Treatment of patients with opioid dependence

NICHOLAS LINTZERIS BMedSci, MB BS, PhD, FAChAM

The prevalence of opioid dependence is growing in Australia with the increased use of pharmaceutical opioids. A number of effective interventions exist for patients with opioid dependence, including withdrawal services, opioid substitution treatment and psychosocial interventions, supported by self-help groups and harm-reduction services.

Opioid dependence is a chronic relapsing condition that affects approximately 1% of the Australian adult population. It is characterised by regular opioid use, tolerance, impaired control over use, persistent use despite related harms, a characteristic withdrawal syndrome and relapse on attempts at stopping or reducing opioid use. Opioid dependence has historically been linked to illicit heroin use. However, over the past 15 years in Australia there has been a marked increase in the use of pharmaceutical opioids, both prescribed and over the counter, usually in the context of chronic pain. This has been associated with an increase in the numbers of individuals who develop opioid dependence and require management of that dependence in addition to any concomitant medical conditions (e.g. chronic pain or depression).

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Associate Professor Lintzeris is the Director of Drug and Alcohol Services, South East Sydney Local Health District, and Clinical Associate Professor in the Discipline of Addiction Medicine at the University of Sydney, Sydney, NSW.

Opioid dependence is associated with a range of biological, psychological and social harms to the individual and wider community. There is a range of effective treatment interventions for opioid dependence, including opioid substitution treatment (OST; with methadone or buprenorphine–naloxone), management of opioid withdrawal (detoxification), psychosocial interventions (counselling or residential rehabilitation) and antagonist medication (naltrexone). Recent national clinical guidelines on medication-assisted treatment of opioid dependence are available from the National Drug Strategy (www.nationaldrugstrategy.gov.au).[1] Local regulations vary, and guidance can be obtained from state and territory health departments. Some practice points regarding management of patients with opioid dependence are summarised in Box 1.

Long-term opioid use: dependence and addiction

Tolerance and opioid withdrawal

The body adapts to regular and prolonged opioid use (neuro-adaptation), characterised by tolerance (diminished effects with repeated use, requiring increased doses to achieve the same effects) and withdrawal. Opioid withdrawal is a specific syndrome following the cessation or reduction in heavy and prolonged opioid use. It is characterised by a range of signs and symptoms that include generalised aches and pains, arthralgia, cravings, low mood, irritability, agitation, poor sleep, abdominal cramps, nausea, vomiting, diarrhoea, sweating, runny eyes and nose, dilated pupils and increased sensitivity to pain stimuli. The onset and duration of withdrawal symptoms depends on the duration of action of the opioid used (see below).

Addiction versus dependence

The diagnosis of dependence in patients using prescribed medications can be complex. Many pain specialists do not consider

tolerance and withdrawal to be features of 'addiction' to prescribed opioids but rather normal physiological responses to long-term opioid use. For patients to qualify for a diagnosis of 'addiction' to prescribed opioids, they must have other psychosocial features of dependence. These include, most notably, impaired control over opioid use, cravings, continued use despite harms and failed attempts to reduce or cease opioid use. It is estimated that approximately 10% of Australian patients with chronic nonmalignant pain treated long term with opioids meet the criteria for dependence.[2]

Natural history of opioid dependence, morbidity and mortality

Long-term studies of opioid-dependent individuals indicate opioid dependence to be a chronic relapsing condition. Estimates suggest a 2 to 5% annual remission rate (i.e. 2 to 5% will stop using opioids in any one year).

In general, opioids are relatively safe drugs that have been used in many cultures for centuries and are widely prescribed by doctors today. Nevertheless, individuals may experience a range of harms arising from their opioid use. These are:

- physical (e.g. overdose and opioid side effects, including constipation, sedation, sleep and endocrine disorders and hyperalgesia)
- psychological (e.g. depression, anxiety, cognitive impairment and suicide)
- social (e.g. financial problems, impaired relationships or legal problems and stigma).

The harms vary according to type and route of opioid use, frequency of use and related behaviours.

The estimated mortality rate (from all causes) for untreated heroin users is around 1 to 2% per annum – approximately 10 to 15 times higher than mortality among age- and sex-matched control subjects in the community. The main causes of death in this population are overdose and/or suicide (in approximately one-third of cases), trauma (in approximately one-third) and infectious diseases (e.g. hepatitis C-related liver disease, HIV infection and endocarditis). Much of the overdose-related mortality associated with dependence on opioids is linked to use of other sedative drugs (e.g. benzodiazepines, antidepressants) and drugs that contribute to hepatic toxicity (e.g. alcohol). Effective treatment (e.g. OST) is associated with a three to fivefold reduction in mortality.

Management of opioid dependence

Goals of treatment and treatment planning

Although many patients, their families and the broader community have the goal of sustained abstinence after a short treatment episode (e.g. a one-week withdrawal intervention), the chronic nature of opioid dependence suggests that effective treatment usually requires longer-term treatment, extended over months or years. More realistic and immediate goals for most people entering treatment include a reduction in high-risk patterns of drug use (e.g. polydrug use, injecting drug use), reductions in opioid use and improvements in health and psychosocial functioning. Patients with concomitant chronic pain and opioid dependence need treatment plans that address both conditions.

Opioid dependence is often associated with other harmful patterns of substance use (e.g. alcohol, tobacco, benzodiazepines, cannabis) and a range of medical, psychiatric and social problems. These also need to be addressed in any comprehensive treatment approach. Treatment planning should involve the patient and reflect their circumstances and case complexity, and also often involves co-ordination across multiple health and welfare providers.

Informed consent is important in the management of opioid dependence. Patients should understand the implications of different treatment options, including potential risks and benefits, side effects and financial and other commitments. Written information and opportunities to ask questions or consider alternatives should be provided. Cognition, literacy, language and cultural factors should be considered.

1. PRACTICE POINTS

- Opioid dependence, a chronic condition characterised by impaired control over the use of opioids and related harms, is no longer the domain of heroin users but increasingly affects patients using pharmaceutical opioid analgesics.
- Patients with opioid dependence often have a range of medical and social comorbidities that need to be addressed, usually by a range of primary care and specialist services.
- There are effective treatment interventions available for opioid dependence, including detoxification, psychosocial interventions and opioid substitution treatment (OST) with methadone or buprenorphine–naloxone.
- OST treatment is safe and effective for patients with concomitant chronic pain and dependence on opioid analgesics.

Assessment

A comprehensive assessment should be conducted, sometimes completed over several appointments depending on the health care setting and circumstances. Clinicians should initially aim to identify the patient's patterns of substance use and key medical, psychiatric and social complications, and to examine patient treatment goals and preferences. Referral or consultation with a specialist is recommended for patients with complex presentations. Key aspects of the clinical assessment of patients with possible opioid dependence are shown in Box 2.

Overview of treatment interventions

A range of service providers can be involved in delivering treatment services for opioid dependence, including primary care services

2. ASSESSMENT OF PATIENTS WITH POSSIBLE OPIOID DEPENDENCE

Presenting complaint
- Reason for presentation (this affects immediate treatment goals)
- Assessment of chronic pain (this is crucial in those using opioid analgesics)

History of substance use and previous drug and alcohol treatment
- Opioid use: quantity, frequency and route of use, duration of this episode
- Features and severity of dependence: evidence of tolerance, withdrawal, age at first use and first regular use, periods of abstinence, ability to control use, drug-related harms
- Use of other drugs (alcohol, benzodiazepines, cannabis, psychostimulants, tobacco) and other substance-use disorders
- Previous attempts at treatment: what has 'worked' and 'not worked' before

Medical and psychiatric history
- Particular attention to unstable or active conditions that may complicate or require treatment (chronic pain, hepatic and mood disorders are common)
- Risk behaviours, including risk of harm to self or others, polydrug intoxication, history of overdoses, injecting practices

Social circumstances
- Home environment, social supports, employment, financial and legal issues, child protection or domestic violence concerns, barriers to change
- Motivations and goals for treatment (an understanding of the reasons for seeking treatment and patient goals and expectations is essential to selecting the appropriate treatment)

Examination
- Vital signs (blood pressure, pulse, respiratory rate)
- Evidence of intoxication or withdrawal from opioids or other drugs
- Evidence of drug use and related complications (e.g. injection sites, hepatic disease, infections)
- Mental state and cognitive assessment

Investigations
- Urine drug screens (these can confirm or clarify recent substance use)
- Viral serology (HIV, hepatitis B and C) for patients with a history of injecting drug use
- Monitoring of hepatic function in patients with liver disease

(general practice, allied health, community pharmacy), specialist drug and alcohol services (government and nongovernment organisations) and hospital and other specialist providers (e.g. mental health and pain services).

Evidence-based interventions for opioid dependence are summarised in the flowchart. They include:[1]
- withdrawal (detoxification) services – short-term interventions (usually five to 14 days) that aim to interrupt a pattern of heavy use, ameliorate the discomfort of withdrawal symptoms and link patients with ongoing services; these interventions may be delivered in outpatient, residential or hospital settings and usually achieve only short-term benefits
- OST – a longer-term approach (months or years) that involves the use of methadone or buprenorphine–naloxone, regular clinical reviews and monitoring, and psychosocial interventions
- psychosocial interventions – including counselling, case management and residential rehabilitation
- antagonist-assisted treatment – involving the use of oral naltrexone and potentially useful for highly motivated patients with good social supports.

Other important approaches include:
- self-help groups, which provide structure and support networks for patients (e.g. Narcotics Anonymous, SMART Recovery)
- harm reduction services, which may be relevant for some individuals who continue to use opioids; they include access to a needle and syringe program, peer support and overdose prevention services, including prescription of take-home naloxone.

Interventions for opioid withdrawal

Withdrawal from short-acting opioids (e.g. heroin, oxycodone and codeine) generally starts within eight to 24 hours of last use and peaks at 48 to 96 hours. Most physical symptoms subside within five to 10 days, although some symptoms (e.g. disturbed sleep and mood, and cravings) often persist for weeks. Withdrawal from long-acting opioids (e.g. methadone and buprenorphine) has a more protracted course.

Setting

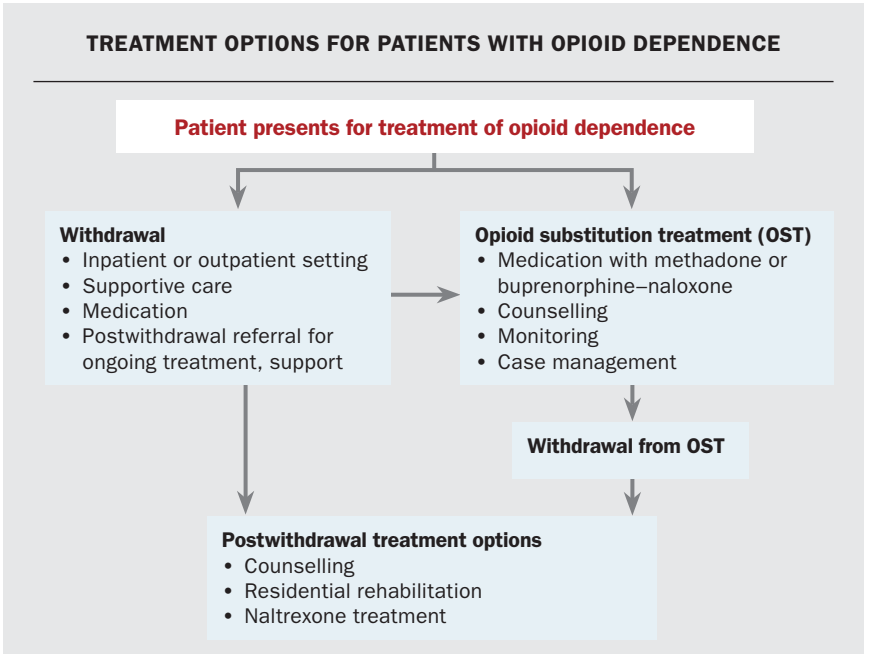
Patients can usually safely complete opioid withdrawal as outpatients. Those with severe or unstable medical or psychiatric conditions may require hospitalisation. Residential services may be warranted for patients with unsupportive home environments (e.g. living alone or with other drug users) or following failed outpatient attempts. Many patients undergo opioid withdrawal during hospital admissions for other conditions, and hospital drug and alcohol consultation liaison services should be consulted.

Supportive care

Supportive care includes daily review with a health worker (e.g. doctor, nurse or drug and alcohol worker, face to face or by telephone). Counselling during withdrawal focuses on coping with cravings, symptoms and maintaining motivation. Advice to patients includes avoiding dehydration (ensure fluid intake) or excessive caffeine, alcohol or other drug use. Social supports should be identified and plans developed for dealing with potential complications. Patients should also be warned about the risk of overdose if they resume opioid use after even a short period of abstinence.

Medication

Buprenorphine–naloxone is the preferred medication for managing opiate withdrawal, administered as a sublingual film. Evidence supports its use over symptomatic medications, and it is easier to use and to cease than methadone. Buprenorphine is a partial opioid agonist; naloxone is included to deter misuse by injection, as it is not absorbed after sublingual administration but may cause opioid withdrawal when injected. A short-term regimen of buprenorphine–naloxone should be



attempted (five to 14 days, depending on factors such as duration of inpatient admission), with progress reviewed within a few days. If buprenorphine is unavailable or contraindicated then methadone or medications to relieve symptoms may be used. Medication options for withdrawal are outlined in Box 3.[3]

Links to ongoing treatment and support

Withdrawal treatment can be life saving for some patients but on its own rarely results in long-term abstinence. Ongoing participation in treatment such as counselling, OST or residential rehabilitation is usually required to achieve long-term changes. Longer-term OST with buprenorphine or methadone is recommended for patients who:

- cannot stop or markedly reduce their opioid use during the withdrawal episode
- relapse into regular opioid use as the dose of buprenorphine is reduced or ceased, and/or
- do not feel confident about maintaining abstinence and want to avoid opioid relapse.

Patients should also be linked to services addressing broader health and welfare needs.

Opioid substitution treatment

OST is a long-term treatment approach (usually months or years) that involves daily dosing with a long-acting opioid medication such as methadone or buprenorphine (usually as buprenorphine–naloxone) to:

- prevent withdrawal
- reduce cravings
- reduce the reinforcing effects of any additional unsanctioned opioid use.

Although OST is still controversial in some quarters – being considered by some as 'replacing one drug with another' – extensive evaluation demonstrates it to be a safe and cost-effective treatment approach for most patients. OST reduces substance use, transmission of bloodborne viruses, mortality and crime, and improves general health, psychosocial function, community reintegration and quality of life.[1,4]

Methadone or buprenorphine–naloxone is usually administered as daily doses under supervision at a clinic or community pharmacy. However, as patients reduce their substance use and risk behaviours, medication can be dispensed in advance (take-away doses), enabling greater reintegration into activities such as work, study, parenting and social activities. Patients are reviewed regularly by a medical practitioner, nurse or drug and alcohol worker, and usually undergo regular urine drug testing to monitor their use of opioids and other drugs. The long-term nature of treatment provides opportunities to address related health and social problems, and engage with psychosocial interventions such as counselling.

The key elements of safe and effective OST include:

- establishing a safe and effective dosing regimen, including appropriate dosing conditions (pharmacy, clinic or take-away)
- undertaking regular clinical reviews and monitoring
- ensuring the patient participates in psychosocial interventions

3. OVERVIEW OF MEDICATION REGIMENS FOR OPIOID WITHDRAWAL

Buprenorphine–naloxone sublingual film

- Initiate 4 to 8 mg buprenorphine–naloxone at onset of opiate withdrawal (use a clinical scale such as the Clinical Opiate Withdrawal Scale)[3]
- On days 2 to 4, titrate dose to achieve cessation of other opioid use and comfortable withdrawal symptoms (usually 8 to 16 mg per day)
- Taper dose over next two to seven days

Methadone oral liquid

- Use reducing doses over 10 to 20 days, commencing at 20 to 30 mg and reducing by 2.5 mg every one to two days

Symptomatic medications

- Antiemetic (e.g. metoclopramide 10 mg four times daily for up to three to four days)
- Antidiarrhoeal (e.g. atropine–diphenoxylate, one to two tablets three times daily for up to three to four days)
- Antispasmodic (e.g. hyoscine butylbromide 10 to 20 mg four times daily for up to three to four days)
- Anti-inflammatory (e.g. ibuprofen 400 mg four times daily for up to a week)
- Low dose benzodiazepines – can be useful but are not recommended beyond three to five days (e.g. diazepam 5 mg twice daily for two days, then 5 mg at night for two days)

4. METHADONE USE IN MANAGING OPIOID DEPENDENCE

Clinical pharmacology
- Methadone is a potent synthetic opioid agonist, well absorbed orally, with effects that are qualitatively similar to those of morphine and other opioids
- It has an onset of effects in 30 to 60 minutes, peak effects 2 to 4 hours after oral dosing, and a half-life of 15 to 30 hours
- Steady-state equilibrium is achieved three to seven days after daily dosing, with cumulative effects over this time
- It is metabolised by the hepatic cytochrome (CYP450) enzyme system to inactive metabolites, with important clinical implications for drug–drug interactions and particular disease states (e.g. liver failure)
- Methadone can also prolong QTc intervals, and electrocardiography monitoring may be required

Side effects and safety issues
- Side effects are similar to those of other opioids, most commonly constipation, sedation, sweating, nausea and reduced libido. These usually occur when starting treatment and often subside with time
- Methadone toxicity (severe sedation, respiratory depression, death) early in treatment is related to the use of other sedatives, inadequate assessment of tolerance, inadequate supervision of methadone dosing, starting on doses that are too high and/or too rapid dose escalation

Dosing
- Dosing usually commences at low doses (20 to 30 mg daily) and gradually increases by 5 mg every three to five days to achieve treatment objectives: reduction in withdrawal, cravings and cessation of additional opioid use. This is usually achieved for most patients with 'maintenance' doses of 60 to 100 mg daily

Issues in pain management
- Methadone oral tablets may be used for pain management only in nondependent patients; their use for pain management in drug-dependent patients requires specific local health department approval
- Effective pain management often requires lower methadone doses (e.g. 20 to 50 mg in two to three divided doses)

- addressing medical, psychiatric and social comorbidities
- attending to necessary regulatory issues in prescribing OST.

Practical aspects of the use of methadone and buprenorphine–naloxone in the management of opioid dependence are summarised in Boxes 4 and 5, respectively. The choice of methadone or buprenorphine–naloxone is generally driven by informed patient preference.

Eventually, most patients seek to exit OST after a period of reduced drug use and psychosocial stability. Optimal treatment outcomes are achieved in those who have remained in treatment for at least one to two years.[4] Medication cessation usually involves a gradual dose reduction over weeks to months. Most patients experience a mild but prolonged opiate withdrawal syndrome on stopping methadone or buprenorphine–naloxone treatment. Without careful planning, this can serve as a trigger for relapse to unsanctioned opioid use.

Psychosocial interventions

Counselling can be delivered in individual or group settings, targeting the patient's substance use and related comorbidities, such as anxiety, depression, trauma or sleep problems. A range of counselling approaches can be effective. Motivational enhancement approaches can be used to encourage ambivalent patients to engage in treatment. Relapse prevention approaches aim to help patients identify and deal with situations or emotions that are associated with relapse to substance use. Cognitive behavioural therapy (CBT), mindfulness and narrative therapies are also supported by evidence.

Counselling approaches on their own have limited long-term benefit in treating heroin-dependent patients, and combining them with medication (e.g. OST or the opioid antagonist naltrexone) is often recommended, as is common for patients with chronic biopsychosocial conditions such as depression and chronic pain disorders. Social, financial and occupational services are also important as many individuals have disrupted education and occupational backgrounds.

Residential rehabilitation programs have historically been medium- to long-term interventions (weeks to months) that involve treating patients in structured residential settings, using a variety of counselling and self-help or peer-led interventions. Residential rehabilitation programs generally target individuals with severe social problems who need an extended period of stability in a structured environment. Most programs also have community reintegration components to address the high rates of relapse on re-entry into the community.

Peer support approaches can be useful for some patients, particularly in providing social networks and structured activities removed from substance use. Notable examples include Narcotics Anonymous (a 12-step peer support approach similar to Alcoholics Anonymous) and SMART Recovery (a CBT-based peer support approach).

Antagonist-assisted treatment

Antagonist-assisted treatment involves the use of oral naltrexone to discourage the use of additional opioids. This long-acting opioid antagonist blocks the effects of opioid use for 24 to 48 hours, thereby reducing its reinforcing effects. Naltrexone treatment is usually integrated with psychosocial interventions (counselling) and regular clinical reviews with a medical practitioner. Oral naltrexone is usually taken once a day, although it should be administered only after completion of opiate withdrawal, and usually in consultation with a specialist. There is an increased risk of overdose with resumption of opioid use after ceasing naltrexone. Naltrexone is not subsidised by the PBS for opioid dependence, and its cost to consumers is a barrier to its use in Australia.

Because of the low rates of medication adherence with oral naltrexone by opioid users (estimated at less than 10% at

six months), it is usually reserved for individuals with exceptionally high levels of motivation and strong social supports. Furthermore, the role of naltrexone in individuals with concomitant pain conditions is unclear, and it may be contraindicated if continued or episodic opioid analgesia is required. Long-acting naltrexone depot injections (with one-month action) are licensed in some countries but not currently available in Australia. Naltrexone implants are not licensed in Australia.

Conclusion

Although historically most opioid-dependent users in Australia have used illicit opioids such as heroin as their primary drug, increasingly we are encountering patients who either misuse pharmaceutical opioid medications not prescribed for them or, alternatively, develop dependence on opioid medications used in the treatment of chronic pain. This last category is particularly important for all GPs and pain specialists, given the high prevalence of chronic pain in Australia. It is estimated that approximately 10% of patients with chronic non-malignant pain using opioids long term will become opioid dependent.

Importantly, there are safe and effective treatment approaches for opioid dependence, irrespective of the source of the opioids (illicit, over the counter or prescribed). A trial of withdrawal is often warranted, but the long-term nature of opioid dependence generally requires long-term treatment approaches such as OST with buprenorphine–naloxone or methadone and psychosocial interventions.

Opioid dependence is often associated with a range of comorbidities, including pain, mental health problems, hepatic disease, cognitive impairment and impaired social relationships. It is crucial that these comorbidities are addressed, usually through networks of multidisciplinary treatment providers. Primary care practitioners working with patients with complex presentations should consult with addiction medicine and other specialists in developing and implementing effective treatment plans. MT

5. BUPRENORPHINE USE IN MANAGING OPIOID DEPENDENCE

Available formulations

- Buprenorphine is used as a sublingual formulation in treating opioid dependence
- Buprenorphine–naloxone combination sublingual film is the more commonly used formulation, containing dosages of 2/0.5 mg or 8/2 mg buprenorphine/naloxone
- Naloxone is included in the film to deter misuse and administration by injection; it is not absorbed after sublingual administration but may cause opioid withdrawal when injected

Clinical pharmacology

- Buprenorphine is a semisynthetic partial opioid agonist with high affinity for opioid receptors
- Peak clinical effects are achieved 1 to 4 hours after sublingual dosing
- Buprenorphine is metabolised principally in the liver to inactive metabolites, with an elimination half-life of 24 to 37 hours. CYP drug–drug interactions are usually not clinically significant

Side effects and safety issues

- Side effects are similar to those of other opioids, most commonly constipation, sedation, sweating, headaches, disturbed sleep and nausea. These usually occur when starting treatment and often subside with time
- Buprenorphine is less likely to cause respiratory depression and overdose than full agonists (e.g. methadone, oxycodone, heroin). Caution is still required in patients using sedatives (e.g. alcohol, benzodiazepines) and those with low or uncertain opioid tolerance
- The initial dose of buprenorphine can precipitate opioid withdrawal in patients who have recently used a full agonist (buprenorphine has higher receptor affinity but is a partial agonist). This is avoided by delaying the first buprenorphine dose until the patient is experiencing mild to moderate opioid withdrawal. Transfer from methadone to buprenorphine can be complicated, and specialist consultation is recommended

Dosing

- Doses of 4 to 8 mg are initiated when the patient is experiencing early to mild features of opiate withdrawal (e.g. 8 to 24 hours after last heroin use)
- Doses can be increased daily by 2, 4 or 8 mg per day until treatment goals are achieved: reduction in withdrawal and cravings, and cessation of additional opioid use. This is usually achieved for most patients with doses of 8 to 24 mg per day

Issues in pain management

- Buprenorphine transdermal patches or low dose (0.4 mg) sublingual tablets may be used for pain management only in nondependent patients; their use for pain management in drug-dependent patients requires specific local health department approval
- Buprenorphine has analgesic properties and there is emerging evidence that high doses can be effective in treating patients with both chronic pain and dependence[5]

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COMPETING INTERESTS: Associate 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), the manufacturer of Suboxone.