may be indicated
Prescribed codeine (oral)	Permit for codeine as a single ingredient (S8) before treatment. Combination (S4) products have fewer regulatory requirements	Yes (indicated for pain not opioid dependence)	No RCTs, limited evidence in literature with mixed outcomes[13,14]	• Uses the same opioid that the patient is tolerant to • Combination (S4) products may have fewer prescribing restrictions	• Short-acting agents are not ideal for taper; use of the opioid that led to dependence is also not ideal • Limited evidence to support this approach • Combination products introduce risks of taking high doses of simple analgesics in addition to codeine	• Up to 30 to 60 mg four times a day, reducing over 5 to 7 days (not more than 50% of stated codeine OTC dose); reduce the dose over 7 to 10 days
Buprenorphine (transdermal patch)	Permit before treatment if patient is drug dependent	Yes (indicated for pain not opioid dependence)	None – no RCTs or published cases	• Good safety profile	• Dose likely to be insufficient for patients with clear evidence of opioid dependence	• 5, 10 or 20 mcg weekly patches are available • A single patch should be sufficient for taper from oral codeine
Symptomatic medications	Only those relating to S4/OTC medications	No (if use is consistent with product indication)	Moderate to high – well-conducted RCTs demonstrate efficacy; however, poorer outcomes than buprenorphine or tramadol[15]	• Fewer prescribing restrictions • Relatively safe in outpatient setting	• Shown to be less effective than buprenorphine and tramadol • Multiple medications can be confusing • Caution using sedative medications in outpatient setting • Clonidine can cause severe hypotension	• See Table 1

Abbreviations: OTC = over the counter; RCT = randomised controlled trial.

If opioid withdrawal symptoms are not relieved by buprenorphine or symptomatic medications then this may indicate a higher level of dependence. Where the treating doctor does not possess relevant training and experience, these patients may require referral for management by an addiction medicine specialist in an inpatient or outpatient setting. Maintenance treatment with opioid agonists (buprenorphine–naloxone or methadone) should be considered for these patients.

Prescribing of opioids for the management of codeine withdrawal should be limited to a maximum of seven to 10 days. If longer periods of medication are required then these should be provided in the context of medication-assisted treatment for opioid dependence (buprenorphine–naloxone or methadone) in accordance with national and jurisdictional guidelines.[5] There is little evidence to support the use of medications other than

9. COMPONENTS OF THE CLINICAL OPIATE WITHDRAWAL SCALE FOR ASSESSING SIGNS AND SYMPTOMS[19]

Sign or symptom	Score
Resting pulse rate measured after patient is sitting or lying for one minute (beats/min)	
≤ 80	0
81 to 100	1
101–120	2
>120	4
Sweating over past half hour not accounted for by room temperature or patient activity	
No report of chills or flushing	0
Subjective report of chills or flushing	1
Flushed or observable moistness on face	2
Beads of sweat on brow or face	3
Sweat streaming off face	4
Restlessness observed during assessment	
Able to sit still	0
Reports difficulty sitting still, but is able to do so	1
Frequent shifting or extraneous movements of legs/arms	3
Unable to sit still for more than a few seconds	5
Pupil size	
Pinned or normal size for room light	0
Possibly larger than normal for room light	1
Moderately dilated	2
So dilated that only rim of iris is visible	5
Bone or joint aches (only the additional component attributed to opiates withdrawal is scored)	
Not present	0
Mild diffuse discomfort	1
Patient reports severe diffuse aching of joints/muscles	2
Patient is rubbing joints or muscles and is unable to sit still because of discomfort	4
Runny nose or tearing not accounted for by cold symptoms or allergies	
Not present	0
Nasal stuffiness or unusually moist eyes	1
Nose running or tearing	2
Nose constantly running or tears streaming down cheeks	4

Sign or symptom	Score
Gastrointestinal upset over previous half hour	
None	0
Stomach cramps	1
Nausea or loose stool	2
Vomiting or diarrhoea	3
Multiple episodes of diarrhoea or vomiting	5
Tremor in outstretched hands	
None	0
Tremor can be felt, but not observed	1
Slight tremor observable	2
Gross tremor or muscle twitching	4
Yawning observed during assessment	
None	0
Once or twice during assessment	1
Three or more times during assessment	2
Several times/minute	4
Anxiety or irritability	
None	0
Patient reports increasing irritability or anxiousness	1
Patient obviously irritable or anxious	2
Patient so irritable or anxious that participation in the assessment is difficult	4
Gooseflesh skin	
Skin is smooth	0
Piloerection of skin can be felt or hairs standing up on arms	3
Prominent piloerection	5

Data are from Wesson and Ling (2003).[19]

For each item, the assessor should allocate the score for the best description of the patient's sign or symptom. Only signs and symptoms related to opiate withdrawal should be rated. For example, if the patient's heart rate is increased because they were jogging just before the assessment, the increased pulse rate would not be included in the score.

Scores are defined as:

- 5–12 = mild withdrawal
- 13–24 = moderate withdrawal
- 25–36 = moderately severe withdrawal
- more than 36 = severe withdrawal

10. DRUG AND ALCOHOL SERVICE CONTACT DETAILS AND HEALTH DEPARTMENT LINKS WITH INFORMATION ABOUT OPIOIDS

Australian Capital Territory
- ACT Health Services Alcohol and Other Drugs 02 6207 9977
- http://www.health.act.gov.au/our-services/alcohol-and-other-drugs/opioid-maintenance-treatment
- http://health.act.gov.au/public-information/businesses/pharmaceutical-services/controlled-medicines

New South Wales
- Alcohol and Drug Information Service (ADIS)
  - Sydney 02 9361 8000
  - Regional NSW 1800 422 599
- Drug and Alcohol Specialist Advisory Service (DASAS)
  - Sydney metropolitan 02 9361 8006*
  - Regional and rural NSW 1800 023 687*
- http://www.health.nsw.gov.au/pharmaceutical/doctors/Pages/Prescribe-S8-opioid.aspx
- http://www.health.nsw.gov.au/pharmaceutical/doctors/Pages/otp-medical-practitioners.aspx

Northern Territory
- Alcohol and Drug Information Service (ADIS) 1800 131 350
- Drug and Alcohol Clinical Advisory Service (DACAS) 1800 111 092*
- https://health.nt.gov.au/professionals/environmental-health/medical-practitioners-schedule-8-medicines

Queensland
- Alcohol and Drug Information Service (ADIS) 1800 177 833
- https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/qld-opioid-treatment
- https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence?a=167256

Tasmania
- Alcohol and Drug Information Service (ADIS) 1800 811 994
- DACAS 1800 630 093*
- http://www.dhhs.tas.gov.au/__data/assets/pdf_file/0018/112527/2012_TOPP_Document.pdf

Victoria
- DirectLine 1800 888 236
- DACAS 1800 812 804*
- https://www2.health.vic.gov.au/public-health/drugs-and-poisons/treatment-approvals/schedule-8-permits-and-notifications
- https://www2.health.vic.gov.au/public-health/drugs-and-poisons/pharmacotherapy

Western Australia
- Alcohol and Drug Information Service (ADIS)
  - Perth 08 9442 5000
  - Regional WA 1800 198 024
- WA Clinical Advisory Service 08 9442 5042*
- http://www.mhc.wa.gov.au/about-us/our-services/community-pharmacotherapy-program
- http://ww2.health.wa.gov.au/Articles/N_R/Opioids-benzodiazepines-and-other-S8-medicines

South Australia
- Alcohol and Drug Information Service (ADIS) 1300 131 340
- DACAS 08 7087 1742*
- http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/health+topics/health+conditions+prevention+and+treatment/medicines/opioid+dependence+treatment
- http://www.sahealth.sa.gov.au/wps/wcm/connect/Public+Content/SA+Health+Internet/Clinical+resources/Clinical+topics/Medicines+and+drugs/opioids

*24-hour hotlines are available in most states for healthcare professionals to call for advice.

methadone and buprenorphine–naloxone, and for this reason these other approaches are not recommended. It is strongly recommended not to transfer patients to strong opioids such as oxycodone, oxycodone–naloxone or fentanyl.

Patients should be in contact with an experienced healthcare professional while undergoing opioid withdrawal, and this contact should be at least daily during the first few days to allow clinical review and dose adjustment. Because of interpatient variability in the opioid effects of codeine, the risk of either undertreatment or oversedation should be considered. Review of patients is recommended a few hours after the first dose of buprenorphine–naloxone. Patients should be warned that they may have difficulty fulfilling their usual roles during this time; they may need time off work or to make alternative child care arrangements and they may not be able to drive a car (depending on the strength of the medication prescribed and how it affects them). If necessary, opioid withdrawal can be conducted in a residential facility such as a drug and alcohol detoxification service.

Buprenorphine in management of codeine withdrawal

The largest body of evidence is for the use of buprenorphine in the clinical management of opioid withdrawal.[16] The efficacy of buprenorphine is supported by a Cochrane review, and the most clinical experience exists for buprenorphine to treat codeine dependence.[16,17]

Buprenorphine is ideal for management of opioid withdrawal as it is a partial agonist with a ceiling on respiratory depressant effects and can be administered with once-daily supervised dosing.[18] A sample

buprenorphine–naloxone withdrawal regimen is shown in Box 8.

When a patient commences buprenorphine, key considerations include avoiding 'precipitated withdrawal'. This occurs when buprenorphine is administered while a full opioid agonist is still active in the body. Buprenorphine displaces the full opioid agonist at the mu-opioid receptor, leading to opioid withdrawal symptoms. To avoid precipitating opioid withdrawal, standard procedures outlined in guidelines include waiting until mild to moderate opioid withdrawal symptoms are observable, typically around 12 hours after the last dose of a short-acting opioid such as codeine. The Clinical Opioid Withdrawal Scale is a useful tool to assess opioid withdrawal (Box 9).[19]

GPs unfamiliar with their local state and territory requirements on prescribing buprenorphine should contact their local health department or addiction specialists for advice and support (see Box 10 for contact details). Advice is also available from local drug and alcohol services, which in most states provide 24-hour telephone advice lines (Box 10). Before buprenorphine treatment begins, an authority is required from the state or territory health department. In states such as Victoria, South Australia and Western Australia, GPs can commence buprenorphine–naloxone treatment without being accredited prescribers or with minimal additional training. However, most other jurisdictions require doctors to undergo some training before being authorised to prescribe buprenorphine. Buprenorphine (usually as buprenorphine–naloxone) is dispensed only by specific pharmacies. The pharmacy should be contacted in advance to confirm that it can accept the patient.

Longer-term treatment with buprenorphine–naloxone should be considered when there is a clear diagnosis of opioid dependence, including difficulty controlling use, continued codeine use despite harm, clear tolerance and withdrawal symptoms on cessation. For some people with codeine dependence, ongoing treatment with buprenorphine–naloxone or methadone has been lifesaving.

When a patient commences buprenorphine, key considerations include avoiding 'precipitated withdrawal'.

Conclusion

Over the next few months, as patients present to their GPs requesting codeine or reporting previous OTC codeine use, careful assessment may identify unmanaged tolerance or opioid dependence. The change in codeine availability may provide an opportunity for better management of chronic pain conditions. Depending on the pattern of codeine use, different management strategies may be appropriate. For most patients who report infrequent codeine use, alternative nonopioid analgesia will be appropriate. Where patterns of high-dose use are identified, medication-assisted treatment in consultation with drug and alcohol experts may be required. Where the level of opioid tolerance and dependence is unclear, supporting the patient to cease codeine in the short term is recommended in the first instance. MT

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COMPETING INTERESTS: Dr Nielsen has been an investigator on projects supported by untied educational grants from Indivior, and has received travel expenses and/or received honoraria to speak on codeine dependence or related topics from Indivior, Pharmaceutical Society of Australia, TGA, Pharmacy Guild of Australia, Royal Australian College of General Practitioners, Primary Health Networks and Drug and Alcohol Networks around Australia. She is currently the recipient of an NHMRC Fellowship (#1132433).
Dr Wilson has been paid honoraria by Indivior to present educational activities. Associate Professor Clark and Dr Reynolds: None.

Tips for talking about codeine

Guidance for health professionals with prescribing authority

NATIONALLY COORDINATED CODEINE IMPLEMENTATION WORKING GROUP*

With the upscheduling of codeine, many patients who have been taking over-the-counter codeine preparations may present to GPs asking for a prescription or for help with pain. The TGA has developed sample responses and management tips for a range of patient presentations.

As a health professional with prescribing authority, you may see more people requesting codeine for pain management since codeine became a Prescription Only Medicine on 1 February 2018.

It is important to:

- develop your practice policies for prescribing medicines for pain
- know how to manage pain without reliance on opioids
- know when to refer to an allied health professional for other therapies, to a pain specialist or clinic for assessment and management, and/or to drug and alcohol services.

MedicineToday 2018; 19(3 Suppl): 24-27

The Nationally Coordinated Codeine Implementation Working Group (NCCIWG) was established to assist with providing consistent communications to inform and educate the public and health professionals about the changes to the availability of codeine-containing medicines in Australia. NCCIWG includes representatives from state and territory health departments and peak professional bodies representing consumers and health professionals.

* This article was first published by the TGA, 2017 (www.tga.gov.au/tips-talking-about-codeine-guidance-health-professionals-prescribing-authority).

'I need something to help with my pain. I used to take codeine but it is no longer available in the pharmacy.'

Sample responses

- What have you tried for your pain in the past?
- Over-the-counter (OTC) codeine-containing medicines have been used in the past for the self-treatment of chronic pain problems. However, we know these are not effective at the OTC dose, can have serious and potentially life-threatening side effects and are not first-line in treating chronic pain so we don't always prescribe them.
- Sometimes long-term pain may indicate an underlying problem. Can you tell me more about your pain? How long have you had the pain for? Can you describe the pain you are experiencing (dull, sharp, tingling etc.)?
- What would you like to achieve with your pain management? (For example, a higher level of functioning. However, pain free may not be achievable.)

Tips

Asking open ended questions about pain will help with your assessment.

You will need to perform a comprehensive clinical assessment of the person's pain rather than just treating the pain as a symptom.

Don't assume that if someone asks you to assist them with pain that they are looking for pain tablets. Explore other options such as physiotherapy, massage, acupuncture, exercise, lifestyle changes and active self-care management.

Manage expectations of the person to whom you are providing care. Inform them that sometimes pain management is a long-term process and requires more than medicines.

Discuss all of the person's concerns and needs as they arise. Schedule another appointment for further discussions if required.

'I am worried about the changes to codeine access.'

Sample responses

- What are you most worried about with the changes?
- Did you know codeine ...? (Inform about risks of long-term codeine-containing medicine use.)

Tips

There is evidence that low-dose codeine (less than 30 mg/dose) does not provide any more symptomatic relief from pain than OTC products without codeine (for example paracetamol, ibuprofen or a combination of both).

Codeine (more than 30 mg/dose) is indicated for acute, mild to moderate pain. It is not indicated for the treatment of chronic pain; however, low-dose OTC codeine is currently being used for the self-treatment of chronic pain. Incorrect long-term use of low-dose codeine for chronic pain is associated with health risks, specifically developing tolerance and dependence, and associated side effects from long-term consumption of paracetamol and ibuprofen which are potentially life threatening.

'My pain has not resolved as expected!'

Sample response

- It sounds like you have acute pain. Acute pain can sometimes be adequately treated by OTC medicines without codeine that are available in the pharmacy. In your case it was great that you were referred to me to discuss whether you need additional pain relief. Let me ask you a few more questions to establish what treatment options are going to be best for you.

Tips

'Acute pain' is pain of recent and sudden onset that in most cases is a symptom of injury or tissue damage (such as a broken bone or sprained joint), an infection in the skin/internal organ (such as appendicitis or tonsillitis) or blocking of blood supply to a limb or the heart. It is important, and usually possible, to identify the cause of the pain, direct treatment to that cause, and to try and reduce the pain itself. This might involve medicines available through the pharmacy and/or nonmedicinal options or self-management approaches.

The term 'acute pain' is also often used by people who have longstanding pain to describe the worsening of that pain. Here the word 'acute' refers more to severity than to duration.

'I have had my pain for longer than expected and it has an impact on my life.'

Sample response

- It sounds like you have chronic pain.
- Chronic pain is when the pain has been present for more than three months. In order for me to treat you correctly, we need to do a comprehensive clinical assessment of your pain and its cause.

Tips

'Chronic pain' is usually defined as pain that is present after a normal time of healing (typically more than three months, but not always). Not all cases of 'chronic pain' however start with an episode of acute tissue damage. Although most episodes of acute pain resolve when the underlying injury or disease process heals, some conditions, such as in inflammatory arthritis or peripheral neuropathy, are characterised by ongoing disease processes that may cause 'persistent pain'. In some cases, the originating process is no longer active but pain persists because

of lasting changes within the nervous system; and in other cases the cause of the pain is unclear and develops without any readily recognised pathology.

Many cases of 'chronic pain' are complex, as they involve not only what may be happening in the person's body, but also what is happening in their lives. Just as 'acute pain' can be accompanied by anxiety, 'chronic pain' can be associated with major changes in mood and how the person functions at home, work, with family or in society. This multidimensional aspect of pain means that the person may require a skilled and comprehensive assessment and a multimodal approach to treatment that does not rely on medicines alone.

Ensure your practice has policies on how to prescribe opioids and other strong pain medicines if/when they are appropriate. Referral to pain specialists may be required for cases unresolved in the practice. Consider nonpharmacological therapies first if there is not an immediate need for drug therapies.

'Can I treat my pain with something other than medicine?'

Sample response

- Yes, there are other pain management strategies available. (Discuss the different options.)

Tips

Other pain management strategies (non-drug) include physiotherapy, mind–body techniques, psychological techniques, occupational therapy, massage, acupuncture, exercise, lifestyle changes and active self-care management.

'I have used different pain medicines for a while and nothing seems to help.'

Sample response

- Although we have tried many things to help with your pain, both drug and nondrug therapies, we do not seem to be making progress. I would like you to be seen by a specialist pain medicine physician, someone who has more expertise in dealing with complex situations such as yours.

Tips

Specialist pain medicine physicians (pain specialists) have expertise in both the physical and psychological aspects associated with patients experiencing chronic pain. They are skilled in multidisciplinary assessment and management and in tailoring a treatment program to the individual. Such programs may use medicines but this is usually in combination with a variety of nonpharmacological approaches. Specialist pain medicine physicians should be consulted early, especially when you and the person to whom you are providing care feel that adequate progress is not being made.

'I have used codeine for a long time and it works well. When I don't use it I have headaches, body aches and diarrhoea. Codeine is the only thing that works for me. I want my medicine.'

Sample responses

- How long have you used this medicine? Did you get it from the pharmacy, was it prescribed or did someone else give it to you?
- I am concerned about that and your health. A request like this can sometimes be a sign of dependence on the medicine. How much you are taking?
- Pain medicines with codeine only provide a short-term benefit. If your pain is worse when you don't take them, it may be because you have become dependent on them. Using other medicines or nondrug methods have been shown to have better long-term benefits.
- I am concerned that providing ongoing medicine is not good for your overall health. I suggest that we trial a graduated withdrawal program, or I can refer you to a specialist?
- Thank you for coming to see me. I am unable to prescribe the medicines that you requested today, because I don't believe it is in your best interest in terms of your overall health. I have mentioned alternative methods of exploring and treating your pain. We can begin to trial an alternative option today, or you can give some further thought to my advice and we can make another appointment to trial other options.
- I believe you. You do have pain. You do believe codeine (opioids) are necessary and this is of overwhelming importance to you. You can see your pain levels improve every time you take codeine (opioids). However, short-term results do not mean that codeine (opioids) are effective or safe. We can assess your pain and work together to determine what is safe and effective for your type and level of pain.
- I understand that you are experiencing pain, and I would like to fully assess you to determine how best to care for you in terms of your pain and your request for codeine (opioids). Please understand that this is complex. For this reason I will do what I can to help you today, and we will get the ball rolling at your next visit regarding your pain management.

Tips

Substance use disorder (SUD) is a medical condition where a person loses control over the amount of medicine they use and can continue to use medicines despite experiencing harm. It is important to remember that these people are presenting symptoms of a condition, and the medical and social circumstances of these people can often be complex.

People with potential SUD may present to your practice, including those that have been using OTC low-dose codeine to self-manage pain.

Ensure your practice has a 'drugs of dependence therapy agreement' policy to inform people about the risks of the drug and expectations for ongoing care using drugs of dependence.

Symptoms of opioid SUD can include a strong desire for opioids, inability to control or reduce use, continued use despite interference with major obligations or social functioning, use of larger amounts over time, development of tolerance, spending a great deal of time to obtain and use opioids, and withdrawal symptoms that occur after stopping or reducing use, such as negative mood, nausea or vomiting, muscle aches, diarrhoea, fever and insomnia.

An SUD presentation will provide the opportunity to organise proper care for these people. As a health professional, you need to be nonjudgemental, use a neutral matter-of-fact tone of voice and be empathetic. Don't be afraid to explore the issues around SUD. Once SUD is identified and discussed, you may have an opportunity to provide treatment within your practice with practice policies and support from drug and alcohol specialists, or refer these people to the local drug and alcohol services to ensure they get the care they need. You may want to refer to Alcohol and Drug Information Service (ADIS) for counselling and referral.

If the person does not accept your advice and continues to pressure you, you can ask them to leave, but provide them an option to return for further help with their SUD when they are ready.

'OK, you won't give me codeine, how about some Endone or Oxycontin?'

Sample responses

- We don't just prescribe strong pain-relieving drugs to people who ask for them. We need to have another look to establish what treatment options are best for you. (Discuss other options.) It may be best if you take into consideration what we have discussed today about alternative treatments.
- As your doctor, I would like to make a diagnosis first to determine what options are available to you that are safe and effective. I hope that we can work together to get the best health outcome for you.

Tips

You can only legally prescribe medicines for their intended use in the treatment of a person under your care. You must take all the reasonable steps to ensure a therapeutic need exists.

You can't legally prescribe drugs merely to support a person's drug dependence.

'I don't need anything else today.'

Sample responses

- Is there something that you were hoping to discuss that we haven't yet?
- Do you have any questions about the recommendations we've discussed?
- Do you have any other concerns about how we might work together to manage your pain?
- Do you understand that as your pain has been present for more than three months, a different treatment approach might be more effective, including assessment by a pain specialist?
- Do you understand that dependence on codeine is a medical condition? Effective treatments are available and we need to treat it properly.

Tips

You may wish to ask the person to whom you are providing care to briefly summarise your discussion to see if they understand the outcomes.

If required, give them written information on the topics you have discussed.

If you are referring them to a specialist, write down the details for their reference.

If you are helping them with gradually tapering off a medicine, write down the expected outcome and timeline. MT

A man using codeine long term for foot pain: alternative pain management and opioid cessation

BRIDIN MURNION FRACP, FFPMANZCA, FAChAM

A 38-year-old man presents to his GP as he can no longer buy ibuprofen plus codeine over the counter. He has been taking up to 12 tablets per day for foot pain that developed six months ago when he started running for exercise. His GP initiates other pain management and a codeine cessation plan.

KEY POINTS

- In patients who have been taking over-the-counter codeine products for pain, the first step is to identify the pain diagnosis.
- The pain diagnosis must be managed, which often means nonpharmacological strategies.
- Opioid cessation can cause pain exacerbation as a manifestation of withdrawal.
- Trial of cessation of opioids is reasonable, particularly when the opioid use disorder is mild and there are no other major substance use problems.
- Explanation, reassurance and treatment planning are crucial to achieving good outcomes.
- Footwear is important in managing foot pain.

Presentation

Kevin, aged 38 years, presents to your general practice because he will soon run out of an ibuprofen plus codeine medication he has been buying over the counter from a local pharmacy. He has been told it is no longer available without a prescription.

Kevin first presented to you six months ago when he moved to your area for an administrative job with the local council. At that time, he was overweight with a BMI of 29 kg/m^2 and centripetal obesity. He was not hypertensive, and his lipid profile and glucose level were normal. He reported binge drinking occasionally with his mates after watching football, but no use of tobacco or other drugs. You advised lifestyle modification with diet and exercise.

Kevin reports that after this, he started running and after a few weeks developed inferior heel pain in the right foot. This progressively worsened, until he was no longer able to run and was in fact finding it very difficult to walk first thing in the morning. He started taking the ibuprofen plus codeine product purchased from his local pharmacy, and it initially helped. However, over subsequent months he found his dose escalating, and he has sometimes been taking up to 12 tablets a day on 'bad days'.

MedicineToday 2018; 19(3 Suppl): 29-30

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‘As the extent and duration of Kevin’s medication overuse is modest and there is a clear diagnosis and management plan, you decide to trial cessation.’

What would you do first?

You examine Kevin. He has tenderness on the medial plantar aspect of the right foot. His BMI is now 31 kg/m^2. He is wearing unsupportive thong-style sandals.

On specific questioning, Kevin says he is currently taking eight to 12 tablets a day of the ibuprofen plus codeine product (ibuprofen 200 mg/codeine phosphate 12.8 mg). He is not taking any paracetamol plus codeine products or paracetamol or codeine single products, nor any prescription opioids or illicit opioids. He denies any symptoms of opioid withdrawal. He has tried to stop the ibuprofen plus codeine but when he does his pain worsens. He does not describe any dyspeptic symptoms, and denies melaena. There is no abdominal tenderness or fluid overload.

You organise a full blood count and measurement of electrolytes, urea and creatinine levels to exclude gastrointestinal bleeding and renal dysfunction from excess NSAID use, and a plain foot x-ray to exclude calcaneal stress fractures.

How can you help this patient?

You make a diagnosis of plantar fasciitis and explain to Kevin the likely cause (starting running) and contributory factors (obesity, poor footwear). You also explain to him that opioids such as codeine are not appropriate medication for pain management in plantar fasciitis.

You encourage Kevin to wear supportive footwear such as athletic shoes, and discourage the use of unsupportive sandals or barefoot walking. On the basis of cost and convenience, Kevin decides to try using prefabricated shoe inserts, which can be purchased from pharmacies and supermarkets, and will consider custom-made orthotics (obtained from orthotists) if other interventions are not effective.

You also advise against running, and suggest stretching and pool-based exercise as an alternative. You refer Kevin to a dietitian. Corticosteroid injection of the plantar fascia can be considered if the above measures are not successful.

There are several considerations in approaching Kevin’s medication overuse. He has developed some tolerance to codeine but his use is still modest. Options are to cease the ibuprofen plus codeine product, to reduce it over a few weeks or to substitute with another opioid to manage tolerance and misuse.

As the extent and duration of Kevin’s medication overuse is modest and there is a clear diagnosis and management plan for his painful condition, you decide to trial cessation. As his foot pain worsened on previous abrupt cessation, you suggest he cease the ibuprofen plus codeine product over a weekend when he has no work commitments and can ‘take it easy’, with a plan to review him on the following Monday. You recommend he continue taking ibuprofen 200 mg three times daily for five days after stopping the ibuprofen plus codeine product to assist with the transition. To help with withdrawal pain, you suggest he takes paracetamol 1 g as needed, to a maximum of 4 g daily, and maintain his fluid intake. You also suggest he use over-the-counter loperamide if he develops withdrawal diarrhoea.

The outcome

You review Kevin on the following Monday. He ceased the ibuprofen plus codeine product on Friday and had a pain exacerbation on Saturday. However, this improved on Sunday and the pain is almost back to baseline. You are now happy for Kevin to go back to work, start a stretching and exercise program and cease ibuprofen, paracetamol and loperamide.

Three months later, Kevin is well. He has lost 10 kg and enjoys swimming four days a week. He wears supportive footwear with a prefabricated insert. He has no resting foot pain and can walk 5 km without discomfort. He takes no medications for pain. MT

Further reading

Buchbinder R. Plantar fasciitis. UpToDate. 2017. Available online at: https://www.uptodate.com/contents/plantar-fasciitis (accessed February 2018).

COMPETING INTERESTS: None.

A woman with pain and codeine withdrawal: treatment to support opioid cessation

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A 42-year-old woman presents to her GP with a urinary tract infection, pain and opioid withdrawal symptoms after running out of her regular ibuprofen plus codeine tablets. She wants to cease all opioids. As symptomatic medications do not control her pain, her GP prescribes a short course of a buprenorphine patch to reduce her symptoms.

KEY POINTS

- A short period (e.g. six months) of daily codeine use in the context of a pain condition does not necessarily warrant a diagnosis of opioid use disorder.
- Opioid withdrawal can be managed with supportive care and symptomatic medication for patients who do not want to start opioid substitution treatment.
- In this case, abdominal pain exacerbated during codeine withdrawal was successfully managed with a short course of the partial opioid agonist buprenorphine.
- The conditions underlying opioid use also require management: in this case recurrent urinary tract infections (contributing to episodes of pain) and anxiety disorder (contributing to codeine overuse).
- Consider a stepped care approach, whereby more intensive interventions such as opioid substitution treatment are introduced only if simpler approaches prove ineffective.

Presentation

Kate, aged 42 years, is a long-term patient in your general practice with a history of recurrent urinary tract infection (UTI), treated with episodic courses of antibiotics, and anxiety, treated with venlafaxine 75 mg for the past two years. She presents early one morning with a discharge letter from the local hospital emergency department (ED), following a presentation overnight. The discharge letter states she presented with a UTI, loin pain and features of opiate withdrawal, having run out of over-the-counter (OTC) ibuprofen plus codeine tablets 24 hours before the ED presentation. The ED staff initiated a course of sulfamethoxazole–trimethoprim for the UTI and also administered diazepam 10 mg, paracetamol 1000 mg and metoclopramide 10 mg for the codeine withdrawal. They sent her home for review by her local GP and recommended an appointment with a renal physician.

What would you do first?

You ensure that Kate is taking the prescribed antibiotics and confirm an appointment for her with a renal physician. You also take a history of her pain and OTC codeine use. She started taking ibuprofen plus codeine episodically about nine months ago following a UTI, started daily use about six months ago, and reports taking 20 tablets containing 15 mg codeine (in combination with either ibuprofen or paracetamol)

MedicineToday 2018; 19(3 Suppl): 31-32

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'As the symptomatic medications have not been effective in controlling Kate's abdominal pain, a short course of a low-potency opioid can be used.'

per day in the past four months. She felt too embarrassed to disclose this to you in recent appointments, where she complained of left-sided loin pain. She now complains of typical symptoms of opiate withdrawal (increased anxiety, sweating, nausea, abdominal cramps and increased loin pain) and has dilated pupils and clammy skin but no fever. She says the medications she received in the ED 'are barely helping', and she needs more assistance coping with her symptoms. She states that she wants to stop all the opioid medications, as they have been causing arguments with her partner, who is generally supportive.

How can you help this patient?

You explain codeine withdrawal, including the likely duration of symptoms (five to 10 days, with peak symptoms in the first two to three days), and that pain symptoms may worsen before they improve. You discuss options for managing withdrawal: supportive care (light diet, maintain hydration, avoid stressors, relaxation strategies, light exercise) and medications.

Medications to help manage withdrawal include symptomatic medications for three to five days, comparable to those she received in the ED: antiemetics (metoclopramide), antispasmodics (e.g. hyoscine butylbromide 20 mg three times daily), antidiarrhoeal agents (e.g. loperamide) and low-dose sedative hypnotics (e.g. diazepam 5 mg twice daily or temazepam 20 mg at night). High-dose clonidine is another option to treat opioid withdrawal but is generally not recommended in general practice as experience in use of these high doses and close monitoring of patient blood pressure are required.

As the symptomatic medications have not been effective in controlling Kate's abdominal pain, you discuss further options to help her. Although she is opioid tolerant you do not consider there is sufficient evidence to diagnose her with opioid dependence at this time. An option to treat her pain is a short course of a low-potency opioid, such as a buprenorphine transdermal patch (20 mcg/h or 40 mcg/h for a week) or oral tramadol (100 mg twice a day for three days, then 50 mg twice a day for three to four days, then cease).

As buprenorphine is a partial opioid agonist and tramadol behaves as a weak opioid, both are less likely to cause significant rebound pain or withdrawal symptoms or to be associated with dose escalation than full-agonist opioids such as morphine or oxycodone. If buprenorphine or tramadol (note they should not be used together) are initiated then other sedatives such as benzodiazepines should be discontinued.

These opioids should be discontinued after about a week, and the patient may expect some mild rebound pain symptoms for a few days. If the patient relapses to opioid use after a period of discontinuation (e.g. using supplies from friends or relatives or doctor shopping) then consider a diagnosis of opioid dependence (mild or severe opioid use disorder). Management options include a longer period of treatment with high-dose sublingual buprenorphine–naloxone and referral for counselling, or referral to an addiction specialist for treatment.

Outcome

Kate completes the course of antibiotics and starts using a 40 mcg/h topical buprenorphine patch, which markedly reduces her symptoms of pain and opioid withdrawal. At one-week follow up, she still complains of mild loin pain and poor sleep but has not used any other analgesics. She is reluctant to cease buprenorphine but agrees to reduce to a lower-dose patch (10 mcg/h) for seven days, and then ceases buprenorphine.

She continues to complain of increased anxiety and poor sleep. You refer her to a counsellor to address these problems and increase her venlafaxine dose to 150 mg daily. Three months later she has not relapsed to analgesic use (confirmed with a urine drug screen negative for opioids), and her sleep is much improved. MT

COMPETING INTERESTS: Professor Lintzeris has received honoraria for presenting professional education in the area of opioid dependence, and educational grants for investigator-led research with buprenorphine–naloxone from Reckitt Benckiser (now Indivior). Associate Professor Demirkol: None.

A man taking large codeine doses who wants to cease: a buprenorphine–naloxone taper

HESTER WILSON BMed(Hons), FRACGP, FAChAM

A 45-year-old man who started taking ibuprofen plus codeine occasionally after a car accident a year ago has gradually increased his dose to over 30 tablets per day. He wants to stop opioids completely but is having trouble going 'cold turkey'. His GP prescribes a five-day tapered course of buprenorphine–naloxone.

KEY POINTS

- Assessment of withdrawal symptoms is important in patients who have been taking codeine-containing medications.
- Buprenorphine–naloxone treatment can be helpful to decrease codeine withdrawal symptoms.
- Patients should not start buprenorphine–naloxone until they exhibit withdrawal symptoms.
- GPs can contact their local drug and alcohol service for help with devising a treatment plan for individual patients.
- GPs should check the regulations in their jurisdiction about prescribing buprenorphine–naloxone.
- Close follow up of patients is needed to ensure whether they have successfully withdrawn from codeine or may require a longer duration of treatment with buprenorphine–naloxone.

Presentation

John, aged 45 years, presents to your surgery after his pharmacist suggests he needs to see you about his codeine use. You have seen him for various conditions and three years ago you referred him to a psychologist after diagnosing depression. He saw the psychologist for a few months and found his mood improved. John works full time and lives with his wife and three teenaged children. Six months ago, his 17-year-old son was diagnosed with depression after a suicide attempt.

What would you do first?

You take a history. It becomes clear that John is taking 30 to 35 ibuprofen plus codeine tablets every day (oral morphine equivalent, about 55 mg per day). He started taking the medication after a minor motor vehicle accident last year in which he suffered a whiplash injury. At first, he took the tablets occasionally for neck discomfort. Over the past four to five months he has progressively increased the dose to the current amount. He says there have been some stressful issues in his life with a restructure at work and his son's depression. He has noticed that when he cuts down the tablets or skips a day, he does not sleep well and feels stressed and nauseated, with abdominal discomfort and diarrhoea.

MedicineToday 2018; 19(3 Suppl): 33-34

Dr Wilson is a Staff Specialist at South Eastern Sydney Local Health District Drug and Alcohol Services, Sydney, NSW.

‘I tried to stop last week and just felt horrible, so anxious, with gut pains, and lying awake half the night worrying.’

When he heard about the change in codeine availability he decided to stock up. He says, ‘I feel very bad about this, I’m lying to my family. I want to change this but I don’t think I can do it on my own. I tried to stop last week and just felt horrible, so anxious, with gut pains, and lying awake half the night worrying. And all this improves when I take the tablets, but I am about to run out now and don’t know what to do.’ He has read about the issues with codeine and is keen to look at other options.

How can you help this patient?

You confirm to John the problems with codeine-containing medications and explain the treatment options. He decides that he wants support to stop the ibuprofen plus codeine medication completely. Given his history of withdrawal symptoms and lack of success in trying to stop ‘cold turkey’, he wants to try buprenorphine.

As you do not have much experience with this you contact your local drug and alcohol clinical advisory service. The consultant you speak to agrees that a course of sublingual buprenorphine–naloxone would be an appropriate initial treatment for John’s opioid dependence. They send you information explaining the rules of your local jurisdiction, how to get a permit for buprenorphine–naloxone, and what doses to use. (Note that in some jurisdictions, GPs require additional training or accreditation to prescribe sublingual buprenorphine–naloxone and must commence the treatment.) The consultant suggests that John starts on buprenorphine–naloxone at his local pharmacy tomorrow morning. As they explain, he needs to stop taking the codeine medication today and wait until he experiences some symptoms of withdrawal before he starts buprenorphine. This both confirms his degree of tolerance to opioids and ensures that buprenorphine (which is a partial mu-opioid receptor agonist) does not precipitate withdrawal.

You telephone a pharmacy that dispenses buprenorphine, which agrees to take John as a client for a week. You organise to obtain a permit for buprenorphine–naloxone, prescribe an initial dose of 2 mg buprenorphine–0.5 mg naloxone, and fax a copy of the prescription to the pharmacy. You instruct John not to take any more codeine so that when he arrives at the pharmacy in the morning he will have some mild withdrawal symptoms. You ask him to come back and see you that afternoon.

John takes some time off work to go through the withdrawal from codeine. The next afternoon he reports to you that he started on buprenorphine–naloxone at the pharmacy at 9 a.m. and his symptoms settled initially but that he is starting to feel unwell again now and is worried that he will not sleep well tonight. You prescribe a five-day course of buprenorphine–naloxone, starting with an additional 4 mg for today, 8 mg tomorrow, and then reducing by 2 mg each day after that. John also re-engages with his psychologist and confides in his wife about his codeine problem.

The outcome

You review John a week later, two days after he finishes the course of buprenorphine. He reports that the first three days were the hardest, with feelings of anxiety and not sleeping, and the pain in his neck was worse than usual, although it improved day by day. You prescribe a paracetamol plus ibuprofen combination for the neck pain.

When you review John a few weeks later, he seems much better. He says, ‘It’s such a relief to be off that codeine stuff, I felt so guilty and awful. I’m actually sleeping better now that I’m not taking anything.’ MT

COMPETING INTERESTS: Dr Wilson has been paid honoraria by Indivior to present educational activities.

An anxious man with codeine dependence: opioid maintenance therapy

CRAIG RODGERS BMed, MPH, FRACGP, FAChAM

A 29-year-old man has been taking up to 45 tablets of ibuprofen plus codeine per day for 12 months as 'a crutch' and 'to relax his nerves'. He experienced withdrawal symptoms when he tried to stop. His GP prescribes sublingual buprenorphine–naloxone to manage his withdrawal symptoms and cravings. The patient opts to taper this slowly.

KEY POINTS

- Many people are not aware that they can develop a tolerance to codeine and are therefore not aware of the withdrawal symptoms they will experience if they reduce their use or stop taking it.
- Patients may be concerned about taking yet another 'addictive' medication to treat opioid withdrawal symptoms, and the reasons to use a medication such as buprenorphine–naloxone need to be carefully explained before its commencement.
- There are initial restrictions on the provision of treatment with buprenorphine–naloxone, such as requiring a nominated pharmacy and daily dispensing. Less frequent dispensing (possibly monthly, depending on the jurisdiction) may be possible when more stability is achieved.
- It is better not to rush to 'come off' buprenorphine–naloxone as relapses may occur. The time needed to wean off maintenance therapy may be similar to the duration of codeine use.

Presentation

Richard, aged 29 years, presents to you, his GP, for help with managing his codeine dependence as the low-dose ibuprofen plus codeine product he has been taking is no longer available without a prescription and he is running out of supplies.

Richard began taking ibuprofen plus codeine about three years ago when he had an infected wisdom tooth. He took it only intermittently at that time and stopped after the tooth was removed. However, he started to take it again as 'a crutch' and to help 'relax his nerves', and this use then increased significantly because he was being bullied at work. He says that he has been taking up to 45 tablets of ibuprofen plus codeine each day for the past 12 months (576 mg codeine per day, equivalent to 75 mg morphine per day).

Richard tried 'going cold turkey', stopping the medication completely two to three months ago, but experienced symptoms such as sweating, shaking, poor concentration, nausea and vomiting and so started taking it again. He says that he often feels ashamed on his regular visits to his local pharmacy to buy the medication and he has 'shopped around' at other pharmacies.

What would you do first?

You complete an assessment that covers Richard's social circumstances, physical and mental health reasons for codeine use, recent codeine use patterns and other substance use history. He is currently working as a bartender and lives in stable rental accommodation. He denies any history of other illicit drug use. He does not report any injecting drug use and drinks alcohol only on one day per week, consuming up to four standard drinks each time. He has been a cigarette smoker for 15 years and currently smokes about 20 cigarettes per day.

MedicineToday 2018; 19(3 Suppl): 35-36

Dr Rodgers is Senior Staff Specialist at the Alcohol and Drug Service, St Vincent's Hospital, Sydney, NSW.

‘At his present level of codeine use it will be difficult to taper off the drug.’

How can you help this patient?

You explain to Richard that the symptoms he describes when he stopped taking ibuprofen plus codeine a few months ago are consistent with opioid withdrawal and that at his present level of codeine use it will be difficult to taper off the drug. You consider he is opioid dependent and discuss with him the use of sublingual buprenorphine–naloxone to manage his withdrawal symptoms and cravings. He is interested but finds it daunting that he would need to attend a pharmacy to collect the treatment each day until he is stable, and also that an ‘authority’ to prescribe the medication will be required.

You provide information about the daily dispensing requirements with buprenorphine–naloxone, including that they would probably only be temporary and eventually he would be able to collect the medication weekly or even monthly. In addition, you discuss that as the buprenorphine component of buprenorphine–naloxone is also an opioid medication, there are certain restrictions to its prescribing in NSW and there needs to be only one nominated prescriber. You mention that naloxone is included to prevent injecting drug use. You complete the necessary paperwork and arrange a dedicated pharmacy for him to attend, with treatment to commence the following Monday. You advise him to not take ibuprofen plus codeine from Sunday evening.

You also suggest to Richard that he see a psychologist for help with his anxiety and offer him a Mental Health Treatment Plan.

The outcome

You assess Richard at 10 a.m. on Monday morning. He states that he last took ibuprofen plus codeine at 9.30 p.m. the previous evening. As buprenorphine–naloxone can itself precipitate opioid withdrawal, you need to ensure that Richard is experiencing some withdrawal symptoms before giving him the first dose. He has mild restlessness and myalgia with some nasal stuffiness and slight anxiety — all common symptoms of withdrawal. You assess him with the Clinical Opiate Withdrawal Scale (COWS), on which he scores four out of a possible 48, indicating he is not experiencing significant withdrawal symptoms. You therefore suggest he return for review later in the day.

On review at 2 p.m., Richard is flushed and sweating and complains of feeling agitated and significant diarrhoea. His score on the COWS is now 10, indicating mild withdrawal. You start him on buprenorphine–naloxone 4 mg/1 mg with the option of another 4 mg/1 mg dose later in the day. You inform him that he can increase his dose of buprenorphine by 4 mg each day if he requests it, and organise a review for two days later. You call the pharmacy at 6.30 p.m. and are told he received another 4 mg/1 mg dose later in the afternoon, so used a total of 8 mg buprenorphine on the first day.

On review two days later, Richard reports he has received 16 mg buprenorphine that day and feels fine. He has no withdrawal symptoms and says that, despite an uneasy sleep on the first night of taking buprenorphine–naloxone, he slept well the second night. He is surprised there is no euphoric feeling but is happy not to be experiencing any withdrawal symptoms. You and he agree that he stays on buprenorphine–naloxone 16 mg/4 mg and attends for review the following week.

After taking buprenorphine–naloxone for one month, Richard feels well and happy. He finds he is more energetic and motivated at work and has a much more stable mood as he is not experiencing withdrawal or spending excessive amounts of time attempting to acquire codeine. You discuss with him a plan to slowly decrease his buprenorphine–naloxone dose (by 2 mg every few weeks).

As he now picks up his buprenorphine–naloxone monthly (allowable in NSW, but varies between states and territories), Richard does not feel he needs to decrease the dose rapidly. After 12 months he is taking 4 mg buprenorphine each day. Despite being referred to a psychologist early in treatment, he did not attend. However, after 12 months of buprenorphine–naloxone therapy he decides to pursue psychological therapy to help with his anxiety. He is aware that he can reduce the buprenorphine–naloxone further if he wants, and continues to see you every three months for a prescription. MT

COMPETING INTERESTS: None.