Misappropriation of the 1986 WHO analgesic ladder: he pitfalls of labelling opioids as weak or strong

Jos Crush[1], Nicholas Levy[1], Roger D Knaggs[2,3], Dileep N Lobo[4,5]

1. Department of Anaesthesia and Perioperative Medicine, West Suffolk Hospital NHS Foundation Trust, Bury St. Edmunds, UK
2. Division of Pharmacy Practice and Policy, School of Pharmacy, University of Nottingham, Nottingham, UK
3. Pain Centre Versus Arthritis, University of Nottingham, Nottingham, UK
4. Nottingham Digestive Diseases Centre, National Institute for Health Research, Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Queen's Medical Centre, Nottingham, UK
5. MRC Versus Arthritis Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, UK

Correspondence to:
Professor D. N. Lobo
Nottingham Digestive Diseases Centre
National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre
Nottingham University Hospitals NHS Trust and University of Nottingham
Queen's Medical Centre
Nottingham NG7 2UH, UK
Tel: +44-115-8231149
Fax: +44-115-8231160
Email: Dileep.Lobo@nottingham.ac.uk

Short title: Weak and strong opioids

Key words: analgesics; dependence; non-cancer pain; opioid use disorder; strong opioids; weak opioids; WHO analgesic ladder

Summary

Opioids have a vital role in alleviating pain from cancer and surgery. Despite good intentions, it is now recognised that the original World Health Organization Cancer Pain Relief guidance from 1986, in which opioids were classified as either weak or strong, has been both inadvertently and purposefully misused, thereby contributing to harm from opioid use and misuse. However, the recommendation in the 2018 update of the WHO analgesic ladder that a combination of a high potency opioid with simple analgesics is better than alternative analgesics for the maintenance of pain relief is also applicable to patients who require short term opioids. Furthermore, because potential harm through opioid use and misuse is intrinsic to all opioids, whether weak or strong, we argue that the arbitrary classification of opioids either as weak or strong should be discontinued as this description is not helpful to either prescribers or consumers.

In response to inadequate cancer pain relief globally, the World Health Organisation (WHO) published in 1986 its cancer pain relief guidelines to reduce the burden of unmanaged cancer pain especially in low- and middle-income countries.[1] The guidelines advocated the use of a three-step analgesic ladder, with the recommendation of escalation to the next step if the pain persisted or increased. The use of non-opioid agents alone or with adjuvants was recommended for Step 1, with addition of weak opioids to Step 1 being advocated for Step 2. Step 3 comprised the use of strong (instead of weak) opioids ± non-opioid agents with or without adjuvants.[1]

The recommended non-opioid analgesic was aspirin, with paracetamol as the alternative; the recommended weak opioid was codeine, with dextropropoxyphene as the alternative; and the recommended strong opioid was morphine, with methadone, pethidine, buprenorphine, standardised opium, hydromorphone and levorphanol as alternatives. Oral formulations of all drugs were advocated to allow the patient to be cared for at home.[1]

Despite citing evidence to support the use of strong opioids and non-opioid agents, the authors of the WHO report were unable to cite any literature demonstrating the clinical effectiveness of weak opioids.[1] Moreover, they acknowledged that opioid abuse was more common with weak opioids than strong ones. The original WHO cancer pain relief guidelines postulated that one of the main causes of inadequate cancer pain relief in low- and middle-income countries (LMICs) were the legal and other constraints that limited access to strong opioids.[1] Thus, it can be surmised that the value of weak opioids in the WHO analgesic ladder was to facilitate and legitimise the use of strong opioids in regions of the world where the use of opioids is illegal or objectionable.[2]

With the assimilation of new knowledge, new drugs, and the passage of time, the WHO published new guidance on the pharmacological and radiotherapeutic management of cancer pain in 2018.[3] Pertinently, since there is no pharmacological rationale for weak opioids in cancer pain, and because low doses of strong opioids generally provide quicker and better relief from pain than weak opioids, the new guidance specifically removed advocation for the explicit use of weak opioids within the three-step analgesic ladder.[3] Furthermore, it now states that the evidence suggests that a combination of a high-potency opioid with simple analgesics is better than alternative analgesics for maintenance of pain relief. Correspondingly, step 2 is now "opioid for mild to moderate pain with or without non-opioid agent, and with or without adjuvant."[3]

In recognition that cancer pain can sometimes be effectively addressed by anti-cancer treatment, and that there is a need to prevent opioid dependence and promote deprescribing of opioids in cancer survivors, the 2018 WHO cancer pain guidelines discuss the importance of tapering and deprescribing of opioids.[3] This addition further ensures that the WHO guidelines remain contemporary for the management of patients who suffer pain from cancer.

Misappropriation of the three-step analgesic ladder

In the 1980s, in addition to relief of cancer pain being poor, pain relief after surgery was also very poor. This led the Royal College of Surgeons of England and the then College of Anaesthetists to commission a report on the management of pain after surgery.[4] This report focussed on the introduction of acute pain services and the reliance on technology, including patient-controlled analgesia and epidural analgesia to manage postoperative pain.

Although the efficacy of non-steroidal anti-inflammatory drugs and multimodal analgesia for the management of postoperative pain was demonstrated in the 1990s, in the absence of specific guidance, the original WHO three-step ladder for cancer pain was surreptitiously adopted as a framework to manage postoperative pain.[5] With the benefit of hindsight, this can be perceived as illogical. Most importantly, the step-wise escalation is not appropriate in the management of postoperative pain. This is because postoperative pain is normally most intense in the first 24 hours after surgery, after which it typically diminishes with time. Thus, there is a need to manage the initial postoperative pain aggressively, and then taper and deprescribe analgesics as pain diminishes and function improves.[6] This is in contrast to cancer pain which, if untreated, generally increases with time due to local and metastatic spread, and thus lends itself to step-wise escalation. In addition, as for cancer pain, routine advocation of the use of weak opioids, rather than lower doses of strong opioids, within the second step is cause for concern for multiple reasons. These include lack of efficacy and genetic polymorphisms affectiong some weak opioids leading to variable response and unpredictable analgesic action.[7] Furthermore, it is now increasingly recognised that all prescribed opioids predispose to the risk of developing opioid use disorder; and that codeine, the archetypal weak opioid, may be more addictive than some strong opioids.[8] Thus, as in the management of cancer pain, the value of step 2, advocating the use of weak opioids, in the management of postoperative pain requires scrutiny and re-evaluation.

In the 1990s, there was also the recognition that chronic non-cancer pain needed to be managed more effectively. Purdue Pharma and its subsidiaries, including NAPP and Mundipharma, marketed modified-release oxycodone aggressively to manage chronic non-cancer pain.[9] In their US product information brochure from 2000, Purdue stated that OxyContin® "logically fits steps 2 and 3" of the analgesic ladder to treat moderate to severe

pain.[10] As a result of aggressive marketing, coupled with doctors being actively misled that addiction to prescribed opioids was rare, opioids and the WHO analgesic ladder inappropriately became accepted strategies for managing chronic non-cancer pain.[9, 11] It is now well recognised that the misappropriation of the WHO analgesic ladder is one of the main contributory factors to the prescribed opioid crisis.[9, 11] As there is increasing concern that opioids may only help a very small proportion of people with chronic non-cancer pain, the three-step analgesic escalation ladder can no longer be recommended for the management of chronic non-cancer pain.[11]

Opioid dependence

The causes of the global prescribed opioid crisis that started in North America are multifactorial.[12] Despite this, there remains controversy about defining prescribed opioid misuse and addiction. The Diagnostic and Statistical Manual of Mental Disorders defines opioid use disorder as a 'problematic pattern of opioid use leading to clinically significant impairment or distress'.[13]

The 11th edition of the International Classification of Diseases (ICD-11) defines opioid dependence as "a disorder of regulation of opioid use arising from repeated or continuous use of opioids. The characteristic feature of opioid dependence is a strong internal drive to use opioids, which is manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences…Physiological features of dependence may also be present, including tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in

use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms."[14]

Meanwhile, "addiction is characterised by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of significant problems with one's behaviours and interpersonal relationships, and a dysfunctional emotional response."[15]

Despite these inconsistencies in definitions, there is overwhelming evidence that while the perception that addiction to or dependence on weak opioids is rare,[16] dependence on weak opioids is actually common.[7, 8, 17, 18]

Weak opioids

The definition of whether an opioid is weak or strong more reflects its pharmacodynamic (i.e., efficacy and potency) rather than its pharmacokinetic properties. Weak opioids include partial agonists and mixed agonist-antagonists. As well as having a ceiling effect, and being less efficacious, there is evidence that weak opioids are potentially more addictive than strong opioids.[8, 17] **Table 1** summarises the properties of weak and strong opioids.

Codeine is the archetypal weak opioid and is the recommended opioid for step 2 of the original WHO analgesic ladder.[1] As a prodrug, genetic polymorphisms in cytochrome P450 2D6 (CYP2D6) can affect the rate of metabolism into morphine to an unknown dose of delivered analgesic.[7] This may result in either completely ineffective analgesia in people who are poor metabolisers, or extensive metabolism that can risk respiratory depression.[7] Thus, despite perceptions around that codeine is safe, codeine related deaths are increasingly recognised.

Tramadol is classified by the British National Formulary as a strong opioid,[19] but others including the WHO considers it to be a weak opioid,[20] and as a result, it is commonly placed in step 2 of the WHO ladder.[5, 21] This conflict of opinion may be due to it having a ceiling dose and low opioid potency. Furthermore, it was initially not regulated under the Misuse of Drugs Act, leading to popularity amongst prescribers for moderate pain.[21] Nevertheless, the discrepancy by various authorities in the labelling tramadol as either a weak or strong opioid, highlights the futility of this arbitrary classification.

Tramadol is a prodrug and is an atypical analgesic with dual opioid and serotonin/norepinephrine reuptake inhibitor (SNRI) effect, and variable CYP2D6 metabolism, which means there is individual variation in its analgesic and side effect profile.[22] This includes ineffective analgesia for poor metabolisers and increased nausea and respiratory depression in ultra-rapid metabolisers. The distribution of genetic variants explains a geographic predisposition to tramadol-related tolerance, prescribing and addiction.[22] The SNRI mechanism and the risk of serotonin syndrome leads to significant drug-drug and drug-disease interactions which all complicates its use.

Tramadol is subject to further complexity from drug-drug interactions caused by drugs that either induce or inhibit CYP2D6. Drugs that inhibit CYP2D6, including fluoxetine, paroxetine, monoamine oxidase inhibitors and metoclopramide have the net effect of reducing the clinical efficacy of tramadol, whilst increasing the risk of tramadol induced serotonin syndrome.[22]

Thus, tramadol has several significant drug-drug and drug-disease interactions that complicate its clinical role. The drug-drug interactions involve antidepressants, antimigraine drugs, antiarrhythmics, antipsychotics, anticonvulsants, antiparkinsonian agents and

ondansetron. Its most important drug-disease interaction is epilepsy as it can precipitate seizures. These drug interactions may also contribute to tramadol-related deaths, which have increased dramatically.[21]

Although initially thought to have a low addiction rate, tramadol is now recognised as a drug that can promote high levels of dependence and addiction particularly in African and Middle Eastern countries where ultra-rapid metabolisers are more prevalent.[22] With the increasing concerns of death, abuse and diversion associated with tramadol use, a more restrictive scheduling has been adopted in many countries including the UK and the US.[21]

Dextropropxyphene is a weak opioid which is less commonly used. It was discontinued as a licensed medicine in the UK and many other countries due to cardiac toxicity concerns and relatively weak analgesic properties.[19] Meptazinol is a weak opioid commonly used in the elderly due to reduced likelihood of respiratory depression. However, it's use is associated with diarrhoea and gastrointestinal discomfort.[19]

Dihydrocodeine is another weak opioid. It is not a prodrug and, therefore, is not subject to variability in efficacy caused by genetic polymorphism. This does make it a more reliable alternative to codeine and tramadol. However, there is increasing concern that dihydrocodeine is particularly toxic in overdose, and subsequently there is a call for it to be prescribed with caution, particularly to individuals at risk of self-harm.[23]

Concerns associated with use of weak opioids

Weak opioids have several problematic characteristics that can be overlooked due to their lower potency and perceived safety. However, data from the Office for National Statistics for deaths related to drug poisoning demonstrate that deaths from tramadol, codeine and

dihydrocodeine account for approximately a quarter of all opioid related deaths in England and Wales.[24]

Recent modelling data suggest that codeine and oxycodone are the two opioids most likely to cause addiction,[8] perhaps due to 'likeability' (**Table 2**). Further, evidence is emerging that regular users of weak opioids commonly convert to strong opioids, conferring a gateway effect.[25] Qualitative studies have identified poor opioid stewardship as a contributor to the development of addiction,[26] which can arise from initial appropriate prescribing.[16] Codeine-related deaths for non-compound preparations have increased by more than 8-fold over the last 30 years in England and Wales.[24]

Compound analgesic preparations contain a simple analgesic with a weak opioid and reduce the scope for effective titration of the individual components in the management of pain of varying intensity,[6, 19] and reduce the ease of opioid deprescribing.[6, 19] The opioid component cause opioid-related side-effects, in particular the risk of dependence, and yet may not provide significant additional relief of pain.[19] Together this makes compound analgesic preparations particularly inappropriate for postoperative prescribing.[6, 12] Deaths related to compound preparations containing codeine have also increased by more than 6-fold over the last three decades in England and Wales.[24]

The over-the-counter availability of some compound analgesics provides a less monitored route of access to these medicines. Addiction may start by patients using the drug first as an over-the-counter agent, or by continued administration following a prescription.[16, 26] Codeine "shopping", the phenomenon in which people go to multiple pharmacies or online pharmacies to obtain the drug to fuel their opioid dependence, is increasingly recognised.[26] With increased concerns about codeine-related deaths and codeine dependency, stricter

restrictions on codeine are being introduced globally, with Australia being the latest country to remove codeine as an over-the-counter medication.[18]

Opioid stewardship

Categorisation of opioids based on potency or efficacy is of limited functional use, but worse, may actually promote harm, as weak opioids may be more likely to promote opioid dependence.[17] To prevent harm, a more generalised and patient-centred approach to opioid prescribing should be advocated, namely, opioid stewardship. Opioid stewardship has been defined as "coordinated interventions designed to improve, monitor, and evaluate the use of opioids to support and protect human health".[27] As part of opioid stewardship, prescribers must take responsibility for prescribing the appropriate opioid for an appropriate duration, and simultaneously institute a deprescribing plan.[28] Patients should be educated about the implications of driving whilst prescribed opioids and avoiding drug driving, as well as safe storage and disposal of opioids to protect family and friends from the risks of opioid diversion and accidental overdose.[6, 19]

Conclusion

Opioids have a vital role in alleviating pain from cancer and surgery, and despite the risks of opioid use disorder, their use must be allowed to continue. However, despite good intentions, it is now recognised that the original WHO guidance from 1986[1] has been both inadvertently and purposefully misused, thereby contributing to opioid misuse. Opioids have no place in the first line management of chronic non-cancer pain. However, the recommendation in the 2018 edition of the WHO ladder[3] that a combination of a high

potency opioid with simple analgesics is better than alternative analgesics for the maintenance of pain relief is also applicable to patients who require short-term opioids. In terms of guidance for the management of postoperative pain, rather than reliance on the WHO cancer pain guidelines, it is increasingly recognised that procedure-specific as well as an individualised approach is required. In line with guidance from the Medicines and Healthcare products Regulatory Agency, patients prescribed opioids for non-cancer pain should receive guidance on deprescribing on commencement of the opioid course.[27, 28] Finally, due to the fact that harm through opioid use and misuse is intrinsic to all opioids, the arbitrary classification of opioids either as weak or strong should be discontinued as this description is not helpful to either prescribers or the consumers.

References

1 World Health Organization. *Cancer Pain Relief*. Geneva: World Health Organization, 1986. Available from https://apps.who.int/iris/handle/10665/43944 (Accessed 22 February 2022)

2 Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res* 2016; **9**: 515-34

3 World Health Organization. *WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents*. Geneva: World Health Organization, 2018. Available from https://www.who.int/publications/i/item/9789241550390 (Accessed 22 February 2022)

4 Royal College of Surgeons of England. Commission on the Provision of Surgical Services. Working Party on Pain After Surgery, College of Anaesthetists. *Report of the Working Party on Pain After Surgery*. London: Royal College of Surgeons of England, 1990

5 Koneti KK, Jones M. Management of acute pain. *Surgery (Oxford)* 2016; **34**: 84-90

6 Levy N, Quinlan J, El-Boghdadly K, et al. An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients. *Anaesthesia* 2021; **76**: 520-36

7 Roxburgh A, Hall WD, Burns L, et al. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *Med J Aust* 2015; **203**: 299

8 Rivas SR, Tessner AC, Goldwyn EE. Calculating prescription rates and addiction probabilities for the four most commonly prescribed opioids and evaluating their impact on addiction using compartment modelling. *Math Med Biol* 2021; **38**: 202-17

9 Rummans TA, Burton MC, Dawson NL. How good intentions contributed to bad outcomes: the opioid crisis. *Mayo Clin Proc* 2018; **93**: 344-50

10 Purdue Pharma. D4900 Oxycontin® Product Data Brochure. 2000. Available from https://repository.library.brown.edu/studio/item/bdr:841739/ (Accessed 22 February 2022)

11 Yang J, Bauer BA, Wahner-Roedler DL, Chon TY, Xiao L. The modified WHO analgesic ladder: is it appropriate for chronic non-cancer pain? *J Pain Res* 2020; **13**: 411-7

12 Macintyre PE, Quinlan J, Levy N, Lobo DN. Current issues in the use of opioids for the management of postoperative pain: a review. *JAMA Surg* 2022; **157**: 158-66

13 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5)*. 5th Edn. Washington, D. C.: American Psychiatric Publishing, 2013

14 ICD-11 for Mortality and Morbidity Statistics (Version : 05/2021). 6C43.2 Opioid dependence. 2021. Available from https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1120716949 (Accessed 22 February 2022)

15 U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force report: updates, gaps, inconsistencies, and recommendations. 2019. Available from https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html (Accessed 22 February 2022)

16 Cooper RJ. 'I can't be an addict. I am.' Over-the-counter medicine abuse: a qualitative study. *BMJ Open* 2013; **3**: e002913

17 Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth* 2018; **120**: 1335-44

18 Richards GC, Aronson JK, MacKenna B, Goldacre B, Hobbs FDR, Heneghan C. Sales of over-the-counter products containing codeine in 31 countries, 2013-2019: a retrospective observational study. *Drug Saf* 2022 [Epub ahead of print] doi: 10.1007/s40264-021-01143-2

19 Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press, 2021. Available from https://about.medicinescomplete.com/#/browse/bnf (Accessed 22 February 2022)

20 WHO Expert Committee on Drug Dependence. Forty-first report. (WHO Technical Report Series, No. 1018). Geneva: World Health Organization, 2019. Available from https://www.who.int/publications/i/item/9789241210270 (Accessed 22 February 2022)

21 Gibbison B, Bailey CR, Klein AA. Tramadol - the Marmite(TM) drug. *Anaesthesia* 2015; **70**: 125-30

22 Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. *Anesth Analg* 2017; **124**: 44-51

23 Hawton K, Ferrey A, Casey D, et al. Relative toxicity of analgesics commonly used for intentional self-poisoning: A study of case fatality based on fatal and non-fatal overdoses. *J Affect Disord* 2019; **246**: 814-9

24 Office for National Statistics. Dataset: Deaths related to drug poisoning by selected substances. 2021. Available from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/death

s/datasets/deathsrelatedtodrugpoisoningbyselectedsubstances (Accessed 22 February 2022)

25 Lalic S, Gisev N, Bell JS, Ilomaki J. Transition to high-dose or strong opioids: a population-based study of people initiating opioids in Australia. *Addiction* 2020; **115**: 1088-97

26 Kinnaird E, Kimergard A, Jennings S, Drummond C, Deluca P. From pain treatment to opioid dependence: a qualitative study of the environmental influence on codeine use in UK adults. *BMJ Open* 2019; **9**: e025331

27 Levy N, Lord LJ, Lobo DN. UK recommendations on opioid stewardship. *BMJ* 2021; **372**: m4901

28 Medicines and Healthcare products Regulatory Agency. *Drug Safety Update* 2020; **14 (2)**: 1-14. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/920770/Sept-2020-DSU-PDF.pdf (Accessed 22 February 2022)

Funding: No external funding

Declaration of interests: None of the authors has a conflict of interest to declare.

Author contributions: All authors contributed equally to this article and have approved the final submission.

Table 1: Strong and weak opioids

	Strong Opioids	**Weak opioids**
Examples	Morphine, methadone, pethidine, buprenorphine, standardised opium, hydromorphone, tapentadol, tramadol* and levorphanol	Codeine, tramadol*, dextropropoxyphene, dihydrocodeine and meptazinol
Potency	Considered more potent (except for pethidine which has low potency)	Lower
Efficacy	Considered as full opioid agonists	Lower efficacy as either partial agonist or agonist-antagonist
Predisposition of opioid withdrawal symptoms	Cessation of any opioid after a course may predispose to withdrawal symptoms and necessitate either slow tapering or opioid agonist therapy	
Predisposition to dependency/opioid use disorder	All opioids predispose to dependency. Oxycodone, codeine, tramadol and hydrocodone cause addiction in decreasing order Weak opioids are associated with a higher incidence of opioid dependence and abuse than strong opioids	
Predisposition to death	Generally perceived to be higher	Perceived to be lower but in 2020 in England and Wales weak opioids caused 26% of all opioid related deaths Dihydrocodeine has a greater propensity for harm from intentional self-poisoning

* The British National Formulary designates tramadol as a strong opioid, but the WHO defines it as weak.

Table 2: Mechanisms of weak opioids acting as drivers of opioid use disorders

Driver Domain	Comment
"Likeability"	Whilst the pharmacodynamic properties make oxycodone the most "likeable" prescription opioid, increasing evidence suggests codeine is also "likeable". This enhances the risk of dependence
Opioid "personality"	The term "weak opioid" conjures up a psychological perspective of a safe opioid
Lack of deprescribing advice	There is a lack of patient education that opioids are to be used as a course, and have a definite end date. The UK Medicines and Health products Regulatory Agency has aimed to rectify this
Internet shopping	Internet purchasing of codeine has been demonstrated to be a source of opioids for people with opioid use disorder
Lack of safe storage	May predispose to opioid diversion amongst family and friends
Lack of disposal	May predispose to further use beyond the initial prescribed episode
Large pack size	May predispose to further use beyond the time of tissue healing
Repeat prescriptions	Repeat prescriptions are one of the most important causes of opioid use disorder
Withdrawal symptoms	In a similar way that cessation of prolonged use of strong opioids will cause signs and symptoms of opioid withdrawal, so will cessation of weak opioids
Myth that weak opioids are not addictive	To promote opioid sales, certain pharmaceutical companies created and perpetuated the myth that prescribed opioids were not addictive
Readily accessible over the counter preparations	Over the counter purchasing of codeine has been demonstrated to be a source of opioids for people with opioid use disorder
Compound opioid preparations	Weak opioids are often conjugated with simple analgesics, which hinders deprescribing and weaning
Opioids being used inappropriately to treat chronic non-cancer pain	Increasing evidence demonstrates that treatment of chronic non cancer pain with opioids results in minimal clinical benefit, and predisposes to opioid use disorder
Opioids being used inappropriately to treat minor self-limiting pain	Readily accessible over the counter opioid preparations predispose to opioid use disorder