Medicines Adverse Reactions Committee

Meeting date	2/12/2021	Agenda item	3.1.1
Title	**Dihydrocodeine benefit-risk review: referral to the Committee under section 36(2) of the Medicines Act 1981**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**TT50**	**Approval date**	**Sponsor**
Dihydrocodeine 60 mg	DHC Continus	4823	26/3/1992	Mundipharma NZ Ltd
	Dihydrocodeine Controlled Release Actavis (not available)	9106	2/7/2015	Teva Pharma (NZ) Ltd

PHARMAC funding	Yes. DHC Continus is funded in the community and in hospitals.
Previous MARC meetings	186th meeting – held 10 June 2021: Options for minimising opioid abuse, misuse and dependence 184th meeting – held 3 December 2020: Opioids and abuse, misuse and dependence 169th meeting – held 9 March 2017: Concomitant use of opioids, benzodiazepines and other CNS depressants and the risk of serious side effects
International action	No recent action specifically relating to dihydrocodeine
Prescriber Update	No specific PU articles for dihydrocodeine. The following is a list of recent opioid-related articles: • The paradox of opioid-induced hyperalgesia (June 2021) • Spotlight on tramadol including updated advice for use in children June 2020 • Spotlight on Codeine June 2018
Classification	Prescription medicine and a Class C2 Controlled drug
Usage data	See section 4.1
Advice sought	**The Committee is asked to advise:** • Whether the benefit-risk balance is favourable for the use of dihydrocodeine for pain treatment. • If any regulatory action is required to improve the balance of benefits and risks.

TABLE OF CONTENTS

1 PURPOSE

This paper is a benefit-risk review of dihydrocodeine, with a referral of two dihydrocodeine products (DHC Continus and Dihydrocodeine Controlled Release Actavis) to the Medicines Adverse Reactions Committee (the Committee) under section 36(2) of the Medicines Act 1981.

In December 2020, Medsafe presented a paper to the Committee regarding opioid abuse, misuse and dependence. The Committee recommended that Medsafe to bring back an options paper concentrating on actions for weak opioids but also considering appropriate changes to data sheets, other regulatory options, education of prescribers and consumers and working with other agencies if appropriate.

In June 2021, Medsafe presented the options paper for minimising opioid abuse, misuse and dependence in New Zealand. At this meeting, the Committee queried the clinical benefits of dihydrocodeine in pain management. The Committee noted that while the prescribing of dihydrocodeine was low in New Zealand, the proportion of patients hospitalised from substance abuse and poisoning, associated with this medicine, was high. The Committee expressed that the literature showed safety concerns with dihydrocodeine use and the benefits in pain management were questionable. The Committee recommended Medsafe undertake a benefit-risk review of dihydrocodeine.

On 12 July 2021, Medsafe issued a section 36(1) of the Medicines Act 1981 (the Act) notice to the sponsors of dihydrocodeine products. Under this section of the Act, the Director-General of Health may request the sponsor to provide evidence that a product is safe and effective for the therapeutic purpose for which it is sold. If the sponsor is unable to satisfy the Director-General that the product is safe and effective for its therapeutic purpose, conditions on the use of the medicine may be imposed or the consent for distribution of the product may be revoked.

On 12 August 2021, Medsafe published a monitoring communication seeking feedback from consumers and healthcare professionals regarding the risks and benefits of dihydrocodeine.

Under section 36(2) of the Act, Medsafe is now referring the two approved dihydrocodeine products to the Committee. Section 36(2) of the Act provides:

36 Control of established medicines

(2) If the Director-General is not satisfied, by evidence supplied to him pursuant to a notice under subsection (1) or otherwise, of the safety and efficacy of a medicine to which that notice relates, he may at any time after the expiration of 60 days from the date of that notice refer a description of the medicine to the appropriate committee, and shall forthwith by notice in writing inform the importer or manufacturer that he has done so.

2 BACKGROUND

2.1 Pain

Acute (short term) pain is usually related to an obvious injury such as dental disease, fracture or operation [1]. Chronic pain (pain lasting longer than 3 months) sometimes begins with an acute injury, but the pain does not resolve as expected; often it is not clear how a chronic pain has started. Common types of chronic pain include low back pain, pain related to arthritis and neuropathic pain.

Both types of pain can range from mild or severe with the difference being the duration of symptoms [1]. Chronic pain is usually not a sign of on-going tissue damage but may relate to changes in the peripheral and central nervous system that occur over time so that the pain signalling becomes self-sustaining over a prolonged period.

Cancer pain is usually described separately and may be short or long lasting [1]. The pain can relate to the cancer itself or the cancer treatment. Additionally, patients with cancer may experience acute or chronic pain unrelated to their cancer.

2.2 Misuse, abuse and dependence

The reasons why people misuse medicines that are prescribed to them are multi-factorial and complex, including sociodemographic factors, pain and drug-related factors, genetics and environment, psychosocial and family history, alcohol and substance use disorders and challenging or traumatic life events [2, 3]. The risk of prescription drug misuse, abuse and dependence is greatest when risk factors in 3 categories, (ie, psychosocial factors, drug related factors, and genetic factors) occur in the same individual [3]. Prescribers can also significantly influence medicine misuse, in both positive and negative ways, eg, continuing a medicine without assessing its ongoing benefit [2].

In the USA, approximately 88% of people who reported misuse or abuse of prescription opioid pain relievers in the past year stated they obtained their most recently used drugs from their own prescriptions or from a friend or relative [4]. In addition, many people who begin with misuse of prescription opioids transition to illicit substances.

There are no universally accepted definitions and criteria for substance use disorder, meaning that rates of misuse, abuse, and iatrogenic addiction have historically been difficult to estimate in chronic pain treatment with opioid analgesics [3]. However, common definitions of relevant concepts for opioid misuse, abuse and dependence are shown in Table 1 below.

Table 1: Common definitions of relevant concepts for opioid misuse, abuse and dependence

Source: Kaye A, Jones M, Kaye A, et al. 2017. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: Part 1. *Pain Physician* 20(2S): S93-S109. URL: https://www.painphysicianjournal.com/current/pdf?article=NDIwMw%3D%3D&journal=103 (accessed 5 November 2020).

In studies in which opioid use disorder (OUD) has been carefully defined, rates of OUD among individuals who were prescribed opioids to help them manage their pain have averaged about 8 percent, and estimates of combined rates of misuse, OUD, and aberrant behaviours thought to be indicative of OUD among people taking opioids for pain have ranged from 15 to 26 percent [5]. Because of these risks, no widely accepted guideline for opioid prescribing recommends the use of opioids as a first-line therapy for management of chronic noncancer pain.

2.3 Position statements/Guidelines

There are many guidelines for prescribing opioids, and there is a growing consensus on best practice when considering or initiating opioids [6]. This includes recognising and dealing with psychosocial aspects of pain, managing patient expectations about the degree of pain relief likely to be achievable, starting with a therapeutic trial and an agreement to stop or reduce opioids when they do not work, and recording care plans agreed with patients to guide all subsequent prescribers in maintaining the plan. Some recent New Zealand and Australian guidelines are summarised below.

2.3.1 Acute pain

Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine

Acute Pain Management: Scientific Evidence (Fifth edition 2020 [7]

Acute Pain Management: Scientific Evidence aims to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice guidelines.

This document covers a wide range of clinical topics, divided into the following sections: Physiology and psychology of acute pain, assessment and measurement of pain and pain treatment, provision of safe and effective acute pain management, analgesic medicines (including opioids), administration of analgesic medicines, patient-controlled analgesia, non-pharmacological techniques, specific clinical situations, other specific patient groups, and the paediatric patient. There are specific recommendations for the use (or not) of particular opioids, including types of pain being treated, route of opioid administration, duration of treatment and safety concerns.

Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine

Position statement on the use of slow-release opioid preparations in the treatment of acute pain – 2018 [8]

Recommendation: Slow-release opioids are not recommended for use in the management of patients with acute pain.

Mounting evidence highlights the inappropriate use of slow-release opioids for the treatment of acute pain. This statement reflects an evaluation of best available evidence and expert advice, and is in response to significant adverse events. It has been written to inform and recommend, and to encourage practice reflection. It is not intended to mandate practice or replace clinical judgement based on individual patient circumstances.

The inappropriate use of slow-release opioids for the treatment of acute pain has been associated with a significant risk of respiratory depression, resulting in severe adverse events and deaths.

The position statement describes concerns about the use of slow-release opioids in the management of acute pain, and includes practice points for treating acute pain.

[Note that this position statement was written before the Opioid Reforms were implemented in Australia – see section 4.5.1. An updated statement has not yet been published).

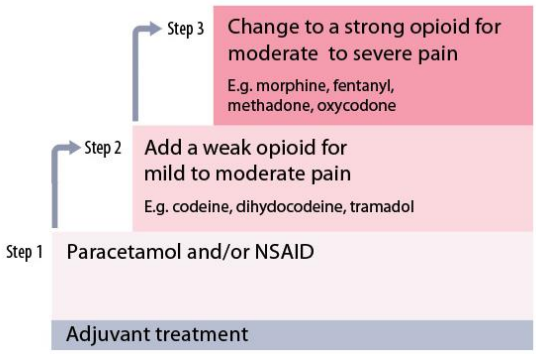
Best Practice Advisory Centre (bpac^{NZ})

The principles of managing acute pain in primary care – 2018 [9]

This article provides guidelines for NZ primary care providers for managing acute pain. It states that after treating the cause of the pain, the primary aim of acute pain management is to provide treatment that reduces the patient's pain, with minimal adverse effects, while allowing them to maintain function. A secondary aim is to prevent acute pain from progressing to chronic pain.

The article recommends regular assessment of pain to improve management and outcomes. A pharmacological treatment regimen for acute pain can be based on the WHO analgesic ladder. In patients with severe acute pain, the WHO analgesic ladder (Figure 1) is generally used in reverse, eg, for severe acute pain, start with morphine at step 3, then as pain resolves, reduce to codeine at step 2, then continue with paracetamol at step 1 until pain is negligible. Adjuvant treatments (physiotherapy on non-analgesic medicines) are continued throughout treatment as appropriate. The article reminds prescribers that the response to opioid analgesia is variable, so an analgesic regimen needs to be individualised. Multi-modal analgesia (concurrent use of analgesics with different modes of action) improves pain management. Prescribers should consider the need for additional medicines such as laxative, anti-nausea medicines and gastro-protection. Provide patients with a written analgesia plan and include non-pharmacological treatment as appropriate.

Figure 1: The WHO analgesic ladder of medicines



Source: BPAC NZ. 2018. *The prinicples of managing acute pain in primary care* February 2018. URL: https://bpac.org.nz/2018/acute-pain.aspx (accessed 10 November 2020).

2.3.2 Chronic non-cancer pain

Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine

Statement regarding the use of opioid analgesics in patients with chronic non-cancer pain – PS01(PM) 2020 [10]

This position statement was published by ANZCA's Faculty of Pain Medicine in 2020, in acknowledgment of the lack of definitive evidence to support the long term effectiveness of opioid analgesics in people experiencing chronic non-cancer pain (CNCP) and the substantial evidence for harm. It also recognises the changed regulatory environment introduced in Australia by the TGA, where modified release products are not indicated for use in CNCP other than in exceptional circumstances. This position statement is an interpretation of "exceptional circumstances" and describes the current position of the FPM regarding the prescription of opioids in CNCP, presented as a series of principles, including (but not limited to) the following:

- First line therapy for CNCP involves engaging the person to develop pain self-management skills.
- Second line therapies in CNCP include drug treatment which, while not a core component of a management plan, may play a role in facilitating functional goals and maintaining social roles including employment.
- Opioid treatment (in the context of exceptional circumstances) in CNCP is always an ongoing trial individual trial of therapy, and is contingent up demonstration of benefit, active surveillance for harms, periodic attempts at dose minimisation.
- Opioid treatment requires regular, documented assessment that addresses the "5As": analgesia, activity, adverse effects, affect, aberrant behaviour.

2.3.3 Cancer pain

Palliative Care Australia

Sustainable access to prescription opioids for use in palliative care - Position statement 2019 [11]

In this position statement, Palliative Care Australia, with endorsement numerous Australian and New Zealand organisations, is highlighting that research demonstrates opioids as a safe, effective medication for patients with distressing symptoms related to life-limiting illness, when prescribed in conjunction with clinical practice guidelines. They provide eight recommendations (summarised below):

- appropriate access to opioids without regulatory burden
- palliative care and opioid management education built into undergraduate medical, nursing, allied health and pharmacist curricula
- ensuring adequate supply
- nationally consistent prescribing approval policies that promote pain and addiction specialists working closely with palliative care
- introduction of national real time electronic monitoring for all opioid prescriptions
- palliative care to work with acute services to develop opioid stewardship policies informing clinical plans to ensure appropriate prescribing, de-prescribing, and dispensing of opioids
- review of the Palliative Care Schedule of the Pharmaceutical Benefit Scheme (PBS).
- review of the Medicare Benefits Schedule (MBS) specific to palliative care by way of item numbers and explanatory notes to facilitate consultation in primary and specialist practice.

3 DIHYDROCODEINE

Dihydrocodeine (DHC) is a semi-synthetic analogue of codeine. Although dihydrocodeine was first synthesised in 1911 and has been used as an antitussive agent since 1913, its properties as an analgesic agent were not identified until the first clinical studies in 1956. Since 1956 dihydrocodeine has been primarily used in the management of moderate to severe pain and as a cough suppressant in single doses of 10 to 60 mg up to a total maximum dose of 80 to 240 mg per day. The slow-release formulation, requiring only twice-daily application, was introduced in the UK in 1986 and in other countries soon after.

Like other opioid analgesics, DHC exerts its analgesic action through affinity to μ-, κ - and δ -opioid receptors mainly in the central nervous system.

Opioids are often defined as 'strong' or 'weak', based on how much is needed to produce the desired pain-relieving effect, often in comparison with morphine [12]. 'Strong' opioids are more potent, so a smaller amount is required to relieve pain compared with a 'weak' opioid. Oxycodone is more potent than morphine, as is fentanyl, which is considered to be up to 100 times as potent as morphine. Dihydrocodeine, codeine and tramadol are considered weak opioids. See Table 2.

Table 2: Opioids, by increasing strength relative to oral morphine, by type

Opioid	Strength	Strength relative to oral morphine[a,b]	Type
Codeine	Weak	0.13	Naturally-derived
Dihydrocodeine	Weak	0.17	Semi-synthetic
Tramadol	Weak	0.20–0.24	Synthetic
Pethidine	Strong	0.4	Synthetic
Morphine	Strong	1.0–3.0	Naturally-derived
Oxycodone	Strong	1.5–3.0	Naturally-derived
Methadone	Strong	4.7–13.5	Synthetic
Buprenorphine	Strong	38.8–85.0	Naturally-derived
Fentanyl	Strong	100	Synthetic

a. Based on milligrams of each opioid equivalent to 1 milligram of oral morphine.
b. Different preparations of each medicine may equate to a different oral morphine equivalent; these are represented by a range.

Source: Modified from Australian Institute of Health and Welfare. 2018. *Opioid Harm in Australia and Comparisons Between Australia and Canada*. URL: https://www.aihw.gov.au/getmedia/605a6cf8-6e53-488e-ac6e-925e9086df33/aihw-hse-210.pdf.aspx?inline=true (accessed 24 June 2020).

3.1 Classification

Dihydrocodeine is classified as prescription medicine under the Medicines Act 1981 and a Class C2 controlled drug under the Misuse of Drugs Act 1975. It is classified as a Class C6 controlled drug when it is (i) Compounded with one or more other pharmacologically active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield which would constitute a risk to health; and (ii) Containing not more than 100 milligrams of the substance in each dosage unit and with a concentration of not more than 2.5 percent in undivided preparations.

The Misuse of Drug Regulations 1977 specify the restrictions on controlled drug prescribing. Table 3 shows the maximum period of supply by professional group for dihydrocodeine as a Class C controlled drug.

Table 3: Maximum period of dihydrocodeine supply (as a Class C controlled drug) by professional group

Professional group	Maximum period of supply
Medical practitioners	3 months Dispensed at 1-monthly intervals unless specified by the prescriber
Nurse practitioners	3 months Dispensed at 1-monthly intervals unless specified by the prescriber
Dentists	7 days
Midwives	Cannot prescribe
Designated prescriber nurses	3 days and only in an emergency
Designated prescriber pharmacists	3 days and only in an emergency

Source: Ministry of Health. 2019. *Controlled drugs* 13 February 2010. URL https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/controlled-drugs (accessed 11 November 2021).

Every prescription for a controlled drug must be signed physically by the prescriber in his or her own handwriting. Details required on each prescription are set out in Regulation 29 and include:

- the date
- the name and address of the patient
- name of the medication
- the dose and frequency
- the prescriber's name and address.

Prescriptions for children under 12 years require the age in years and months to be written on the prescription form. Prescriptions for Class C controlled drugs must be dispensed within 6 months of the prescribing date. Amendments to controlled drug prescriptions may only be made by the prescriber, who must sign the changes.

3.2 Pharmacodynamics and pharmacokinetics

Dihydrocodeine is an opioid agonist with no antagonistic action [13]. The principal actions of therapeutic value of dihydrocodeine are analgesia and an antitussive effect (depression of the cough reflex by direct effect on the cough centre in the medulla). Dihydrocodeine may produce respiratory depression by direct action on brain stem respiratory centres. Dihydrocodeine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

The analgesic effect of DHC is similar to codeine and approximately twice as potent as tramadol for an oral route [14]. In patients with postoperative pain after subcutaneous administration of 30 mg DHC analgesia was similar to that induced by 10 mg of morphine.

Dihydrocodeine follows a two-compartment distribution model [15]. After oral administration, absorption was relatively quick with mean peak concentrations at 1.6–1.8 hours. The mean bioavailability was 21% (range 12-34%). The mean half-lives varied between 3.3–4.5 hours depending upon dose. Peak concentrations of metabolites occurred between 1.8–2.0 hours after oral administration and 2.2–2.5 hours after intravenous administration suggesting substantial first-pass metabolism.

Absorption and clearance of dihydrocodeine is delayed in the presence of renal insufficiency such that a reduction in dose is recommended [13]. It is also recommended to reduce dosage in the presence of impaired hepatic function.

Dihydrocodeine is metabolised in the liver to three main metabolites: dihydromorphine (DHM) via CYP2D6, its 6-glucuronide (DHC-6-G), and nordihydrocodeine (NORDHC) via CYP3A4 [16]. NORDHC is further glucuronidated to NORDHC-6-glucuronide and O-demethylated to nordihydromorphine. DHM undergoes glucuronidation to dihydromorphine-3-glucuronide (DHM-3-G), and dihydromorphine- 6-glucuronide (DHM-6-G) and N-demethylation to nordihydromorphine. See Figure 2 for a schematic of DHC metabolism.

Figure 2: Dihydrocodeine metabolism

The most important compounds responsible for DHC analgesia are marked in bold.

Source: Leppert W. 2011. CYP2D6 in the metabolism of opioids for mild to moderate pain. *Pharmacology* 87(5–6): 274–85. URL: https://www.karger.com/Article/Pdf/326085(accessed 2 November 2021).

The analgesic activity of dihydrocodeine has often been attributed to the DHM metabolite based on DHM having a binding affinity to μ receptors similar to that of morphine and possessing approximately 100 times the activity of the parent drug [15]. However, CYP2D6 enzyme mediates the conversion of DHC to DHM. Inter-ethnic differences (greater than 10% of Asians lack the functional activity of CYP2D6) suggest that the analgesic effects of dihydrocodeine might be diminished in those races with high prevalence of the poor metaboliser phenotype of CYP2D6. However, it has been observed that the analgesic effect following dihydrocodeine ingestion was mainly attributed to the parent drug rather than its DHM metabolite. This contradicts the view that polymorphic differences in dihydrocodeine metabolism to dihydromorphine have little or no effect on the analgesic affect. Others have confirmed that CYP2D6 phenotype has no major impact on opioid receptor-mediated effects of a single 60 mg dihydrocodeine dose, despite the essential role of CYP2D6 in the formation of highly active metabolites.

Therefore, DHC analgesia seems to be irrespective of CYP2D6 activity due to parent compound analgesic effects, multiple metabolic pathways (Figure 2) and limited role of dihydromorphine in DHC analgesia [14]. This is in contrast to tramadol and codeine, where metabolism is highly dependent on CYP2D6. CYP2D6 is highly polymorphic – over 100 allelic variants have been identified, resulting in wide variability in function [7]. Ultrarapid metabolisers may experience excessive adverse effects and poor metabolisers may have impaired analgesia after codeine and tramadol administration [14].

3.3 Prescribing information

The following information is summarised from the DHC Continus data sheet [13] (updated September 2021). This product was the first DHC product approved in New Zealand – consent was granted on 26 March 1992.

The Dihydrocodeine Controlled Release Actavis product was approved on 2 July 2015, but it is not available and there is no published data sheet. DHC Continus is the reference product for Dihydrocodeine Controlled Release Actavis.

3.3.1 Content and indication

One tablet contains 60 mg of dihydrocodeine hydrogen tartrate, equivalent to 40 mg of dihydrocodeine. The therapeutic indications for dihydrocodeine are:

- treatment of post-operative pain, and pain associated with cancer
- treatment of opioid-responsive, chronic severe pain of non-malignant origin, after other conservative methods of analgesia have been tried. It is indicated for use in accordance with the current guidelines on chronic pain management and where there is no psychological contraindication, medicine-seeking behaviour or history of medicine misuse.

Each bottle contains 60 tablets.

3.3.2 Dosing

The tablets must be swallowed whole and not broken, chewed or crushed.

For adults and children over 12 years of age: The tablets should be taken at twelve-hourly intervals at a dose of 60-120 mg twice daily depending on the severity of the patient's pain. The maximum recommended dose is 240 mg daily since higher doses do not provide any further analgesic effect.

Children: Not recommended for children aged 12 years and under.

Elderly and special risk groups: administered initially at the lowest dose possible in elderly or debilitated patients, patients with impaired renal function, impaired hepatic function, or hypothyroidism.

3.3.3 Contraindications

- Known hypersensitivity to dihydrocodeine hydrogen tartate or to any of the excipients
- Severe chronic obstructive lung disease
- Severe *cor pulmonale* (alteration in the structure and function of the right ventricle of the heart)
- Severe bronchial asthma
- Severe respiratory depression with hypoxia
- Concomitant use with monoamine oxidase inhibitors or within two weeks of such therapy as the respiratory depressant effects of dihydrocodeine may be enhanced

3.3.4 Special warnings and precautions for use

Administer with caution in elderly patients or patients with:

- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Biliary tract disorders
- Pancreatitis
- Impairment of hepatic function
- Severe renal dysfunction
- Chronic obstructive pulmonary disease
- Cor pulmonale
- Bronchial asthma

- Constipation
- Hypothyroidism
- Prostatic hypertrophy
- Sleep apnoea
- CNS depressants co-administration
- Tolerance, physical dependence and withdrawal
- Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse

There are also warnings/precautions for the following (summarised from the data sheet).

Hazardous and harmful use

Information about abuse, misuse and addiction; risk factors; monitoring for signs of misuse and abuse.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur even when used as recommended. The risk is greatest during initiation of therapy or following an increase in dose – close monitoring is required. The risk is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (use with caution and monitor closely). There is also a risk of sleep-related breathing disorders, including central sleep apnoea and sleep-related hypoxia.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use may result in sedation, respiratory depression, coma and death. Only prescribe for patients for who other treatment options are not possible, use the lowest effective dose for the shortest duration of treatment and closely monitor for signs and symptoms of respiratory depression and sedation. Advise patients and caregivers about the risks of concomitant use.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Current evidence does not support use of opioids for most patients with CNCP. The risks of development of tolerance and physical dependence, adverse effects and hazardous and harmful use increase with duration of treatment. Only use for CNCP if other treatments are not effective, not tolerated or do not provide adequate pain management. Initiate as a trial in accordance with clinical guidelines and biopsychosocial assessment. Regularly assess clinical need for ongoing treatment. Slowly taper off if treatment is no longer needed.

Tolerance, physical dependence and withdrawal

Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid. Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate. Gradually taper the dose when ceasing opioid treatment in someone who may be physically dependent.

Controlled release tablets

The tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release tablets leads to a rapid release and absorption of a potentially fatal dose of dihydrocodeine and may result in overdose effects.

Accidental ingestion/exposure

Accidental ingestion or exposure of DHC Continus, especially by children, can result in a fatal overdose. Instruct parents and caregivers on safe storage and disposal.

Hyperalgesia

May occur, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain; may lead the patient to seek other sources of licit or illicit opioids. Withdraw by tapering the dose slowly – consider dose and duration, type of pain being treated, psychological attributes of the patient. Use a multimodal approach to pain management before tapering. Regularly review and support the patient during taper. An individualised taper plan is needed – in general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks. Consider the need for medication-assisted treatment and/or specialist referral in patients with suspected opioid use disorder.

Use in Children

Not recommended in children under 12 years of age.

Head Trauma and Increased Intracranial Pressure

Depressant effects may be exaggerated in these patients – use with caution and only if use is necessary.

Asthma

Use with caution – DHC may cause release of histamine. Do not give during an asthma attack.

Special Risk Groups

Reduce the dose in reduced in the elderly, in hypothyroidism, chronic hepatic disease, biliary tract disorder, pancreatitis, impairment of hepatic function, prostatic hypertrophy, severe renal dysfunction, severe chronic obstructive airways disease, severe *cor pulmonale*, and renal insufficiency.

Use with caution in patients suffering constipation. Should not be used where there is a possibility of paralytic ileus. Should paralytic ileus be suspected or occur during use, discontinue immediately.

Effects on hypothalamic-pituitary-adrenal or gonadal axes

Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes, including an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

3.3.5 Interactions

Benzodiazepines and other CNS depressants including other opioids, anxiolytics, hypnotics, general anaesthetics, gabapentin and sedatives (including benzodiazepines), antipsychotics, and antidepressants, phenothiazines and alcohol. Increased risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects.

Monoamine oxidase inhibitors – co-administration with MAOIs or within two weeks of discontinuation of their use is inappropriate.

Alcohol – significant impairment of motor function has been noted with concomitant use.

Tricyclic antidepressants or beta-blockers – concomitant use may enhance the CNS depressant effects of DHC.

Diazepam, when used following high doses of dihydrocodeine hydrogen tartrate, exacerbates the hypotensive effects produced by dihydrocodeine, and is associated with reduced plasma catecholamine levels

3.3.6 Fertility, pregnancy and breastfeeding

Limited evidence in pregnancy, only use where the benefit outweighs the risk. Prolonged use may result in neonatal opioid withdrawal syndrome.

DHC has not been reported to be excreted in breastmilk but should be avoided and only used if essential.

No fertility data is available.

3.3.7 Effects on ability to drive and use machines

May impair the ability of the patient to drive or operate machinery. If so affected, patients should be warned against these activities.

3.3.8 Adverse effects

Table 4: Adverse effects classified by body system according to their incidence (common [≥1%] or uncommon [<1%])

Body system	Common (≥1%)	Uncommon (<1%)	Unknown
Immune system disorders		angioedema	
Psychiatric disorders		confusional state, drug dependence, hallucination, mood altered, dysphoria	
Vascular disorders		hypotension	
Nervous system disorders	somnolence	convulsions, dizziness, headache, paraesthesia, sedation	Sleep apnoea syndrome
Ear and labyrinth disorders		vertigo	
Skin and subcutaneous tissue disorders		hyperhidrosis, pruritus, rash, urticaria	
Gastrointestinal disorders	abdominal pain, constipation, dry mouth, nausea, vomiting	diarrhoea, paralytic ileus	
Hepatobiliary disorders		biliary colic, hepatic enzymes increased	
Renal and urinary disorders		urinary retention	
Respiratory, thoracic and mediastinal disorders		dyspnoea, respiratory depression	
General disorders and administration site conditions		asthenia, fatigue, malaise, withdrawal syndrome	drug withdrawal syndrome neonatal, drug tolerance

3.3.9 Overdose

Can be manifested by somnolence progressing to stupor or coma, miotic pupils, bradycardia, hypotension, rhabdomyolysis and respiratory depression or apnoea, which may result in a fatal outcome.

A patent airway must be maintained. The pure opioid antagonists are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

4 BENEFIT RISK REVIEW

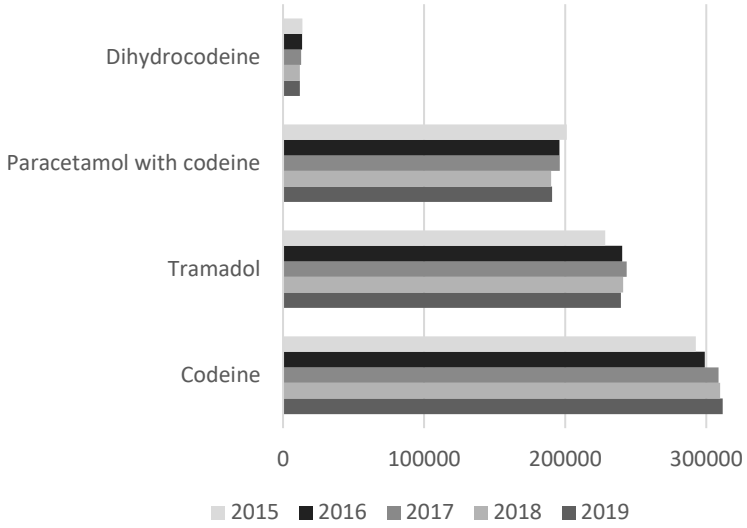
4.1 Usage

Data extracted from the Ministry of Health's Pharmaceutical data web tool and the Pharmaceutical Dispensings Proof of concept Qlik app are summarised below. These provide summary data from the Pharmaceutical Collection about prescriptions and dispensings that were dispensed in the community and funded by the New Zealand Government. They do not provide the indication for use, nor whether the patient took their dispensed medicine as prescribed.

4.1.1 Comparison against other weak opioids

'Weak' opioid (codeine, tramadol, dihyrocodeine and paracetamol + codeine) usage data from the Pharmaceutical collections is shown below. Figure 3 shows the number of people who were dispensed a weak opioid and Figure 4 the number of weak opioid dispensings for the period 2015 to 2019. Dihydrocodeine use is much lower than the other weak opioids.

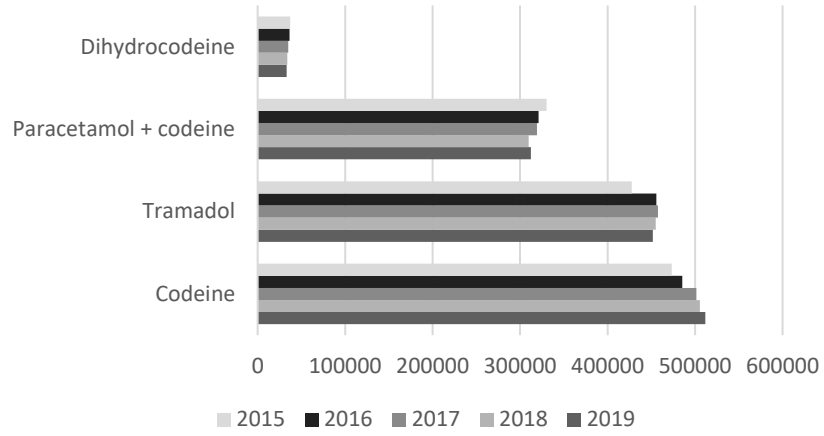
Figure 3: Number of people dispensed a weak opioid, 2015 to 2019



Notes:
The number of people dispensed an opioid is the number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year, as an initial dispensing or all at once (excludes people who only received a repeat dispensing during the year).

Source: Ministry of Health's Pharmaceutical Collection, extracted on 05 March 2020. URL: https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/ (accessed 11 November 2020).

Figure 4: Number of weak opioid dispensings, 2015 to 2019

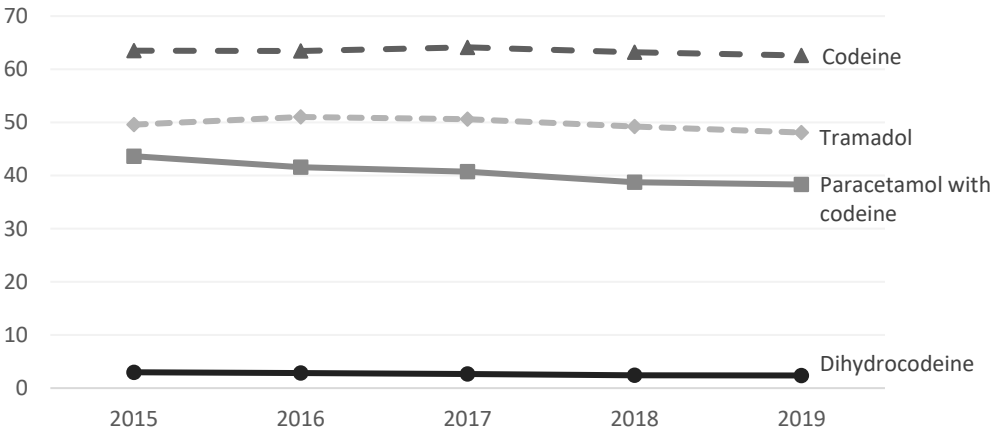


Notes:
The number of opioid dispensings is the number of times the pharmaceutical product is dispensed from a pharmacy to the named person as initial dispensings or all at once during the year.

Source: Ministry of Health's Pharmaceutical Collection, extracted on 05 March 2020. URL: https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/ (accessed 11 November 2020).

Figure 5 shows the people dispensed a weak opioid, as rates per 1,000 population, from 2015 to 2019. While the absolute numbers of people dispensed a weak opioid have increased over the time period (Figure 3 above), the rates per 1,000 population have been relatively stable, with a decreasing trend since 2017.

Figure 5: People dispensed a weak opioid, rate per 1,000 population, 2015 to 2019



Sources:
Ministry of Health's Pharmaceutical Collection, extracted on 05 March 2020. URL: https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/ (accessed 11 November 2020).
NZ.Stat Subnational population estimates (2018), by age and sex, at 30 June 1996-2020. URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509# (accessed 11 November 2020).

Comment

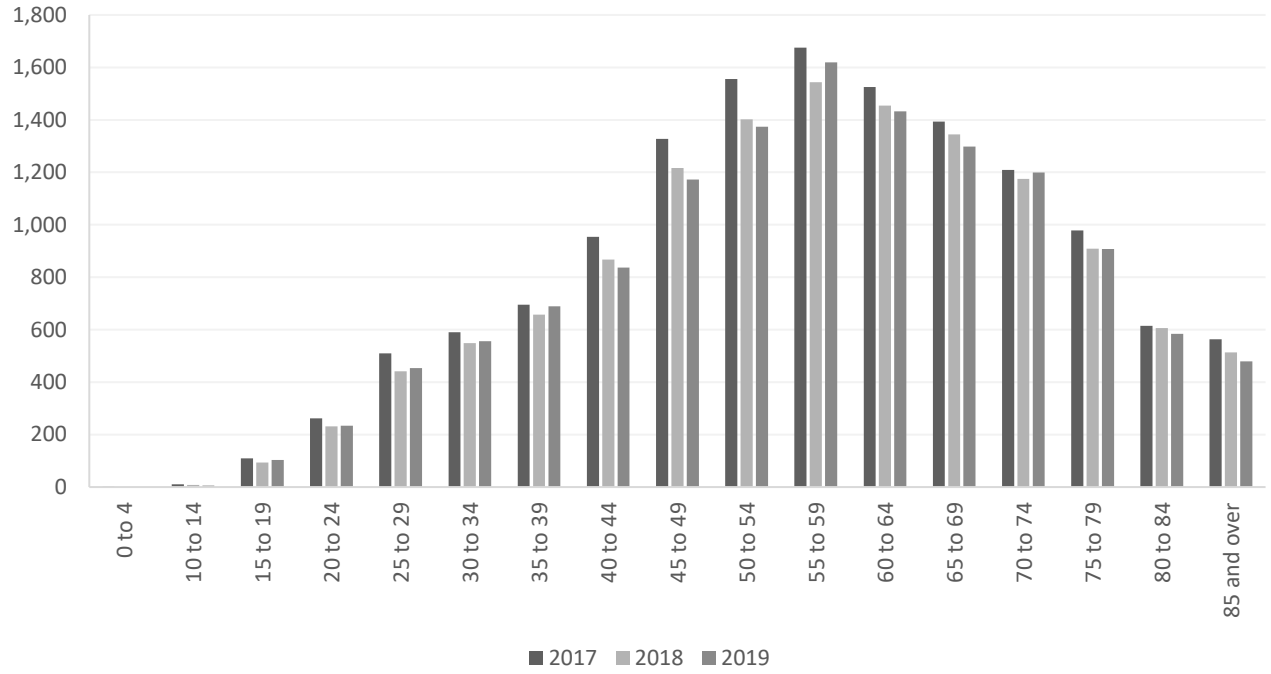
Note that this data does not capture codeine-combination product use when sold as a pharmacy only or restricted medicines, so paracetamol + codeine use may be much higher than shown in Figures 3–5. (All codeine-combination medicines were reclassified from pharmacy only or restricted medicines to prescription medicines on 5 November 2020; codeine-only medicines were already prescription medicines.)

4.1.2 Dihydrocodeine usage information – demographics

4.1.2.1 Age

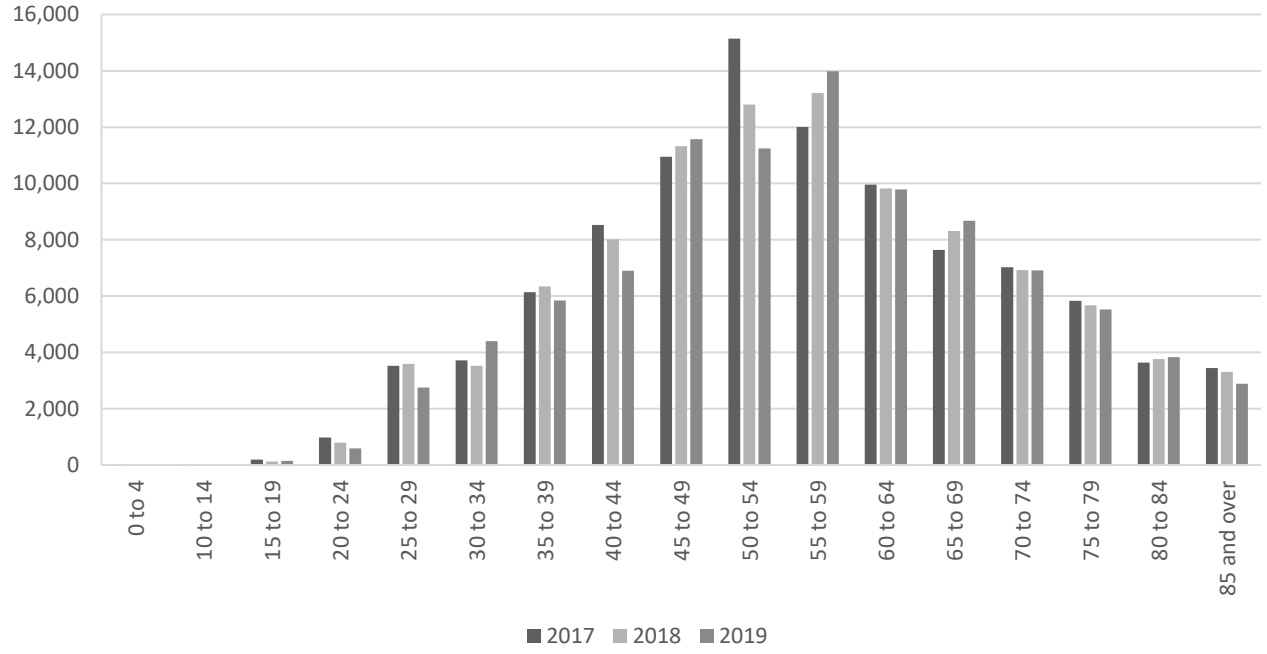
Figure 6 shows the number of people dispensed dihydrocodeine by age group and Figure 7 the number of dispensings by age group for 2017 to 2019. The general pattern is the same for both figures, with numbers increasing with each successive age group, peaking in the 50-60 year age group and then decreasing again.

Figure 6: People dispensed dihydrocodeine by age at dispensing, 5-year age groups, 2017 to 2019



Notes:
Not shown: Age unknown: 68 people in 2017, 52 in 2018, 56 in 2019.
Source: Ministry of Health's Pharmaceutical Dispensings Proof of concept Qlik app, data extracted on 05 March 2020. (accessed 28 October 2021).

Figure 7: Number of dihydrocodeine dispensings by age at dispensing, 5-year age groups, 2017 to 2019

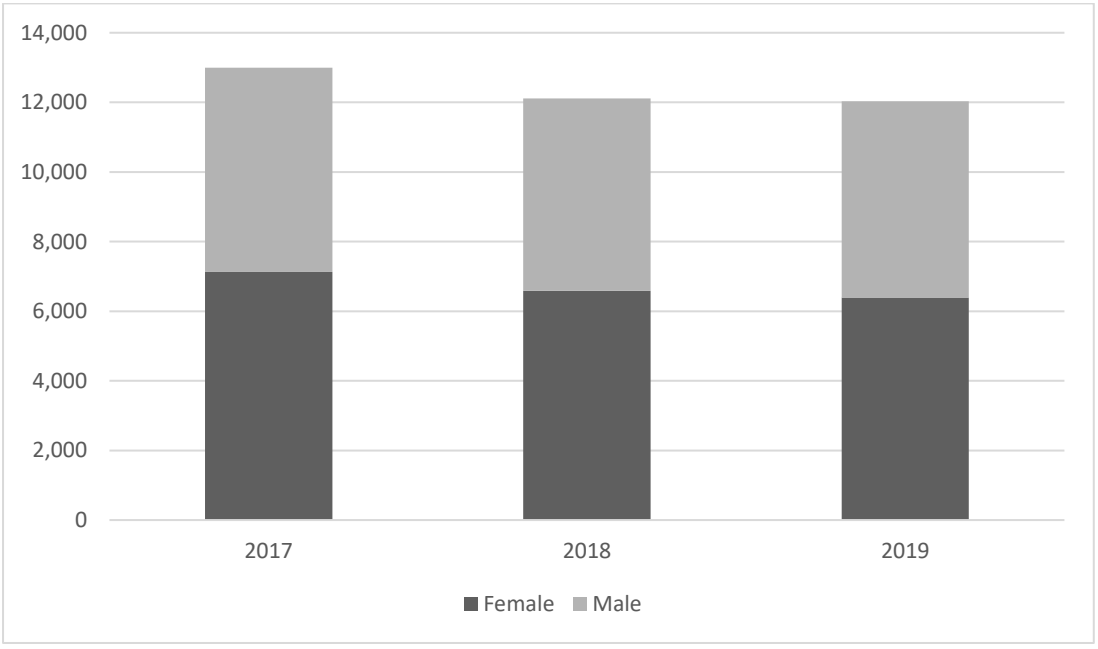


Notes:
Not shown: Age unknown: 68 dispensings in 2017, 52 in 2018, 56 in 2019.
Source: Ministry of Health's Pharmaceutical Dispensings Proof of concept Qlik app, data extracted on 05 March 2020. (accessed 28 October 2021).

4.1.2.2 Gender

Figure 8 shows that slightly more women than men were dispensed dihydrocodeine each year.

Figure 8: Number of people dispensed dihydrocodeine by gender, 2017 to 2019

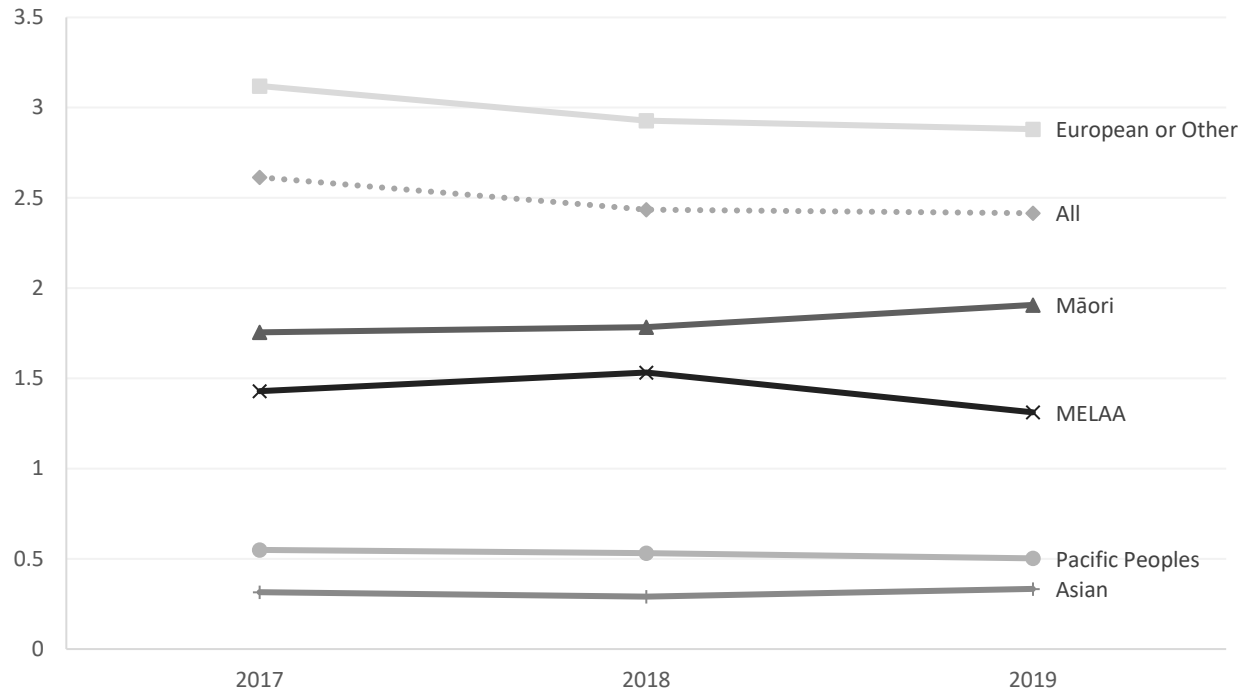


Not shown: Gender unknown: 1 person in 2017, 2 in 2018, 1 in 2019.
Source: Ministry of Health's Pharmaceutical Dispensings Proof of concept Qlik app, data extracted on 05 March 2020. (accessed 28 October 2021).

4.1.2.3 Ethnicity

Figure 9 shows the number of people dispensed dihydrocodeine by ethnicity, as rates per 1,000 population, from 2017 to 2019. The general trend is for a decreasing rate for each ethnic group, with the exception of Maori, for whom the rate is increasing.

Figure 9: People dispensed dihydrocodeine, by ethnicity, rate per 1,000 population, 2017 to 2019



Sources:
Ministry of Health's Pharmaceutical Dispensings Proof of concept Qlik app, data extracted on 05 March 2020. (accessed 28 October 2021).
NZ.Stat Estimated resident population (2018), national population by ethnic group, age, and sex, 30 June 1996, 2001, 2006, 2013, 2018. URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509# (accessed 28 October 2021).

4.2 Harm

4.2.1 Adverse event case reports

Up to 30 September 2021, there were 30 cases (79 reactions) reported to CARM where dihydrocodeine was the suspect medicine. The reported reactions by System Organ Class (SOC) and gender are shown in Table 5 and the CARM report is attached as Annex 1.

- The first case was reported in November 1987 and the most recent in June 2020.
- Age was reported in 29 cases and ranged from 17 to 90 years (median 58, mean 57 years).
- Gender: 19 females, 11 males.
- [redacted]
- [redacted]
- The most frequently reported reactions were nausea (12), vomiting (11), pruritis (5) and dizziness (4). These reactions are listed in the DHC Continus data sheet.

- [redacted]

[redacted]

[redacted]

[redacted]

Table 5: Dihydrocodeine reports: reactions by System Organ Class (SOC) and gender

SOC	Reaction	[redacted]	[redacted]	[redacted]
Alimentary	Abdominal pain		[redacted]	[redacted]
	Anorexia	[redacted]		[redacted]
	Constipation	[redacted]		[redacted]
	Diarrhoea	[redacted]		[redacted]
	Intestinal obstruction	[redacted]		[redacted]
	Ischaemic necrosis bowel	[redacted]		[redacted]
	Nausea	[redacted]	[redacted]	[redacted]
	Oesophagitis	[redacted]		[redacted]
	Vomiting	[redacted]	[redacted]	[redacted]
	Total Alimentary	[redacted]	[redacted]	[redacted]
Cardiovascular	Cardiac arrest	[redacted]		[redacted]
	Dizziness	[redacted]		[redacted]
	Flushing	[redacted]	[redacted]	[redacted]
	Palpitation	[redacted]		[redacted]
	Total Cardiovascular	[redacted]	[redacted]	[redacted]
Endocrine/Metabolic	Thirst	[redacted]		[redacted]
	Total Endocrine/Metabolic	[redacted]	[redacted]	[redacted]
Nervous system	Akathisia		[redacted]	[redacted]
	Drowsiness	[redacted]		[redacted]
	Headache		[redacted]	[redacted]
	Sedation	[redacted]		[redacted]
	Shaking		[redacted]	[redacted]
	Stupor	[redacted]		[redacted]
	Tremor		[redacted]	[redacted]
	Total Nervous system	[redacted]	[redacted]	[redacted]
Others	Death	[redacted]		[redacted]
	Drug interaction	[redacted]		[redacted]
	Sweating increased		[redacted]	[redacted]
	Temperature changed sensation	[redacted]		[redacted]
	Total Others	[redacted]	[redacted]	[redacted]
Procedure related	Medication error	[redacted]		[redacted]
	Total Procedure related	[redacted]	[redacted]	[redacted]

SOC	Reaction	[redacted]	[redacted]	[redacted]
Product related	Batch difference		[redacted]	[redacted]
	Brand switch		[redacted]	[redacted]
	Total Product related	[redacted]	[redacted]	[redacted]
Psychiatric changes	Confusion		[redacted]	[redacted]
	Depersonalisation	[redacted]		[redacted]
	Hallucination auditory		[redacted]	[redacted]
	Hallucination visual	[redacted]		[redacted]
	Intentional overdose	[redacted]		[redacted]
	Somnolence	[redacted]		[redacted]
	Suicidal tendency		[redacted]	[redacted]
	Suicide	[redacted]		[redacted]
	Total Psychiatric changes	[redacted]	[redacted]	[redacted]
Respiratory	Respiratory arrest	[redacted]		[redacted]
	Total Respiratory	[redacted]		[redacted]
Skin and appendages	Angioedema		[redacted]	[redacted]
	Pigmentation ABN (Urticaria)		[redacted]	[redacted]
	Pruritis	[redacted]	[redacted]	[redacted]
	Rash	[redacted]	[redacted]	[redacted]
	Rash maculopapular	[redacted]		[redacted]
	Rash petechial	[redacted]		[redacted]
	Urticaria	[redacted]		[redacted]
	Total Skin and appendages	[redacted]	[redacted]	[redacted]
Urinary	Urinary retention	[redacted]		
	Total Urinary	[redacted]	[redacted]	[redacted]
Total reactions		**52**	**27**	**79**

4.2.2 National collections

The following hospitalisation and mortality data is a linked administrative data set from the Pharmaceutical Collection, the National Minimum Dataset (hospital discharges) and the Mortality Collection of patients who were prescribed a particular opioid between 2010 and 2019. The data set includes unidentifiable information on the first and last date of opioid dispensing, along with hospital discharges and mortality information for ICD-10/ICD-10-AM clinical codes associated with mental and behavioural disorders due to psychoactive substance use (F11 and F19) and poisoning due to narcotics and dysleptics (T40, X42, X62, Y12), as described in Table 6.

Table 6: Clinical codes – 4-character subcategories

F11 Mental and behavioural disorders due to use of opioids:
F11.0 acute intoxication F11.1 harmful use F11.2 dependence syndrome F11.3 withdrawal state F11.4 withdrawal state with delirium F11.5 psychotic disorder F11.6 amnesic syndrome F11.7 residual and late-onset psychotic disorder

F11.8 other mental and behavioural disorders F11.9 unspecified mental and behavioural disorder
F19 Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances: F19.0 acute intoxication F19.1 harmful use F19.2 dependence syndrome F19.3 withdrawal state F19.4 withdrawal state with delirium F19.5 psychotic disorder F19.6 amnesic syndrome F19.7 residual and late-onset psychotic disorder F19.8 other mental and behavioural disorders F19.9 unspecified mental and behavioural disorders
T40 Poisoning by narcotics and psychodysleptics [hallucinogens]: T40.2 other opioids T40.3 methadone T40.4 other synthetic narcotics T40.6 other and unspecified narcotics
X42 Accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere specified Includes: cannabis (derivatives) cocaine codeine heroin lysergide (LSD) mescaline methadone morphine opium (alkaloids)
X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified Includes: cannabis (derivatives) cocaine codeine heroin lysergide (LSD) mescaline methadone morphine opium (alkaloids)
Y12 Poisoning by and by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified, undetermined intent Includes: cannabis (derivatives) cocaine codeine

heroin lysergide (LSD) mescaline methadone morphine opium (alkaloids)

Source: International Statistical Classification of Diseases and Related Health Problems 10th Revision
URL: https://icd.who.int/browse10/2019/en

Limitations of the data

- Only includes information for funded prescription opioids that were dispensed in the community. It does not include non-funded prescription medicines, or codeine-combination medicines that were previously available without prescription. It does not include harm from illicit opioid use.
- The data contains only the date of the initial dispensing and the date of the final dispensing for a particular opioid. It is not possible to tell whether the patient took the opioid continuously between the first and last dispensing or if there was a break when the patient did not take the opioid.
- The data does not provide information about why a particular medicine was prescribed and dispensed to a patient, how often it was dispensed, the prescribed dose, or whether the patient took their dispensed medicine as prescribed.
- Linked data showing an association between opioid dispensing and hospitalisation or death does not imply causality. Patient clinical records were not checked to verify that the hospital discharge or cause of death was due to an opioid, or whether other factors were involved, such as co-prescribed medicines, alcohol or illicit drug use.

4.2.2.1 Hospitalisations

Table 7 shows the number of people who were dispensed a weak opioid between 2010 and 2019, and whose hospital discharge codes were associated with mental and behavioural disorders due to psychoactive substance use and poisoning due to narcotics and dysleptics. Also shown is the number of dispensings per year and proportion of hospitalisations compared to dispensings.

Compared to the other weak opioids, dihydrocodeine has the lowest number of hospitalisations and dispensings per year. However, the proportion of people who were hospitalised with a substance abuse and poisoning code is higher for dihydrocodeine compared to the other weak opioids (Figure 10).

Table 7: Number and proportion of people dispensed a weak opioid who were hospitalised with a substance abuse or poisoning clinical code[a] in the same year as the initial dispensing[b], 2010 to 2019

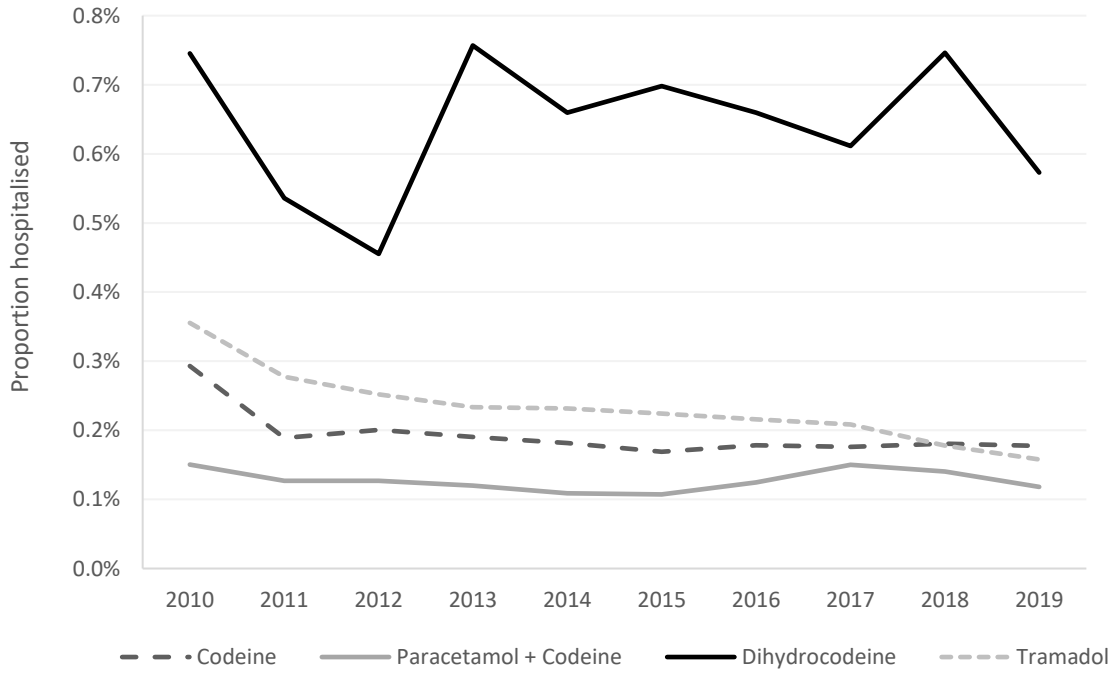
	Dihydrocodeine			Paracetamol + Codeine			Tramadol			Codeine		
Year	Hosp	Disp	%	Hosp	Disp	%	Hosp	Disp	%	Hosp	Disp	%
2010	133	17,846	0.7	302	200,830	0.2	317	89,198	0.4	656	223,882	0.3
2011	50	9,329	0.5	191	150,329	0.1	368	132,654	0.3	333	176,146	0.2
2012	58	12,740	0.5	170	133,986	0.1	332	131,666	0.3	353	175,980	0.2
2013	55	7,268	0.8	140	116,624	0.1	309	132,374	0.2	313	164,277	0.2
2014	45	6,822	0.7	114	104,722	0.1	297	128,167	0.2	287	158,253	0.2
2015	46	6,591	0.7	103	96,043	0.1	285	127,142	0.2	258	152,698	0.2
2016	42	6,370	0.7	111	89,035	0.1	270	125,169	0.2	258	144,666	0.2
2017	35	5,726	0.6	129	85,981	0.2	249	119,543	0.2	248	140,775	0.2
2018	38	5,092	0.7	112	79,905	0.1	200	112,341	0.2	237	131,090	0.2
2019	29	5,062	0.6	93	78,603	0.1	167	105,829	0.2	221	124,526	0.2

Hosp: number of people hospitalised who had an initial opioid dispensing in that year; Disp: number of people who had an initial opioid dispensing in that year.

a. Clinical codes: F11 Mental and behavioural disorders due to use of opioids; F19 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances; T40 code (Poisoning by narcotics and psychodysleptics [hallucinogens] (T40.2, T40.3, T40.4 and T40.6 only); X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.

b. Excludes repeat discharges in the same calendar year.

Figure 10: Proportion[a] of people dispensed a weak opioid who were hospitalised with a substance abuse or poisoning clinical code[b] in the same year as the initial dispensing[c], 2010 to 2019



a. Numerator: number of people hospitalised who had an initial opioid dispensing in that year; Denominator: all people who had an initial opioid dispensing in that year

b. Clinical codes: F11 Mental and behavioural disorders due to use of opioids; F19 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances; T40 code (Poisoning by narcotics and psychodysleptics [hallucinogens] (T40.2, T40.3, T40.4 and T40.6 only); X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62

Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.

c. Excludes repeat discharges in the same calendar year.

4.2.2.2 Mortality

Mortality data is available up to 2016. Of the weak opioids, codeine and tramadol were associated with the highest number of deaths per year due to substance abuse or poisoning codes (Table 8).

Table 8: Number of deaths per year due substance abuse or poisoning codes[a], by dispensed weak opioid, 2010 to 2016

Opioid	2010	2011	2012	2013	2014	2015	2016	Unknown[b]	Total
Codeine	18	17	31	34	27	24	28	3	182
Tramadol	5	15	22	27	26	25	23	2	145
Paracetamol + Codeine	7	9	16	14	15	17	21		99
Dihydrocodeine	6	3	9	12	11	15	6	1	63

a. Clinical codes: F11.2: Mental and behavioural disorders due to use of opioids: dependence syndrome; F19.2 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances: dependence syndrome; X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.

b. A primary cause of death was recorded but the year of death was not.

Table 9 below shows the number of deaths due to poisoning or substance abuse within 100 days of the final dispensing, by weak opioid. This cut-off was chosen to try and focus the data to cases more likely to be related to the prescribing. For each opioid, the number of deaths is lower than in Table 8 above. However, for dihydrocodeine, the reduction in deaths (44%) is less than for each of the other opioids (codeine 59% reduction, tramadol 59%, paracetamol + codeine 77%).

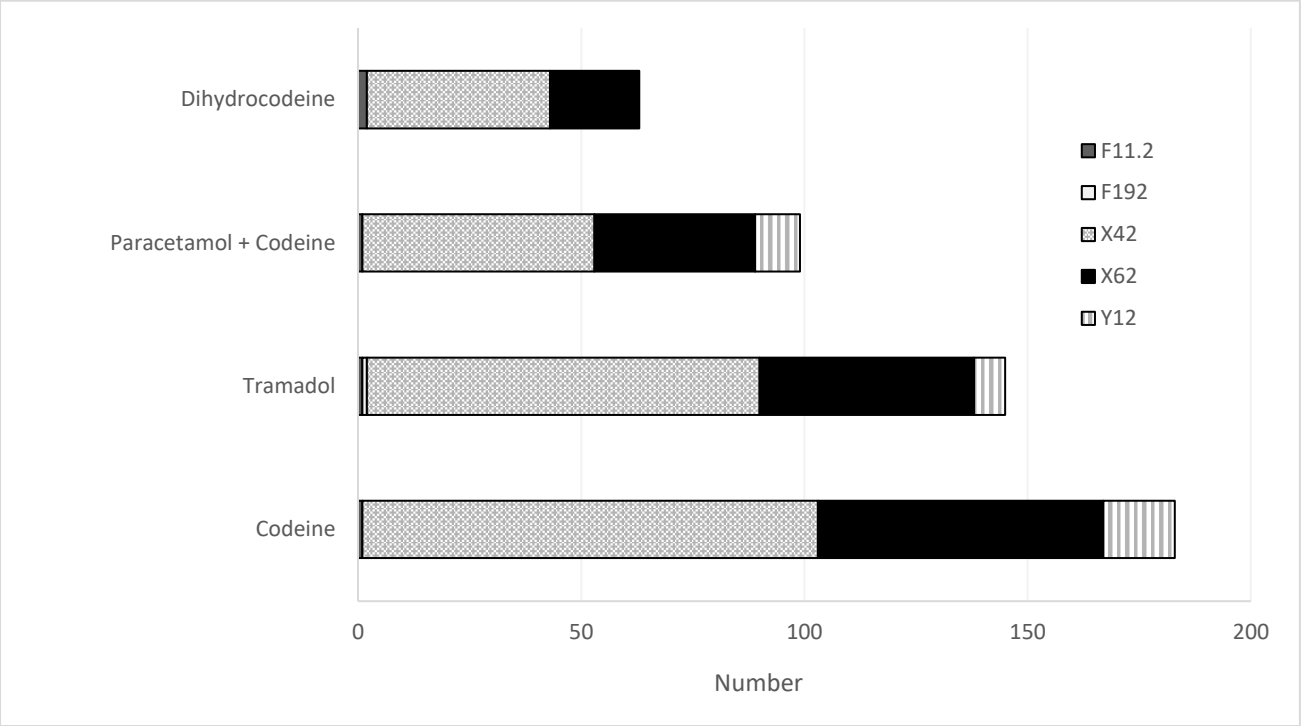
Table 9: Number of deaths per year due to substance abuse or poisoning clinical codes[*], within 100 days of last dispensing, 2010 to 2016

Opioid	2010	2011	2012	2013	2014	2015	2016	Total
Codeine	12	11	6	14	14	6	11	74
Tramadol	4	8	9	11	12	8	7	59
Dihydrocodeine	5	3	5	9	6	5	2	35
Paracetamol + Codeine	5	6	2	2	3	3	1	22

* Clinical codes: F11.2: Mental and behavioural disorders due to use of opioids: dependence syndrome; F19.2 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances: dependence syndrome; X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.

Accidental poisoning (X42) was most frequently recorded as the primary cause of death for the dispensed weak opioids, followed by intentional self-poisoning (X62) (Figure 11).

Figure 11: Total deaths between 2010 and 2016 due to substance abuse or poisoning clinical codes[a], by code and dispensed weak opioid



a. Clinical codes: F11.2: Mental and behavioural disorders due to use of opioids: dependence syndrome; F19.2 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances: dependence syndrome; X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.

Comment

Note that these poisoning codes (X42 and X62) also include exposure to narcotics such as cannabis, cocaine and heroin (see Table 6) – which may have been the cause of the poisoning, rather than the dispensed opioid.

4.2.3 National Poisons Centre

The National Poisons Centre (NPC) provided information on contacts to the NPC between 1 January 2017 and 30 June 2020 for exposures involving specified, funded opioids.

There were 1,889 calls to the NPC for opioid exposures during the time period (Table 10). Codeine and tramadol were the most prevalent opioid exposures reported to the NPC, accounting for 828 (1,137 when including codeine+paracetamol) and 601 exposures, respectively. The number of calls relating to dihydrocodeine exposures was much lower (25).

Table 10: Overall prevalence of opioid substances in contacts to the National Poisons Centre, 1 January 2017 to 30 June 2020

	2017	2018	2019	2020*	Grand Total
Total patients with one or more of the opioids of interest indicated	530	547	542	270	1,889
% of all human exposure patients	2.5%	2.6%	2.4%	2.3%	2.5%
Total human exposure patients	21,066	21,311	22,925	11,798	77,100
Patients "positive" for specific substance of interest (substance present)**					
Buprenorphine + naloxone	0	1	4	1	6
Codeine	233	242	219	134	828
Codeine + paracetamol	81	91	107	30	309
Dihydrocodeine	6	7	8	4	25
Fentanyl	3	3	6	7	19
Methadone	2	11	9	1	23
Morphine	66	56	68	31	221
Oxycodone	20	17	17	11	65
Pethidine	0	2	0	3	5
Tramadol	177	185	163	76	601

*To 30 June 2020. **NOTE: a single patient may have multiple opioids involved in their exposure; therefore total numbers of substance cases do not necessarily match total opioid-positive patients.

4.3 Literature – efficacy

Dihydrocodeine has been used as an analgesic since 1956 and there is a large body of literature. Studies below are from recent years (since 2010) and are relevant for the indications approved in New Zealand.

4.3.1 Yuan et al. 2021. A retrospective analysis of the effects of different analgesics on the pain of patients with traumatic thoracolumbar fractures in the peri-treatment period [17]

Objective To analyse and compare the effects of peri-treatment analgesics on acute and chronic pain and postoperative functional recovery of patients with thoracolumbar fractures, so as to guide the clinical drug use.

Methods 719 patients with thoracolumbar fractures were collected and divided into acetaminophen (paracetamol) + dihydrocodeine, celecoxib, and etoricoxib groups. The main indicators were the degree of postoperative pain (visual analog scale (VAS)), the incidence of chronic pain and postoperative functional recovery (Oswestry dysfunction index (ODI) and Japanese Orthopedics Association score (JOA)), which were continuously tracked through long-term (1 year) telephone follow-up. The correlation analysis of ODI-pain score, peri-treatment VAS score, and ODI index was performed, and bivariate regression analysis was conducted to understand the risk factors for chronic pain.

Results There were no statistically significant differences between the study groups in basic characteristics, preoperative injury, and intraoperative conditions. The number of days of use of analgesics in peri-treatment period (from diagnosis to departure from hospital) in the codeine group was significantly higher than that in the celecoxib and etoricoxib groups (pre-operation 8.80 ± 0.98 vs 5.05 ± 0.37 vs 5.60 ± 0.54; post-operation 4.40 ± 0.49 vs 3.05 ± 0.27 vs 2.60 ± 0.53, $p < 0.01$).

Regression analysis showed that severe spinal cord injury and peri-treatment use of acetaminophen + dihydrocodeine were both one of the risk factors for postoperative chronic pain one year after surgery (Table

11). Note that acetaminophen + dihydrocodeine is abbreviated to codeine in the table (codeine was not used as a treatment).

Table 11: Risk factors for chronic pain 1 year after surgery

[redacted]

Compared with the other two groups, patients in the acetaminophen + dihydrocodeine group had longer peri-therapeutic analgesic use, higher pain-related scores (VAS 1 day preoperatively, VAS 1 month postoperatively, and ODI-pain 1 year postoperatively), higher VAS variation, higher incidence of chronic pain 1 year after surgery, and higher ODI index. Other ODI items and JOA assessments showed no statistically significant differences. In addition, the correlation analysis showed that the peri-treatment pain score was correlated with the severity of postoperative chronic pain.

Patients in the acetaminophen + dihydrocodeine group had a higher incidence of chronic pain after surgery than those in the celecoxib and etoricoxib groups (Table 12). In addition, the ODI-1 (pain score) of each subgroup was compared, and the results showed that the majority of chronic pain in each subgroup was mild pain, and about 11.50–13.90% of patients had moderate pain. Note that acetaminophen + dihydrocodeine is abbreviated to codeine in the table (codeine was not used as a treatment).

Table 12: Comparison of the incidence and severity of chronic pain in 1 year after different analgesics were used in the peri-treatment period of thoracolumbar fracture

[redacted]

Limitations It was impossible to judge the impact of lifestyle on this study because lifestyle habits were difficult to define and categorise – although all patients were given the same lifestyle advice. In addition, patients often had coexisting severe pain before inclusion in this study, making it difficult to measure their pain sensitivity prior to this study. This study is a retrospective analysis, so the results of this study can only be used as a basic understanding of the impact of analgesics on postoperative recovery, and further prospective studies and other research methods with higher evidence level are needed in the later stage.

Conclusion Although the peri-treatment analgesic effect of acetaminophen dihydrocodeine is good, it is still necessary to combine analgesics with different mechanisms of action for patients with severe preoperative

pain of thoracolumbar fracture, so as to inhibit the incidence of postoperative chronic pain and improve the quality of postoperative rehabilitation.

Comment

The combination of acetaminophen (paracetamol) + dihydrocodeine is not available in New Zealand. The dihydrocodeine formulation (modified-release or normal-release) was not stated. However, this study was included to show the comparative effects of dihydrocodeine against NSAIDs in fracture surgery patients. The surgical techniques and post-surgical care may be different in China compared to New Zealand. The generalisability of this study to the NZ population or to different surgeries may be limited.

4.3.2 Busse et al. 2018. Opioids for chronic noncancer pain: a systematic review and meta-analysis [18]

Objective To systematically review randomised clinical trials (RCTs) of opioids for chronic noncancer pain.

Data sources and study selection The databases of CENTRAL, CINAHL, EMBASE, MEDLINE, AMED, and PsycINFO were searched from inception to April 2018 for RCTs of opioids for chronic noncancer pain vs any nonopioid control. Paired reviewers independently extracted data. The analyses used random-effects models and the Grading of Recommendations Assessment, Development and Evaluation to rate the quality of the evidence.

Main outcomes and measures The primary outcomes were pain intensity (score range, 0-10 cm on a visual analog scale (VAS) for pain; lower is better and the minimally important difference [MID] is 1 cm), physical functioning (score range, 0-100 points on the 36-item Short Form physical component score [SF-36 PCS]; higher is better and the MID is 5 points), and incidence of vomiting.

Results Ninety-six RCTs including 26,169 participants (61% female; median age, 58 years [interquartile range, 51-61 years]) were included. Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization (pain present in the absence of tissue damage), and 6 trials of mixed types of pain. Compared with placebo, opioid use was associated with reduced pain (weighted mean difference [WMD], −0.69 cm [95% CI, −0.82 to −0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID, 11.9% [95% CI, 9.7% to 14.1%]), improved physical functioning (WMD, 2.04 points [95% CI, 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID, 8.5% [95% CI, 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-in period). Low- to moderate-quality evidence suggested similar associations of opioids with improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs (pain: WMD, −0.60 cm [95% CI, −1.54 to 0.34 cm]; physical functioning: WMD, −0.90 points [95% CI, −2.69 to 0.89 points]), tricyclic antidepressants (pain: WMD, −0.13 cm [95% CI, 0.99 to 0.74 cm]; physical functioning: WMD, −5.31 points [95% CI, −13.77 to 3.14 points]), and anticonvulsants (pain: WMD, −0.90 cm [95% CI, −1.65 to −0.14 cm]; physical functioning: WMD, 0.45 points [95% CI, −5.77 to 6.66 points]).

Opioids vs Synthetic Cannabinoids Low-quality evidence from 1 crossover trial [19] suggested no difference between dihydrocodeine and nabilone (a synthetic cannabinoid) for chronic neuropathic pain relief (73 patients; mean difference, −0.13 cm [95% CI, −1.04 to 0.77 cm] on the 10-cm VAS for pain, P = .77) or physical functioning (71 patients; mean difference, −1.2 points [95% CI, −4.50 to 2.10 points] on the 100-point SF-36 physical component score, P = .48). Patients received a maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone at the end of each escalating treatment period of 6 weeks. Treatment periods were separated by a 2 week washout period.

Conclusions and relevance In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

Comment

This was a systematic review of randomised clinical trials of opioids for chronic noncancer pain. Of the 44,345 citations identified via the literature search, 96 studies were included in the review. And of these 96 studies, only one was for dihydrocodeine. This was a randomised, double blind, crossover study of 14 weeks' duration, comparing nabilone (a synthetic cannabinoid) with dihydrocodeine [19]. The review authors commented this was low-quality evidence and it suggested no difference between opioids and nabilone for pain relief.

4.3.3 Leppert et al. 2010. The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain [20]

Aim To assess the impact of tramadol and DHC treatment on quality of life (QL) and performance status (PS) of patients with cancer pain.

Patients and methods Randomised, cross-over, clinical study of 40 opioid-naive patients with nociceptive cancer pain who received tramadol or DHC controlled release tablets for 7 days, and then drugs were switched and administered for another 7 days. Pain was assessed by visual analogue scale (VAS), QL by EORTC QLQ C 30, and PS by Eastern Cooperative Oncology Group (ECOG) and Karnofsky.

Results From 40 patients recruited, 30 completed the study. DHC treatment provided better analgesia (VAS). In QL functional scales, better emotional functioning in tramadol group and better global QL and cognitive functioning in DHC group were observed. In symptom scales, less fatigue, pain and sleep disturbances, less nausea and vomiting and better appetite in DHC group were noted. In tramadol group, less constipation and less financial problems were observed. No differences in dyspnoea and diarrhoea were noted. ECOG and Karnofsky PS were low and did not differ between tramadol and DHC groups.

Limitations The results of the study should be interpreted with significant caution, as the authors were not able to demonstrate drug effect in any of the EORTC QLQ C 30 functional or symptom scales, ECOG and Karnofsky PS. The treatment period with each analgesic was 7 days only. Another limitation of the study was non-blinded design and lack of wash-out period, which might have influenced the results after drug switch; however, the latter approach might be justified by ethical reasons in cancer pain management. Patients with neuropathic pain component were excluded as they usually need strong opioids and adjuvant analgesics administration. The number of patients recruited was small; thus the results should be replicated in a controlled study with longer follow up.

Conclusions Dihydrocodeine treatment was associated with better global QL, cognitive functioning, analgesia and appetite, less fatigue, sleep disturbances, nausea and vomiting. Tramadol therapy was connected with better emotional functioning, less constipation and financial problems. PS deteriorated in both tramadol and DHC groups.

Comment

This study by Leppert et al was included in a 2017 Cochrane review: Tramadol with or without paracetamol (acetaminophen) for cancer pain [21]. In that review, the authors considered the risk of bias for the Leppert study to be:

- high for blinding of participants and personnel due to the open-label design (performance bias), blinding of outcome assessment (detection bias), and study size of 40 participants in cross-over
- unclear for random sequence generation and allocation concealment as methods were not reported (selection bias)
- low risk of bias for incomplete outcome data (attrition bias) and selective reporting (reporting bias).

4.4 Literature – safety

As with the efficacy studies, there is a large body of literature for opioid safety. Studies below are from recent years (since 2010), and are relevant for dihydrocodeine adverse effects, including abuse, misuse and dependence.

4.4.1 Fountain et al. 2020. Fatal toxicity indices for medicine-related deaths in New Zealand, 2008–2013 [22]

The fatal toxicity index (FTI) is a measure for assessing the relative risks of death due to the medicines prescribed in a population. This study aimed to calculate FTIs for the New Zealand population using three methodologies.

Methods New Zealand coronial data describing medicine-related deaths (self-inflicted and unintended) from 1 January 2008 to 31 December 2013 were retrospectively extracted from the National Coronial Information System. Three fatal toxicity indices were derived using the number of deaths attributed to each pharmaceutical as the numerator and the total defined daily doses, number of patients and number of prescriptions as denominators (Deaths/10^6 DDD; Deaths/10,000 users; Deaths/10^6 prescriptions, respectively). In cases where more than one medicine was involved, the primary contributor to death was identified if it was the only substance with a blood or tissue level considered to be in the lethal range or the most likely drug to cause fatality and pathological/histological examination supported this finding. In cases where death was determined as due to an adverse drug reaction, the drug identified as primarily responsible for the reaction was considered to be the primary contributor.

Results There were 703 medicine-related deaths, of which 627 were assessed as due to one primary contributor. Median decedent age was 48 years (interquartile range 37–58), and 319 (51%) were male. Deaths were intentional in 252 cases (40%), unintentional in 284 (45%) and unknown in 91 (15%). The majority of deaths (n = 486, 78%) occurred in the community.

Unintentional deaths were most commonly attributed to methadone, morphine and clozapine (Table 13). Opioids, antidepressants, antipsychotics and hypnotic-anxiolytics caused most fatalities (Table 14).

Table 13: Ten leading medicines causing death: decedent age, sex, intent and location of death. New Zealand 2008-2013 (number with percentage in brackets)

[redacted]

Table 14: Deaths by medicine class: decedent age, sex, and location of death. New Zealand 2008–2013 (number with percentage in brackets)

While the FTIs for individual medicines varied by denominator applied, methadone and clozapine fatalities were prominent in all three indices (Table 15). The five leading medicines causing death per million DDDs were morphine, clozapine, methadone, oxycodone, and dosulepin. When FTIs were calculated as deaths per 10,000 users, methadone, clozapine, clomipramine, olanzapine and dosulepin were the leading medicines, and when calculated as deaths per million prescriptions, methadone, clozapine, clomipramine, morphine and dihydrocodeine were the leading medicines.

Table 15: Mean fatal toxicity indices and number of medicines deaths in New Zealand, 2008–2013

Limitations Numerator (death) data from coronial records contain variation in assessment between coroners, pathologists and toxicologists, with assessment of post-mortem toxicology results particularly challenging. Denominator (prescribing) data, as used in this study, may be incomplete due to a lack of both hospital prescribing data and the sale of some medicines over-the-counter from pharmacies or direct supermarket sales— potentially overestimating the magnitude of FTIs. This is particularly applicable to both paracetamol and codeine.

Not all medicine-related deaths are notified to the coronial service, and the level of this non-reporting is unknown. This study is likely to be an underestimate of fatalities relating to prescription medicines.

An FTI is not a measure solely of inherent drug toxicity; it also reflects the wider hazard of a medicine to a population. It is influenced by a range of pharmaceutical, individual and socio-cultural variables including drug diversion, abuse, addiction potential, access to and efficacy of medical management, induction of suicidality, cultural perspectives, prescribing indications, patient co-morbidity, intentionality and genetic factors.

Conclusion The authors conclude by stating that New Zealand prescribers should be aware of the high relative risk of death associated with methadone and clozapine; that clomipramine, dosulepin and doxepin were identified as the most dangerous antidepressants; and that zopiclone carries a similar fatal risk to benzodiazepines. Varying results were found between the FTIs calculated, making comparisons, particularly between populations, difficult.

Comment

Compared to codeine and tramadol, dihydrocodeine had a higher FTI for two of the three FTIs and ranked highly compared to many of the medicines included in the study (Table 16).

Table 16: Fatal toxicity indices for dihydrocodeine, codeine and tramadol, and ranking compared to the 24 medicines included in the study

4.4.2 Hawton et al. 2019. Relative toxicity of analgesics commonly used for intentional self-poisoning: a study of case fatality based on fatal and non-fatal overdoses [23]

Methods Using data for 2005-2012 the authors investigated case fatality (number of suicides relative to number of non-fatal self-poisonings) of paracetamol, aspirin, codeine, dihydrocodeine, tramadol, paracetamol with codeine (co-codamol), paracetamol with dihydrocodeine (co-dydramol), ibuprofen and co-proxamol (paracetamol plus dextropropoxyphene; withdrawn in the UK in 2008 due to high toxicity). Data on suicides obtained from the Office for National Statistics and on non-fatal self-poisonings from the Multicentre Study of Self-harm in England. Case fatality for specific drugs was calculated as the ratio between the number of deaths involving each drug to the total number of episodes of non-fatal self-poisoning with each drug. These were related to case fatality for paracetamol (reference drug). Paracetamol was chosen as the reference drug because it has a long history of extensive use in the UK (and other countries), including for intentional poisoning.

Results During the 8-year study period, there were 1,462 single-drug suicide deaths by poisoning, with paracetamol, tramadol, dihydrocodeine and co-codamol (paracetamol + codeine) being the most frequently involved (Table 17). There were a further 471 deaths where multiple drugs were identified and one of the

study analgesics was listed first on the death certificates. The non-fatal self-poisoning rate per 100,000 population was highest for paracetamol.

Compared to paracetamol and based on single drug deaths the case fatality index of dihydrocodeine was considerably elevated (odds ratio (OR) 12.81, 95% Confidence Interval (CI) 10.19 – 16.12) (Table 18). Case fatality indices for tramadol (OR 4.05, 95% CI 3.38 – 4.85) and codeine (OR 2.21, 95% CI 1.81 - 2.70) were also significantly higher than for paracetamol. For dihydrocodeine the relative toxicity index appeared greater in females, although no formal gender comparison was conducted.

The results when multiple drug deaths were included produced similar results (Table 19). The relative toxicity of co-proxamol (paracetamol plus dextropropoxyphene) far exceeded that of the other analgesics – although this was withdrawn in 2008. Overdoses of dihydrocodeine and tramadol were approximately 17 and 6 times, respectively, more likely to result in death than an overdose of paracetamol while an overdose of codeine was almost 3 times more likely to result in death relative to paracetamol.

The authors examined alcohol involvement in fatal single drug overdoses, as this would provide the best evidence for any interaction with specific analgesics. The number and percentage of fatal single drug overdoses in which there was evidence of alcohol involvement were, in order of relative percentages (n, %): aspirin (3, 7.9%); tramadol (27, 14.0%); paracetamol (81, 16.2%); dihydrocodeine (28, 18.7%); paracetamol and dihydrocodeine (6, 20.7%); ibuprofen (3 25.0%); paracetamol and codeine (35, 25.2%) and codeine (37, 27.6%). While there were differences between the study analgesics in terms of the proportion of alcohol involvement these do not seem to suggest major specific interactions consistent with the increases in toxicity. However, involvement of alcohol in overdoses of drugs which are likely to cause respiratory depression, especially opiates, would be expected to increase the risk of death.

The authors noted that the considerably elevated toxicity of dihydrocodeine and codeine was not found where these drugs were combined with paracetamol. They suggest whether there may be confounding factors which influence access to larger amounts of codeine or dihydrocodeine which might affect risk of fatal poisoning in some individuals, such as drug misuse and chronic pain.

Limitations Data on fatal self-poisonings were based on national data, whereas those for non-fatal poisonings were based on local data and may not be nationally representative. A substantial number of the deaths involved ingestion of multiple drugs, for which there must be uncertainty in some cases about which drugs were most likely to have contributed to death and the effect of possible interactions between drugs. However, similar results were obtained when the authors analysed case fatality based on single drug deaths and when multiple drug deaths were used but the study drugs were the first listed on the death certificates. This was based on the assumption that the first listed drug would have been the main contributor to death. For non-fatal poisonings, all drugs ingested in multiple drug overdoses were included, as the authors had no indication of what would have been the "main" drug. There was also no information on dosages of drugs and number of tablets consumed in either fatal or non-fatal overdoses.

Conclusions Dihydrocodeine and tramadol are particularly toxic in overdose and codeine is also relatively toxic. They should be prescribed with caution, particularly to individuals at risk of self-harm (eg, previous history of self-harm, family history of suicidal behaviour, depression, alcohol misuse).

Table 17: Total numbers and rates of deaths by intentional self-poisoning and undetermined intent ('suicides') in England, and the numbers of non-fatal self-poisoning episodes per year, involving each analgesic, with rates of non-fatal self-poisoning in the Multicentre Study of Self-harm in England in persons aged 15 years and over, 2005–2012

[redacted]

Table 18: Case fatality: the ratio of the number of suicides involving each drug to the number of non-fatal self-poisoning episodes relative to the equivalent ratio for paracetamol: single-drug only, by gender

[redacted]

Table 19: Case fatality: the ratio of the number of suicides involving each drug to the number of non-fatal self-poisoning episodes relative to the equivalent ratio for paracetamol: single-drug overdoses combined with multiple drug overdoses where the study analgesic the first listed drug, by gender

[redacted]

Comment

The authors did not postulate as to why toxicity with dihydrocodeine was high. They did state that toxicity of tramadol appears to be related to its tendency to cause seizures and respiratory depression.

All opioids can cause respiratory depression and DHC Continus data sheet contains a warning for respiratory depression. It also contains warnings for misuse and abuse, and is only indicated for use for chronic pain in accordance with the current guidelines on chronic pain management and where there is no psychological contraindication, medicine-seeking behaviour or history of medicine misuse.

4.4.3 Els et al. 2017. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews (Review) [24]

Objectives To provide an overview of the occurrence and nature of adverse events associated with any opioid agent (any dose, frequency, or route of administration) used on a medium- or long-term basis for the treatment of CNCP in adults.

Methods The authors searched the Cochrane Database of Systematic Reviews identify all Cochrane Reviews of studies of medium- or long-term opioid use (2 weeks or more) for CNCP in adults aged 18 and over. They assessed the quality of the reviews using the AMSTAR criteria (Assessing the Methodological Quality of Systematic Reviews) as adapted for Cochrane Overviews. They assessed the quality of the evidence for the outcomes using the GRADE framework.

Main results A total of 16 reviews were included in their overview, of which 14 presented unique quantitative data. These 14 Cochrane Reviews investigated 14 different opioid agents that were administered for time periods of two weeks or longer. The longest study was 13 months in duration, with most in the 6- to 16-week range. The quality of the included reviews was high using AMSTAR criteria, with 11 reviews meeting all 10 criteria, and 5 of the reviews meeting 9 out of 10, not scoring a point for either duplicate study selection and data extraction, or searching for articles irrespective of language and publication type. The quality of the

evidence for the generic adverse event outcomes according to GRADE ranged from very low to moderate, with risk of bias and imprecision being identified for the following generic adverse event outcomes: any adverse event, any serious adverse event, and withdrawals due to adverse events. A GRADE assessment of the quality of the evidence for specific adverse events led to a downgrading to very low- to moderate-quality evidence due to risk of bias, indirectness, and imprecision.

They calculated the equivalent milligrams of morphine per 24 hours for each opioid studied (buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol, tilidine, and tramadol). In the 14 Cochrane Reviews providing unique quantitative data, there were 61 studies with a total of 18,679 randomised participants; 12 of these studies had a cross-over design with two to four arms and a total of 796 participants. Based on the 14 selected Cochrane Reviews, there was a significantly increased risk of experiencing any adverse event with opioids compared to placebo (risk ratio (RR) 1.42, 95% confidence interval (CI) 1.22 to 1.66) as well as with opioids compared to a non-opioid active pharmacological comparator, with a similar risk ratio (RR 1.21, 95% CI 1.10 to 1.33). There was also a significantly increased risk of experiencing a serious adverse event with opioids compared to placebo (RR 2.75, 95% CI 2.06 to 3.67). They found significantly increased risk ratios with opioids compared to placebo for a number of specific adverse events: constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting.

There was no data on any of the following prespecified adverse events of interest in any of the included reviews in this overview of Cochrane Reviews: addiction, cognitive dysfunction, depressive symptoms or mood disturbances, hypogonadism or other endocrine dysfunction, respiratory depression, sexual dysfunction, and sleep apnoea or sleep-disordered breathing. They found no data for adverse events analysed by sex or ethnicity.

Conclusions A number of adverse events, including serious adverse events, are associated with the medium- and long-term use of opioids for CNCP. The absolute event rate for any adverse event with opioids in trials using a placebo as comparison was 78%, with an absolute event rate of 7.5% for any serious adverse event.

Based on the adverse events identified, clinically relevant benefit would need to be clearly demonstrated before long-term use could be considered in people with CNCP in clinical practice. The authors stated that as here is limited evidence to support the efficacy of long-term use of opioids in CNCP, an absence of evidence of improvement in function and pain scores when high doses of opioids are used, and robust evidence of harm associated with medium- to long-term opioid use, prescribers should proceed with caution prior to initiating treatment with opioids and with even greater caution when transitioning from short-term to medium-and long-term use of opioids for people with CNCP. A number of adverse events that they would have expected to occur with opioid use were not reported in the included Cochrane Reviews.

Going forward, the authors recommend more rigorous identification and reporting of all adverse events in randomised controlled trials and systematic reviews on opioid therapy. The absence of data for many adverse events represents a serious limitation of the evidence on opioids. They also recommend extending study follow-up, as a latency of onset may exist for some adverse events.

Comment

This review covered a range of opioids for treatment of chronic noncancer pain; it was not restricted to dihydrocodeine.

4.4.4 Cooper et al. 2017. Prevalence and incidence trends for diagnosed prescription opioid use disorders in the United Kingdom [25]

Aim To examine national trends in the prevalence and incidence of physician-diagnosed opioid use disorders in the UK.

Methods In a retrospective electronic health care database analysis using data from the UK Clinical Practice Research Datalink (CPRD), the authors identified persons receiving a first opioid prescription between January

1, 2008 and December 31, 2012. Persons with an opioid use disorder were identified by Read codes assigned by patients' physicians within 6 months following an opioid prescription. They calculated prevalence and incidence rates by dividing the analysis population by the total number of patients exposed (prevalence) or the total patient-years of exposure (incidence) using the 'exact' Clopper-Pearson Binomial method. Duration of opioid exposure (calculated in days) was estimated based on each prescription date and the quantity of opioid prescribed, as recorded in the CPRD database. Long-term opioid use was defined as a patient having ≥3 consecutive opioid prescriptions within any 6-month period during the duration of the study.

Results 1,550,307 patients were eligible for the analyses, 715 of which were diagnosed with opioid use disorder. Of these 715 diagnosed cases, 465 were true incident cases (developed OUD during the period of the study, and who had an available healthcare record ≥6 months prior to the start of the study with no evidence of a history of opioid use disorders). The analysis included 714,699 person-years of prescription opioid exposure.

Compared to individuals who received an opioid prescription but who did not develop an opioid use disorder, diagnosed patients were more likely to be younger, male and to have a history of smoking and alcohol- and substance-abuse disorders. The baseline characteristics of incident cases were not dissimilar to diagnosed patients as one group (Table 20), except for the percentage of men and the percentage of 'other substance abuse (including alcohol)', both of which were lower among incident cases.

The 5-year period prevalence of opioid use disorders was 4.61 (95% CI 4.28-4.96) per 10,000 individuals, or 0.05%. The incidence rate of opioid use disorders was of 6.51 (95% CI 5.93-7.13) patients per 10,000 patient-years exposed. If all diagnosed patients were considered as incident cases, the 5-year incidence rate as one group would be 9.80 (95% CI 9.10–10.55) per 10,000 patient-years exposed (Table 19). The prevalence and incidence rate for all diagnosed patients was highest among men and those aged 25–34 years, and lowest among women and those aged 55 years and older.

When examined by study year, there was no clear suggestion of a changing trend over time. When stratified by opioid drug, trends in the incidence rate during the study were either stable (ie, codeine and tramadol), increasing (ie, morphine) or decreasing (ie, dihydrocodeine) (Figure 12). They were not able to examine for trends in opioid use disorders for buprenorphine, oxycodone, fentanyl, metazinol, diamorphine, dipipanone, hydromorphone, methadone, papaveretum, pentazocine, pethidine, and tapentadol due to too few cases

The median duration from first opioid prescription to being diagnosed with an opioid use disorder was 0.6 (IQR 0.2–1.9) years for diagnosed patients and 1.1 (IQR 0.3–2.5) years for incident cases. The most frequently first prescribed opioid drug was codeine (40.6%) followed by dihydrocodeine (32.0%), tramadol (15.9%), buprenorphine (4.5%), morphine (4.3%), oxycodone (2.5%), and fentanyl (1.5%). Consistent with this, the opioid drug which was most frequently prescribed in the 6 months prior to a diagnosis of an opioid use disorder was codeine (43.4%) followed by dihydrocodeine (35.8%), tramadol (23.2%), morphine (9.2%), buprenorphine (6.2%), oxycodone (5.2%), and fentanyl (3.9%). Among diagnosed patients, a total of 185 (25.9%) were concomitantly prescribed benzodiazepines and 593 (82.9%) were long-term prescription opioid users. Among patients without a diagnosis of an opioid use disorder, 37.8% were identified as being long-term prescription opioid users.

Table 20: Characteristics of persons prescribed opioids, diagnosed opioid use disorder patients, and incident cases, CPRD: 2008–2012

[redacted]

Table 21: 5-year prevalence and incidence rates of physician-diagnosed opioid use disorders in CPRD: 2008-2012

[redacted]

Figure 12: Trends in prescription opioid use disorders, UK: 2008–2012

[redacted]

Limitations A number of validation studies have demonstrated the high validity of the diagnoses codes recorded in CPRD, reporting strong measures of sensitivity and specificity, but this has not been undertaken for the codes related to problematic opioid use disorders. Data on medications given during hospitalisation, medications provided in specialist care, and medications provided by a hospital following patient discharge are not recorded in patients' medical records. The likely impact of this will have been an underestimation of drug use and, potentially, an underestimation of the extent of opioid use disorders. The authors excluded patients who received an opioid prescription used for the purpose of substitution therapy, however, some of the opioid use disorder cases in the study may have received a diagnosis of an opioid use disorder based on illicit opioid use. This would, however, have led rather to an overestimation of prevalence and incidence. There is also the possibility of significant under-diagnosis of OUD by the patient's physician so additional data sources are needed to confirm prevalence and incidence.

Conclusions The authors concluded that the study demonstrates that despite the marked increase in overall opioid prescribing in the UK in the past decade, there has not been an increase in the incidence of physician-diagnosed opioid use disorders.

Comment

Although New Zealand and the UK have similar publicly funded health systems, the results of this study may not be generalisable to the New Zealand population based on differences in funded opioid medications and prescribing guidelines.

4.4.5 Steynor et al. 2015. Always consider the possibility of opioid induced respiratory depression in patients presenting with hypercapnic respiratory failure who fail to improve as expected with appropriate therapy [26]

This is a case report of hypercapnic respiratory failure in a 65-year-old female patient, in what was initially thought to be an exacerbation of COPD. The patient failed to improve with treatment as expected which led to the empirical administration of naloxone resulting in a dramatic reversal of her respiratory failure. The patient was subsequently discovered to be taking regular dihydrocodeine for chronic back pain. She took modified release dihydrocodeine for back pain and, four days prior to admission, had increased her dose from the British National Formulary recommended maximum of 120 mg bd to 240 mg bd on her own initiative. In addition, approximately 8 hours prior to presentation, she had taken a further breakthrough dose for an exacerbation of her pain.

The authors argue that is important to consider other causes for alteration in mental state in patients with hypercapnic respiratory failure. All opioids have the potential to cause significant respiratory depression. The authors state that while less-commonly encountered, modified-release dihydrocodeine may be favoured by some patients as it provides up to 12 hours of pain relief. In addition, dihydrocodeine has several active metabolites, all of which are active at the mu opioid receptor responsible for mediating respiratory depression. Some patients may therefore be susceptible to side effects of the drug many hours after ingestion. Delayed gastric emptying in the context of acute illness may exacerbate this effect. The sine qua non for diagnosis of opioid induced ventilatory impairment is a prompt therapeutic effect of a trial of naloxone as was seen in this case and a trial of therapy should be given in any suspected case.

Comment

The DHC Continus data sheet contains a warning for respiratory depression, which includes the following:

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of DHC CONTINUS® but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma).

Opioids should be used with caution and with close monitoring in these patients. The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression.

4.4.6 Zamparutti et al. 2011. Deaths of opiate/opioid misusers involving dihydrocodeine, UK, 1997–2007 [27]

Aims Although its effectiveness is somewhat controversial, it appears that dihydrocodeine (DHC) is still prescribed in the UK as an alternative to both methadone and buprenorphine for the treatment of opiate addiction.

Methods The authors analysed National Programme on Substance Abuse Deaths (np-SAD) data covering the period 1997–2007 voluntarily supplied by coroners. The np-SAD was established in 1997 regularly receives information from coroners on a voluntary basis on deaths related to drugs in both addicts and non-addicts in England and Wales, Northern Ireland, the Channel Islands and the Isle of Man. To be recorded in the np-SAD database as a drug-related death, at least one of the following criteria must be met: (i) presence of one or more psychoactive substances directly implicated in death, (ii) history of dependence or abuse of drugs and (iii) presence of controlled drugs at post-mortem. Alcohol is included only when implicated in combination with other qualifying drugs. The response rate from Coroners in England and Wales has been as high as 95%. All cases pertaining to victims with a clear history of opiate/opioid misuse and in which DHC, either on its own or in combination, was identified at post-mortem toxicology and/or implicated in death, were extracted from the database.

Results Dihydrocodeine, either alone or in combination, was identified in 584 fatalities meeting the selection criteria (Table 20). In 44% of all cases, it was directly implicated in the cause of death. These cases represented about 6.8% of all opiate/opioid-related deaths during this period. Typical DHC cases identified were White males in their early thirties (Table 22).

Most (489, 96.1%) victims died from polydrug intake (Table 23, with a mean of 3.30 (SD = 1.25) substances found at post-mortem. A significant difference in the number of drugs ingested between the accidental and intentional deaths groups was identified (3.37 vs. 2.80 respectively, $P < 0.001$). Heroin/morphine ($P < 0.001$), methadone ($P = 0.006$) and hypnotics/sedatives ($P = 0.012$) were more likely to be identified in accidental deaths. Conversely, both paracetamol ($P = 0.043$) and antidepressants ($P = 0.046$) were more frequently identified in the intentional deaths subgroup. DHC was more frequently identified as the only drug at post-mortem in the suicidal subgroup ($P < 0.0001$).

Complete information on prescribed medication was made available for 450 cases only (Table 24). Prior to death, DHC was regularly prescribed to 202 (44.9%) subjects. In comparison to those prescribed with DHC, victims in which illicit DHC was identified were more likely to have been prescribed with methadone ($P < 0.0001$) but presented as well with a higher proportion of deaths due to both street/illicit methadone ($P = 0.002$) and hypnotics/sedatives ($P = 0.029$). Conversely, victims prescribed with DHC were more likely to have been prescribed with hypnotics/sedatives ($P < 0.0001$) as well. In this subgroup, illicit antidepressants were more likely to be identified at post-mortem ($P = 0.006$).

In 14 cases, a concurrent prescription of methadone and DHC was identified. The authors stated that given that all the victims presented with a clear history of opiate/opioid misuse, one could conclude that DHC, although unlicensed for this use, was actually prescribed for the treatment of opiate addiction itself. DHC maintenance treatment deserves more attention compared with methadone or other opioids, as DHC has weaker pharmacological effects and studies about the effectiveness of DHC as a treatment for addiction are limited.

Limitations May include variations in coroners' reporting rates over time, lack of total geographical coverage of coroner's jurisdictions, incomplete information relating to prescription of psychoactive medications in almost one case out of four and lack of information on the concentration of DHC detected in body fluids, so that some victims might have had only traces of the substance. As mortality rates (eg, number of deaths out of

number of DHC prescriptions) were not here calculated, it may be difficult to determine the true extent of risks associated with DHC consumption. The sample did not include deaths related to the prescription of other substitution therapies, so one may be unable to determine whether the DHC prescription was in fact associated with an increased risk of death relative to other modalities.

Conclusions Opiate/opioid misusers should be educated about risks associated with polydrug intake. More in particular, co-administration of DHC with heroin, methadone and benzodiazepines may increase the risk of accidental fatal overdose. Prescribers should carefully consider pharmacological intervention alternative to DHC (eg, methadone, buprenorphine) when managing and treating opiate addiction. More resources are required to do prospective research in this area.

Table 22: Deaths of opiate/opioid misusers involving dihydrocodeine UK, 1997–2007. Victims' basic socio-demographics and comparisons between accidental and intentional subgroups*

Table 23: Deaths of opiate/opioid misusers involving dihydrocodeine UK,1997–2007. Substances identified at post-mortem and comparisons between accidental and intentional subgroups *

Table 24: Deaths of opiate/opioid misusers involving dihydrocodeine (DHC) UK, 1997–2007. Psychoactive medication prescribed, substances identified at post-mortem and comparisons between prescribed and non-prescribed DHC subgroups*

Comment

DHC is not indicated in the UK or NZ to treat opioid use disorder and therefore it is not known if DHC is used off-label in this way in New Zealand. The study population was based on DHC mortality data for victims with a clear history of opiate/opioid abuse. These results may not be generalisable to the general population of DHC users in the UK or NZ. This study was included to show the patterns of polydrug use and poisoning intent (accidental or intentional) in opiate abusers who had died and DHC was implicated in the death.

4.5 International information

4.5.1 Approval status

4.5.1.1 Australia

There is only one DHC product approved and available in Australia: Rikodeine, an oral liquid formulation indicated for relief of stubborn, unproductive cough in children and adults aged 6 years and older [28]. It is a classified as a Pharmacist Only Medicine (Schedule 3) and is available over-the-counter with pharmacist advice. The prescribing information for Rikodeine includes the safety warnings implemented as part of Australia's Opioid Reforms [29].

Although not relevant to the approved dihydrocodeine formulation in Australia, the indications for modified-release and immediate-release opioids were updated as part of the Opioid Reforms [29]. Indications for modified release opioids (eg, sustained-release tramadol, available in Australia and New Zealand as Tramal Sustained Release tablets) are:

> [Product] is indicated for the management of severe pain where:
>
> - other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and

- the pain is opioid-responsive, and
- requires daily, continuous, long term treatment.

[Product] is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.

[Product] is not indicated as an as-needed (PRN) analgesia.

Immediate release products (eg, immediate release tramadol, available in Australia and New Zealand as Tramal Capsules, Solution for Injection and Oral Drops) are:

> [Product] is indicated for the short-term management of severe pain for which other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain.

4.5.1.2 USA

DHC is available by prescription in combination with acetaminophen and caffeine. It is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate (not tolerated or do not provide adequate analgesia) [30]. The product label (ie, the data sheet) has a boxed warning that includes information about addiction, misuse, and abuse.

4.5.1.3 Canada

DHC is not approved in Canada.

4.5.1.4 Singapore

DHC is not approved in Singapore.

4.5.1.5 UK

DHC is available and approved for use in the treatment of mild to moderate pain, as a single substance or in combination with paracetamol. There are 12 products marketed in the UK [31] . All products are prescription except a paracetamol (500 mg) and DHC (7.5mg) combination product which is pharmacy only.

Following a 2019 expert working group review of dependence and addiction to the opioids as a class, the opioid product labelling and product information was updated in the UK [32]. The packaging must have the warnings 'Can cause addiction' and 'Contains opioid'. Product information must include consistent warnings of the risks of tolerance and dependence and addiction.

4.6 Monitoring communication

On 12 August 2021, Medsafe published a monitoring communication seeking feedback from consumers and healthcare professionals regarding the risks and benefits of dihydrocodeine.

Medsafe received five submissions: four from healthcare professionals (individuals and organisations) and one from a patient. The submissions are copied verbatim below (with individual names/identifying information removed).

4.6.1 Healthcare professional feedback

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.6.2 Consumer feedback

[redacted]

Comment

Only five submissions were received so it is difficult to know if the responses truly reflect healthcare professionals' and consumers' views on dihydrocodeine.

Four submissions supported the ongoing use of dihydrocodeine. One of these stated that dihydrocodeine is an effective alternative option in people who can't tolerate other medicines and suggested that it be restricted to specialist pain physicians if there are concerns about misuse and abuse. Another supported its use in the approved indications, with close monitoring and patient education. The consumer respondent stated that if dihydrocodeine was removed or more heavily restricted, then an alternative should be provided in its place.

The GP that did not support its use stated that dihydrocodeine is not appropriate for acute pain, the evidence base is lacking for chronic pain, there are better alternatives for end of life care.

5 SECTION 36(1) NOTICE

5.1 Teva Pharma (Dihydrocodeine Controlled Release Actavis 60mg)

5.2 Mundipharma (DHC Continus 60mg)

5.2.1 A summary of the efficacy of their dihydrocodeine product in the approved indication, including absolute numbers of the patients expected benefits where available and data on the efficacy of comparators.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6 DISCUSSION AND CONCLUSIONS

This paper presents a benefit-risk review of dihydrocodeine based on available usage information, harm identified from spontaneous case reports, hospital discharges and mortality and National Poisons Centre data, efficacy and safety data from the literature, and feedback from New Zealand health care professionals and consumers.

Dihydrocodeine was first synthesised in 1911 and has been used as an analgesic agent since 1956. The modified release form was introduced in the UK in 1986. Dihydrocodeine is only available on prescription in New Zealand and is classified as a controlled medicine, which places restrictions on prescribing and supply. It is indicated for:

- treatment of post-operative pain, and pain associated with cancer
- treatment of opioid-responsive, chronic severe pain of non-malignant origin, after other conservative methods of analgesia have been tried. It is indicated for use in accordance with the current guidelines on chronic pain management and where there is no psychological contraindication, medicine-seeking behaviour or history of medicine misuse.

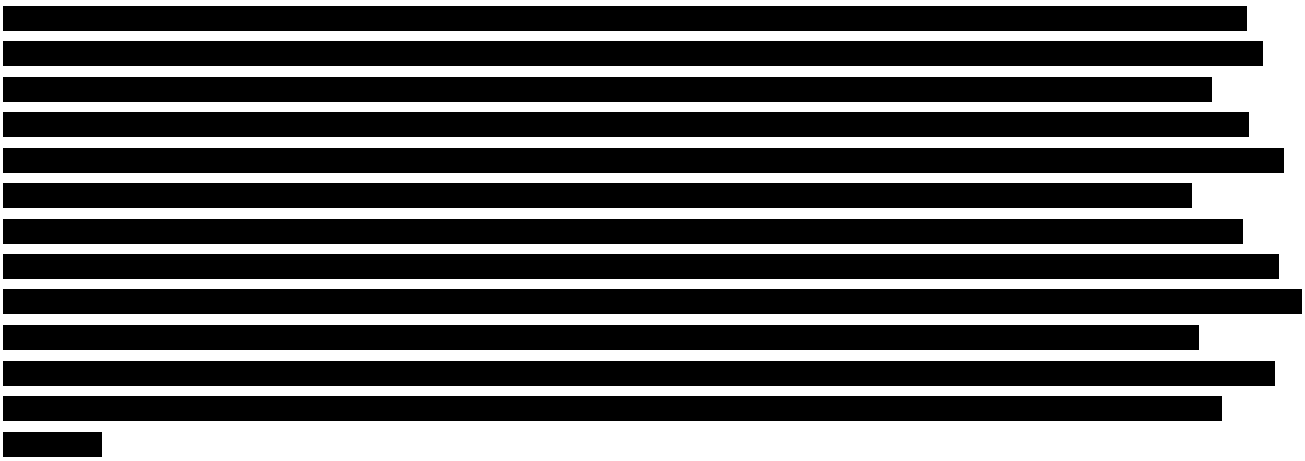
There are two modified-release dihydrocodeine products approved in New Zealand, DHC Continus (approved in 1992) and Dihydrocodeine Controlled Release Actavis (approved in 2015), although only the former is available. Modified release dihydrocodeine is approved in the UK and Switzerland. In Australia, the only approved formulation is an oral liquid, and it is used as an antitussive. In the US, dihydrocodeine is only available in combination with caffeine and acetaminophen (paracetamol).

Prescribing guidelines describe opioids in general, rather than being specific to dihydrocodeine. They do not recommend the use of modified release opioids for acute pain due to the risk of respiratory depression. And they should only be used in exceptional circumstances for chronic non-cancer pain as there is limited evidence for their efficacy. Opioid use in cancer pain is supported, although the evidence for dihydrocodeine is limited.

As with all opioids, dihydrocodeine is associated with numerous adverse effects, some of which have serious and potentially fatal consequences. In overdose, dihydrocodeine appears to be more toxic than other opioids.

Opioids can cause respiratory depression through their action on the mu opioid receptor and dihydrocodeine has several active metabolites, all of which are active at this receptor. Modified-release dihydrocodeine is taken twice a day and provides up to 12 hours of pain relief. Some patients may therefore be susceptible to side effects of the medicine many hours after ingestion.

The sponsors were directed under section 36(1) of the Medicines Act to provide safety and efficacy data for their products. If the sponsor is unable to satisfy the Director-General that the product is safe and effective for its therapeutic purpose, conditions on the use of the medicine may be imposed or the consent for distribution of the product may be revoked.



Following a recommendation from the Committee, the DHC Continus data sheet was recently updated to align with the safety warnings seen in the Australian product information. New warnings were added for: Hazardous and harmful use; Use in chronic non-cancer pain; Accidental ingestion/exposure; Hyperalgesia; Ceasing opioids.

Although dihydrocodeine is not widely used compared to other weak opioids, Medsafe (as the Director General of Health's delegate) has concerns about its safety, particularly in accidental and intentional overdose, and is therefore referring DHC Continus and Dihydrocodeine Controlled Release Actavis to the Committee under section 36(2) of the Medicines Act. If the Committee decides that the benefit-risk balance is not favourable for these products, a recommendation can be made to the Director-General of Health under section 36(1) of the Act to revoke consent for the two approved products or to impose conditions on their use.

As a condition of use, the indications could be restricted to align with modified release indications in Australia:

> [Product] is indicated for the management of severe pain where:
>
> - other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
> - the pain is opioid-responsive, and
> - requires daily, continuous, long term treatment.
>
> [Product] is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.
>
> [Product] is not indicated as an as-needed (PRN) analgesia.

The sponsors could also be directed to provide Consumer Medicine Information leaflets for their products.

7 ADVICE SOUGHT

The Committee is asked to advise:

- whether the benefit-risk balance is favourable for the use of dihydrocodeine for pain treatment
- if any regulatory action is required to improve the balance of benefits and risks.

8 ANNEXES

- Annex 1 – CARM data
- [redacted]
- [redacted]
- [redacted]

9 REFERENCES

1. Faculty of Pain Medicine of the Royal College of Anaesthetists. *About pain* URL: https://fpm.ac.uk/opioids-aware-understanding-pain-medicines-pain/about-pain (accessed 15 November 2020).
2. BPAC NZ. 2018. *Unintentional misuse of prescription medicines* 26 October 2018. URL: https://bpac.org.nz/2018/misuse.aspx (accessed 14 November 2020).
3. Kaye A, Jones M, Kaye A, et al. 2017. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: Part 1. *Pain Physician* 20(2S): S93-S109. URL: https://www.painphysicianjournal.com/current/pdf?article=NDIwMw%3D%3D&journal=103 (accessed 5 November 2020).
4. Substance Use and Mental Health Services Administration. 2020. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health.* URL: https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR1PDFW090120.pdf (accessed 15 November 2020).
5. National Academies of Sciences Engineering and Medicine. 2017. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.* URL: https://www.nap.edu/catalog/24781/pain-management-and-the-opioid-epidemic-balancing-societal-and-individual (accessed 25 June 2020).
6. Foy R, Leaman B, McCrorie C, et al. 2016. Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. *BMJ Open* 6(5): e010276. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874107/ (accessed 25 June 2020).
7. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. 2020. *Acute Pain Management: Scientific Evidence (Fifth edition).* URL: https://www.anzca.edu.au/resources/college-publications/acute-pain-management/apmse5.pdf (accessed 3 November 2021).
8. Australian and New Zealand College of Anaesthetists (ANZCA) and Faculty of Pain Medicine (FPM). 2018. *Position statement on the use of slow-release opioid preparations in the treatment of acute pain.* URL: https://www.anzca.edu.au/getattachment/d9e2a7c5-0f17-42d3-bda7-c6dae7e55ced/Position-statement-on-the-use-of-slow-release-opioid-preparations-in-the-treatment-of-acute-pain (accessed 28 September 2020).
9. BPAC NZ. 2018. *The prinicples of managing acute pain in primary care* February 2018. URL: https://bpac.org.nz/2018/acute-pain.aspx (accessed 10 November 2020).
10. Australian and New Zealand College of Anaesthetists (ANZCA) and Faculty of Pain Medicine (FPM). 2020. *Statement regarding the use of opioid analgesics in patients with chronic non-cancer pain* April 2020. URL: https://www.anzca.edu.au/getattachment/7d7d2619-6736-4d8e-876e-6f9b2b45c435/PS01(PM)-Statement-regarding-the-use-of-opioid-analgesics-in-patients-with-chronic-non-cancer-pain (accessed 28 September 2020).
11. Palliative Care Australia. 2019. *Sustainable access to prescription opioids for use in palliative care - Position statement.* URL: https://palliativecare.org.au/wp-content/uploads/dlm_uploads/2019/05/PalliativeCare-Opioid-Position-Final.pdf (accessed 11 November 2021).

12. Australian Institute of Health and Welfare. 2018. *Opioid Harm in Australia and Comparisons Between Australia and Canada.* URL: https://www.aihw.gov.au/getmedia/605a6cf8-6e53-488e-ac6e-925e9086df33/aihw-hse-210.pdf.aspx?inline=true (accessed 24 June 2020).
13. Mundipharma New Zealand. 2021. *DHC Continus New Zealand Data Sheet* September 2021. URL: https://www.medsafe.govt.nz/profs/Datasheet/d/DHCContinustab.pdf (accessed 27 October 2021).
14. Leppert W and Woroń J. 2016. Dihydrocodeine: safety concerns. *Expert Review of Clinical Pharmacology* 9(1): 9–12. DOI: 10.1586/17512433.2016.1092871 (accessed 2 November 2021).
15. Expert Committee on Drug Dependence. 2019. *Pre- Review Report: Preparations of codeine listed in Schedule lll of the 1961 Single Convention on Narcotic Drugs: Acetyldihydrocodeine, Codeine, Dihydrocodeine, Ethlymorphine, Nicocodine, Nicodicodine, Norcodeine, Pholcodine.* URL: https://www.who.int/medicines/access/controlled-substances/Final_codeine.pdf (accessed 3 November 2021).
16. Leppert W. 2011. CYP2D6 in the metabolism of opioids for mild to moderate pain. *Pharmacology* 87(5–6): 274–85. URL: https://www.karger.com/Article/Pdf/326085 (accessed 2 November 2021).
17. Yuan H, Chang Q-Y, Chen J, et al. 2021. A retrospective analysis of the effects of different analgesics on the pain of patients with traumatic thoracolumbar fractures in the peri-treatment period. *Journal of Orthopaedic Surgery and Research* 16(1): 268. DOI: 10.1186/s13018-021-02401-w (accessed 15 November 2021).
18. Busse J, Wang L, Kamaleldin M, et al. 2018. Opioids for chronic noncancer pain: a systematic review and meta analysis. *Journal of the American Medical Association* 320(23): 2448–60. DOI: 10.1001/jama.2018.18472 (accessed 15 November 2021).
19. Frank B, Serpell M, Hughes J, et al. 2008. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *British Medical Journal* 336(7637): 199–201. DOI: 10.1136/bmj.39429.619653.80 (accessed 2 November 2021).
20. Leppert W and Majkowicz M. 2010. The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain. *International Journal of Clinical Practice* 64(12): 1681–7. DOI: https://doi.org/10.1111/j.1742-1241.2010.02422.x (accessed 2 November 2021).
21. Wiffen P, Derry S and Moore R. Tramadol with or without paracetamol (acetaminophen) for cancer pain. *Cochrane Database of Systematic Reviews* 2017, Issue 5, Art. No. CD012508. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6481722/ (accessed 2 November 2021).
22. Fountain J, Tomlin A and Reith D. 2020. Fatal toxicity indices for medicine-related deaths in New Zealand, 2008–2013. *Drug Safety* 43: 223–32. DOI: https://doi.org/10.1007/s40264-019-00885-4 (accessed 2 November 2021).
23. Hawton K, Ferrey A, Casey D, et al. 2019. Relative toxicity of analgesics commonly used for intentional self-poisoning: A study of case fatality based on fatal and non-fatal overdoses. *Journal of Affective Disorders* 246(Mar 1): 814–19. DOI: 10.1016/j.jad.2019.01.002 (accessed 2 November 2021).
24. Els C, Jackson T, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017, Issue 10, Art. No. CD012509. URL: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012509.pub2/epdf/full(accessed 2 November 2021).
25. Cooper A, Willis J, Fuller J, et al. 2017. Prevalence and incidence trends for diagnosed prescription opioid use disorders in the United Kingdom. *Pain Therapy* 6(1): 73–84. DOI: 10.1007/s40122-017-0070-9 (accessed 15 November 2021).
26. Steynor M and MacDuff A. 2015. Always consider the possibility of opioid induced respiratory depression in patients presenting with hypercapnic respiratory failure who fail to improve as expected with appropriate therapy. *Case Reports in Critical Care* 2015(Mar 29): 562319. DOI: 10.1155/2015/562319 (accessed 15 November 2021).

27. Zamparutti G, Schifano F, Corkery J, et al. 2011. Deaths of opiate/opioid misusers involving dihydrocodeine, UK, 1997–2007. *British Journal of Clinical Pharmacology* 72(2): 330–7. DOI: 10.1111/j.1365-2125.2011.03908.x (accessed 2 November 2021).
28. iNova Pharmaceuticals (Australia) Pty Limited. 2021. *Rikodeine Australian Product Information* 24 August 2021. URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2021-PI-01834-1&d=20211101172310101 (accessed 1 November 2021).
29. Therapeutic Goods Administration. 2021. *Prescription opioids: What changes are being made and why* updated 22 June 2021. URL: https://www.tga.gov.au/prescription-opioids-what-changes-are-being-made-and-why (accessed 10 November 2021).
30. Larken Laboratories Inc. 2021. *Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Tablets - US Product Label* October 2021. URL: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=28bb5975-32f6-414a-84ed-c376da575e3f (accessed 3 November 2021).
31. Electronic Medicines Compendium (eMC). 2021. *Dihydrocodeine - search results* URL: https://www.medicines.org.uk/emc/search?q=dihydrocodeine (accessed 3 November 2021).
32. Medicines and Healthcare products Regulatory Agency. 2020. Opioids: risk of dependence and addiction. *Drug Safety Update* 14(2): 1. URL: https://www.gov.uk/drug-safety-update/opioids-risk-of-dependence-and-addiction (accessed 25 September 2020).
33. WHO Expert Committee on Drug Dependence. 2020. *Forty second report.* URL: https://apps.who.int/iris/bitstream/handle/10665/331486/9789240001848-eng.pdf (accessed 3 November 2021).
34. World Health Organization. 2021. *Expert Committee on Drug Dependence - About us.* URL: https://www.who.int/groups/who-expert-committee-on-drug-dependence/about (accessed 3 November 2021).
35. Al-Asmari A and Anderson R. 2010. The role of dihydrocodeine (DHC) metabolites in dihydrocodeine-related deaths. *Journal of Analytical Toxicology* 34(8): 476–90. DOI: 10.1093/jat/34.8.476 (accessed 16 November 2021).
36. Caré W, Langrand J, Vodovar D, et al. 2020. Trends in severe opioid-related poisonings and fatalities reported to the Paris poison control center – a 10-year retrospective observational study [abstract only]. *Fundamental & Clinical Pharmacology* 34(4): 495–503. DOI: 10.1111/fcp.12534 (accessed 16 November 2021).