Medicines Adverse Reactions Committee

Meeting date	3/12/2020	Agenda item	3.2.2
Title	**Opioids and abuse, misuse and dependence**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Buprenorphine Codeine Dihydrocodeine Fentanyl Methadone Morphine Oxycodone Pethidine Tramadol	**Product name** **Sponsor** See Annex 1 for the full list of opioids approved in New Zealand		
PHARMAC funding	All opioids in Annex 1 have at least one product funded on the Hospital and Community Schedules.		
Previous MARC meetings	169th meeting – held 9 March 2017: Concomitant use of opioids, benzodiazepines and other CNS depressants and the risk of serious side effects		
International action	• FDA - Risk Evaluation and Mitigation Strategy (REMS) required for all opioids; prescribing information updates • MHRA – warnings on package labelling, updates to prescribing information, safety leaflets for patients • TGA – smaller pack sizes, boxed warnings and class statements in prescribing information and consumer medicine information, indication review • Health Canada – Mandatory risk management plans for prescription opioids, Warning sticker and patient information handout		
Prescriber Update	The following is a list of recent articles only. • Spotlight on tramadol including updated advice for use in children June 2020 • Spotlight on Codeine June 2018 • Medicines Interacting with Methadone June 2018 • Transdermal Opioid Patches - Stick to the Correct Application March 2020		
Classification	See Annex 1. Medicines Regulations 1984 and the Misuse of Drugs Act 1975.		
Usage data	See section 2.5		
Advice sought	**The Committee is asked to advise:** • Whether there is evidence of an abuse, misuse and dependence problem with opioids in New Zealand?		

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1 PURPOSE

Opioids are used for pain treatment. They are generally indicated for moderate to severe acute pain and for cancer pain. They are not recommended for chronic non-cancer pain due to concerns over the long-term efficacy and safety of treatment, including the risk of abuse, misuse and dependence.

There has been international concern over increases in opioid prescribing, mainly attributed to prescribing for chronic non-cancer pain [1]. The opioid epidemics in the USA and Canada coincided with sharp increases in prescription opioid-related deaths and overdoses. National governments and their respective medicines regulators have implemented various legislative changes and regulatory actions with the aim of limiting opioid harm in their jurisdictions.

There are a number of opioids available in New Zealand. The purpose of this paper is to review the information on opioid abuse, misuse and dependence.

2 BACKGROUND

2.1 Pain

Acute (short term) pain is usually related to an obvious injury such as dental disease, fracture or operation [2]. 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 [2]. 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 [2]. 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 Opioids

Opioids, which can be chemically synthesised or derived from the opium poppy plant, are a group of compounds that activate the brain's opioid receptors, a class of receptors that influence perceptions of pain and euphoria and are involved in the regulation of breathing [3]. Some of the more commonly known and used opioids are morphine, heroin, methadone, buprenorphine, codeine, tramadol, oxycodone and hydrocodone. They are used as medicines to treat pain and opioid dependence. If used in excess or without proper medical supervision, opioids can cause fatal respiratory depression. See Annex 1 for the opioids currently approved in New Zealand.

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 [4]. '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. Codeine is considered a weak opioid as it must be metabolised to morphine to achieve most of its analgesic effect. See Table 1.

Table 1: 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).

2.2.1 Approval, classification and funding

There are many opioid products approved in New Zealand. See Annex 1 for a full listing (grouped alphabetically by active ingredient), including the product name, form and dose, sponsor, classification and approval date.

Table 2 below is a summary, by active ingredient, of the classification and funding status for the opioids currently approved in New Zealand. All opioids are classified as prescription medicines under the Medicines Regulations 1984, and most are also classified as Class B or C controlled drugs under the Misuse of Drugs Act 1975. Note that 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 [5].

Table 2: Summary of opioids approved in New Zealand by active ingredient – classification and funding status (community and hospital)

Opioid	Classification		Funded	
	Medicines Regulations 1984	Misuse of Drugs Act 1975	Community[a]	Hospital[b]
Alfentanil	Prescription	Class B3 Controlled Drug	No	Yes
Buprenorphine	Prescription	Class C4 Controlled Drug	No	No
Buprenorphine with naloxone	Prescription	Class C4 Controlled Drug	Yes	Yes
Codeine	Prescription	Class C2 Controlled Drug Class C6 Controlled Drug[c]	Yes	Yes
Codeine combination products	Prescription[d]	-	Yes[e]	Yes[e]
Dihydrocodeine	Prescription	Class C2 Controlled Drug Class C6 Controlled Drug[c]	Yes	Yes
Fentanyl	Prescription	Class B3 Controlled Drug	Yes	Yes
Methadone	Prescription	Class B3 Controlled Drug	Yes	Yes
Morphine	Prescription Pharmacy only[f]	Class B1 Controlled drug	Yes	Yes
Oxycodone	Prescription	Class B3 Controlled Drug	Yes	Yes
Pethidine	Prescription	Class B3 Controlled Drug	Yes	Yes
Remifentanil	Prescription	Class B3 Controlled Drug	No	Yes
Tramadol	Prescription	-	Yes	Yes

a. PHARMAC. 2020. Online Pharmaceutical Schedule – November 2020. URL: https://pharmac.govt.nz/pharmaceutical-schedule/community-section-b/ (accessed 3 November 2020).

b. PHARMAC. 2020. Online HML – November 2020. URL: https://schedule.pharmac.govt.nz/HMLOnline.php (accessed 3 November 2020).

c. A Class C6 Controlled drug when: (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.

d. All codeine combination products were reclassified from pharmacy only or restricted medicines to prescription medicines on 5 November 2020.

e. Paracetamol with codeine is the only funded codeine combination product.

f. Morphine is pharmacy only in medicines for oral use containing not more than 0.2% of morphine, when combined with 1 or more active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield that would constitute a risk to health, when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine.

2.2.1.1 Regulation of controlled drugs

Prescribing of controlled drugs is more tightly controlled than prescribing of other medicines, reflecting the need to restrict access to, and minimise the misuse of, controlled drugs [6]. Class A and B controlled drugs have more restrictions than Class C controlled drugs.

There are restrictions by professional group on the maximum period of supply for controlled drug prescriptions, prescription form requirements (a triplicate controlled drugs prescription form or an electronic form generated from an approved system) and requirements for dispensing within a certain time. In addition, there are further restrictions under s24 of the Misuse of Drugs Act 1975 for treatment of people dependent on controlled drugs [6].

Medicines Control is a regulatory team within the Ministry of Health that oversees the local distribution chain of medicines and controlled drugs within New Zealand [7]. Drug abuse containment activities are carried out by Medicines Control staff in conjunction with two Medical Officers of Health who have wide powers under both the Misuse of Drugs Act 1975 and the Medicines Act 1981 [8].

Activities include [9]:

- liaising with doctors, pharmacists and addiction services in relation to drug abuse and misuse issues
- monitoring controlled drug prescribing
- working with the Medical Officers of Health in the preparation of Restriction Notices for drug seekers and writing to practitioners if there are any concerns regarding possible aberrant prescribing of controlled drugs or medicines
- advising health professionals of current drug misuse issues
- liaising with Police and other agencies locally and nationally on drug misuse
- preparing reports for the disciplinary processes of the Medical Council, Dental Council and Pharmacy Council
- providing advice on the requirements of the Misuse of Drugs Act and Medicines Act.

Where particular drugs are causing problems, there is the ability to reclassify a drug through a process involving the Expert Advisory Committee on Drugs (EACD) who would consider the risk of harm posed.

2.2.2 Indications

Opioids are used to relieve moderate to severe acute pain [10]. They are also used in palliative care patients, with morphine, oxycodone, fentanyl and methadone most commonly used to treat pain in these patients [11]. Opioids are not recommended for treating chronic non-cancer pain (CNCP). This is due to concerns over the long-term efficacy and safety of treatment, including the risk of misuse and addiction [10].

Methadone and buprenorphine with naloxone are used as opioid substitution therapy (OST), for treating patients with opioid dependence [10]. Naloxone is an opioid receptor antagonist that can reverse the effects of agonists such as morphine and methadone [12]. Opioid antagonists with a high affinity for opioid receptors can dislodge opioid agonists from the receptor, thereby precipitating withdrawal. Naloxone is often used therapeutically to reverse the effects of opioid overdose.

Alfentanil and remifentanil are potent, short-acting opioid analgesics that are chemically related to fentanyl [10]. They are indicated for use as analgesics during surgical procedures and as anaesthetic induction/maintenance agents. Alfentanil and remifentanil are not prescribed in the community for pain management. Therefore, the potential for abuse, misuse and dependence is low and they will not be further discussed in this paper.

See section 4.1.1 for indication information in the New Zealand data sheets.

2.2.3 Mode of action

Opioid receptors

Opioids exert their action at opioid receptors, which are distributed widely within the central nervous system and, to a lesser extent, throughout the periphery, occupying sites within the vas deferens, knee joint, gastrointestinal tract, heart and immune system, amongst others [13]. There are three classical opioid receptors, DOP, KOP and MOP (previously known as delta, kappa and mu [δ, κ, μ]), while the novel NOP receptor is considered to be a non-opioid branch of the opioid receptor family.

Opioids act at as agonists, antagonists or partial agonists at opioid receptors [13]. Opioid agonists bind to G-protein coupled receptors to cause cellular hyperpolarisation. Most clinically relevant opioid analgesics bind to MOP receptors in the central and peripheral nervous system in an agonist manner to elicit analgesia. MOP activation inhibits the ascending pain pathway, including neurons passing through the dorsal horn of the spinal cord, brainstem, thalamus and cortex [14]. Opioid MOP agonists also activate the inhibitory descending pain pathway, which involves the brainstem. Peripheral MOP receptors may also mediate analgesia at the site of tissue injury and inflammation. Antagonists bind to receptors but produce no functional response, while at the same time preventing an agonist from binding to that receptor (naloxone) [13]. Partial agonists bind to receptors but elicit only a partial functional response no matter the amount of drug administered (buprenorphine).

In clinical practice, receptor binding produces a range of effects, which are often dependent upon the location of the receptor, along with analgesia [13]. Agonists binding to MOP receptors may cause analgesia, but also sedation, respiratory depression, bradycardia, nausea and vomiting and a reduction in gastric motility. Activation of MOP receptors is also responsible for the euphoria associated with opioids [14]. This effect is different from the pain pathways described above and depends on the mesolimbic dopaminergic system. Activation of DOP receptors can cause spinal and supraspinal analgesia and reduce gastric motility, while KOP receptor stimulation may produce spinal analgesia, diuresis and dysphoria [13].

Non-opioid receptors

Some opioids also act at non-opioid receptors. These actions may be therapeutic or unwanted [14].

- Tramadol inhibits both serotonin and noradrenaline reuptake, and its active metabolite desmethyltramadol inhibits noradrenaline reuptake [14]. These effects contribute to the therapeutic effect of analgesia, but serotonin toxicity is associated with the use of tramadol in combination with other serotonergic drugs, or in overdose.
- Methadone has a long duration of action, limited first-pass metabolism, high bioavailability and more limited potential to cause euphoria and is often used as an oral opioid substitute in individuals addicted to opioids [13]. The d-isomer of methadone is an N-methyl D-aspartate receptor antagonist which contributes to analgesia and is sometimes used in treating opioid-induced hyperalgesia [14] and neuropathic pain [13]. Unwanted effects of methadone acting at non-opioid receptors include inhibition of the hERG potassium channel, prolonging the QT interval in some patients and increasing the risk of cardiac arrhythmia [14].

2.2.4 Pharmacogenomics

Genetic variability can affect how individuals can respond to opioids, particularly codeine, tramadol and oxycodone, which are metabolised by the cytochrome P450 enzyme, CYP2D6.

CYP2D6 is highly polymorphic – over 100 allelic variants have been identified, resulting in wide variability in function [15]. Individuals carrying two wild type alleles display normal enzyme activity and are known as extensive metabolisers [15]; most people fall into this category [16]. Intermediate metabolisers are heterozygotes with one reduced function and one nonfunctional allele, and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity [15]. Ultrarapid metabolisers have multiple copies of the wildtype CYP2D6 alleles. The frequency of poor metaboliser and ultra-rapid metaboliser phenotypes varies between populations [16]. The relative frequencies of these phenotypes in the New Zealand population are not known.

Codeine [16]

Codeine is metabolised by CYP2D6 in the liver to the active compounds morphine and morphine-6-glucuronide. Poor metabolisers are unable to convert codeine to morphine and receive little if any, analgesic benefit. Extensive metabolisers convert 5–15% of codeine to morphine via the CYP2D6 enzyme. In these patients, a 30 mg dose of codeine phosphate would yield approximately 1.5 mg to 4.5 mg of morphine. Ultra-rapid metabolisers convert codeine to morphine very efficiently, which can lead to morphine toxicity, such as respiratory depression and death.

Tramadol [17]

Tramadol's principal active metabolite is O-desmethyltramadol (M1). Animal models show M1 to be six-times more potent than tramadol in producing analgesia and 200 times more potent in MOP receptor binding. Patients with a deficiency of CYP2D6 may have reduced benefit from tramadol. On the other hand, patients who are ultra-rapid metabolisers may be more sensitive to adverse reactions, even at commonly prescribed doses.

Oxycodone [15]

Oxycodone is metabolised primarily to noroxycodone by CYP3A (approximately 80%) and by CYP2D6 to oxymorphone. Oxymorphone may contribute to the overall analgesic effect of oxycodone because it is 14 times more potent than oxycodone as a MOP receptor agonist and has a higher receptor affinity (40 times).

Noroxycodone is only a weak MOP receptor agonist. CYP2D6 polymorphism has a significant impact on oxycodone's pharmacokinetics and pharmacodynamics. Ultrafast metabolisers experience better analgesic effects and higher toxicity, while poor metabolisers experience less analgesic effect.

2.3 Misuse, abuse, 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 [18, 19]. 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 [19]. Prescribers can also significantly influence medicine misuse, in both positive and negative ways, eg, continuing a medicine without assessing its ongoing benefit [18].

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 [20]. 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 [19]. However, common definitions of relevant concepts for opioid misuse, abuse and dependence are shown in the table below.

Table 3: [redacted]

[redacted]

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 [21]. 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.

2.4 Opioid prescribing guidelines

There are many guidelines for prescribing opioids, and there is a growing consensus on best practice when considering or initiating opioids [1]. 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.

2.4.1 Acute pain

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

Acute Pain Management: Scientific Evidence (Fourth edition 2015) [15]

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, the paediatric patient, other specific patient groups. 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.

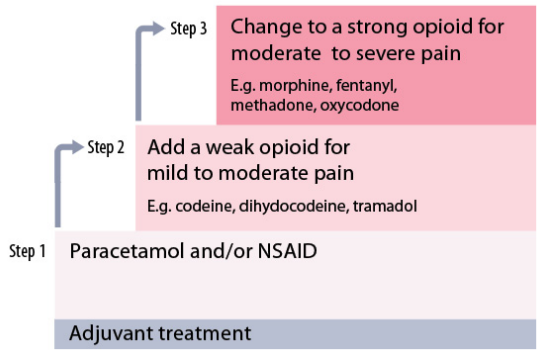
Best Practice Advisory Centre (bpac^{NZ})

The principles of managing acute pain in primary care – 2018 [22]

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).

When to consider strong opioids for patients with acute pain – 2018 [23]

This article reminds prescribers that there are few situations when a strong opioid (eg, morphine) should be initiated in primary care for the management of acute pain. Morphine is the first-line treatment for the management of severe acute pain, with oxycodone a second-line opioid for patients who cannot tolerate morphine. The article poses questions for prescribers to consider before prescribing a strong opioid in primary care, including: Is the underlying cause likely to be causing pain severe enough to require a strong opioid? Is there any suspicion that the patient is seeking a strong opioid for misuse or diversion? Strategies are provided for minimising opioid use, including creating an analgesia plan with the patient, and the concurrent use of paracetamol or an NSAID (multi-modal analgesia) to reduce opioid use. The article recommends patients use strong opioids only for a few days. If patients are taking the equivalent of ≥ 60 mg oral morphine per day for one week or longer, they will require a tapered withdrawal.

2.4.2 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 [24]

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 (see section 3.3). 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.

2.4.3 Misuse, addiction, opioid substitution therapy

Best Practice Advisory Centre (bpac^{NZ})

Codeine: all formulations prescription only – 2020 [25]

This article provides advice following the reclassification of codeine to prescription-only in November 2020. It summarises the reasoning behind the reclassification, provides guidance for managing requests for pain treatment in general practice and in pharmacies, and gives information for how to prescribe codeine safely.

Prescribers in primary care may encounter more requests for codeine or other analgesics once codeine products are no longer available OTC; this is an opportunity to assess patients who may not have previously presented to general practice for their pain-related issue. The possibility of codeine misuse should be considered in patients who specifically request codeine and are unwilling to engage in other treatment strategies.

Codeine reclassified as a prescription-only medicine: a community pharmacist perspective – 2020 [26]

Information for pharmacists to support the reclassification of codeine (described above). Pharmacists will need to recommend other methods to manage pain and people who are accustomed to buying codeine-containing products from pharmacies will need to be informed about the change. People with severe, persistent or recurrent pain should be encouraged to consult with their general practitioner to investigate and treat any underlying caus.

Unintentional misuse of prescription medicines – 2018 [18]

Guiding principles for prescribing medicines that have a higher potential for misuse. It includes strategies to mitigate risk of prescription medicine misuse, including trialling the medicine for a short period, contacting the dispensing pharmacist to share information about the treatment protocol and any early requests for repeats, ensuring that there is a clinical need for any ongoing prescriptions. The article also includes information about identifying medicine misuse.

Identifying and managing addiction to opioids – 2014 [27]

This article describes the international experience with oxycodone misuse, defines terms related to opioid misuse, summarises the New Zealand situation (as at 2014). Clinicians need to be aware of what the misuse and abuse issues associated with prescription opioids are, and how to identify and manage patients with inappropriate opioid use. All patients with non-malignant pain who have been taking opioids for longer than a few weeks should be reviewed, to consider whether treatment is still appropriate and how adequate controls can be ensured. The article provides clinical guidance for withdrawing patients from opioid treatment, including managing symptoms. Opioid substitution treatment in New Zealand is also discussed.

Ministry of Health

Prescribing Controlled Drugs in Addiction Treatment 2018: Guidance for nurse practitioners, designated prescriber nurses and designated prescriber pharmacists

Guidance to help addiction treatment services comply with section 24A of the Misuse of Drugs Act 1975 as it relates to nurse practitioners, designated prescriber nurses and designated prescriber pharmacists who are authorised to prescribe controlled drugs as a treatment for people dependent on controlled drugs.

New Zealand Practice Guidelines for Opioid Substitution Treatment – 2014 [12]

This document contains advice for clinicians on best practice for the clinical assessment and treatment of clients with opioid dependence. These guidelines endorse a path that moves away from a maintenance-treatment model and towards client-led, recovery-focused treatment. The guidelines aim to highlight the importance of early transition planning, with an emphasis on transitioning stable clients to primary level care.

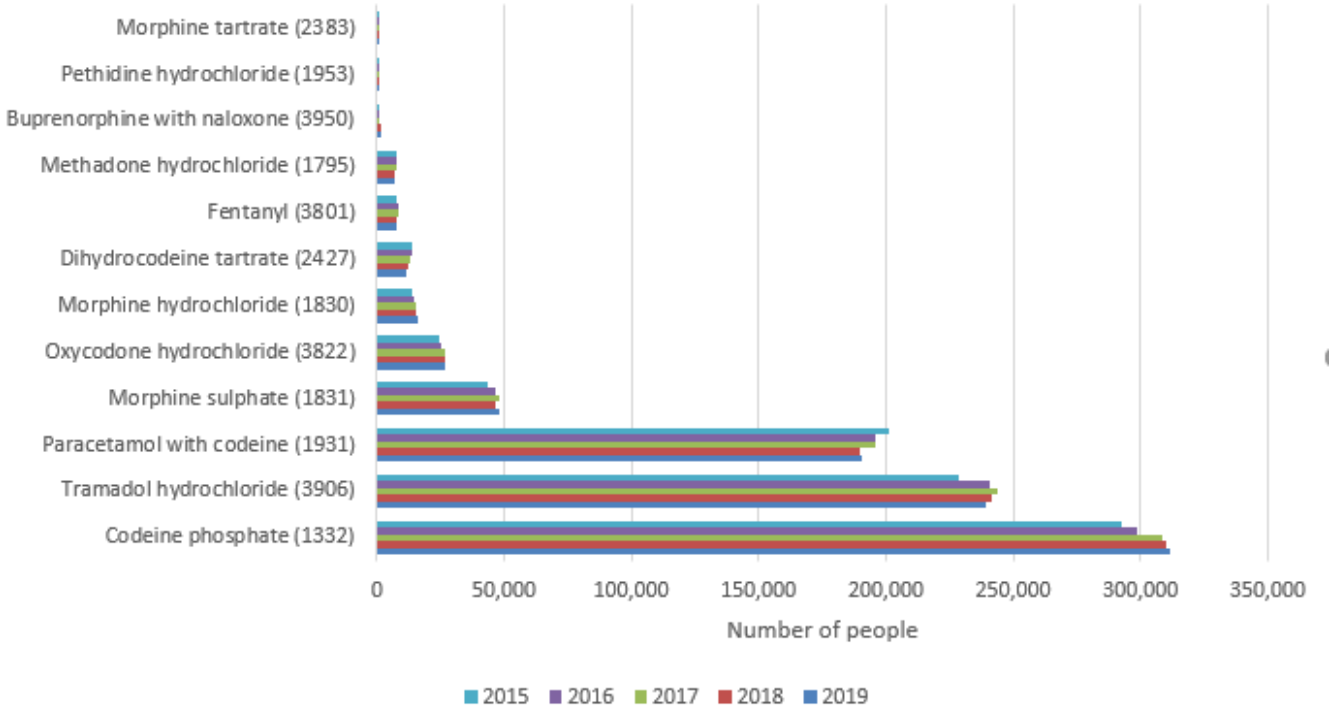
2.5 Usage data

2.5.1 Pharmaceutical collections

Data extracted from the Pharmaceutical data web tool are summarised below. This tool provides summary data from the Pharmaceutical Collection about prescriptions and dispensings that were dispensed in the community and funded by the New Zealand Government. It does not provide the indication for use, nor whether the patient took their dispensed medicine as prescribed. See Annex 2 for demographic information from 2019 for each opioid, including age, gender, ethnicity, socioeconomic status and DHB of residence.

Figure 2 below shows the number of number people dispensed an opioid (by chemical) for 2015 to 2019. Codeine phosphate, tramadol hydrochloride and paracetamol with codeine were dispensed to the greatest number of people. The number of people dispensed codeine phosphate has increased each year, whereas tramadol peaked in 2017 but decreased in 2018 and 2019.

Figure 2: Number of people dispensed a particular opioid (by chemical ID), 2015 to 2019

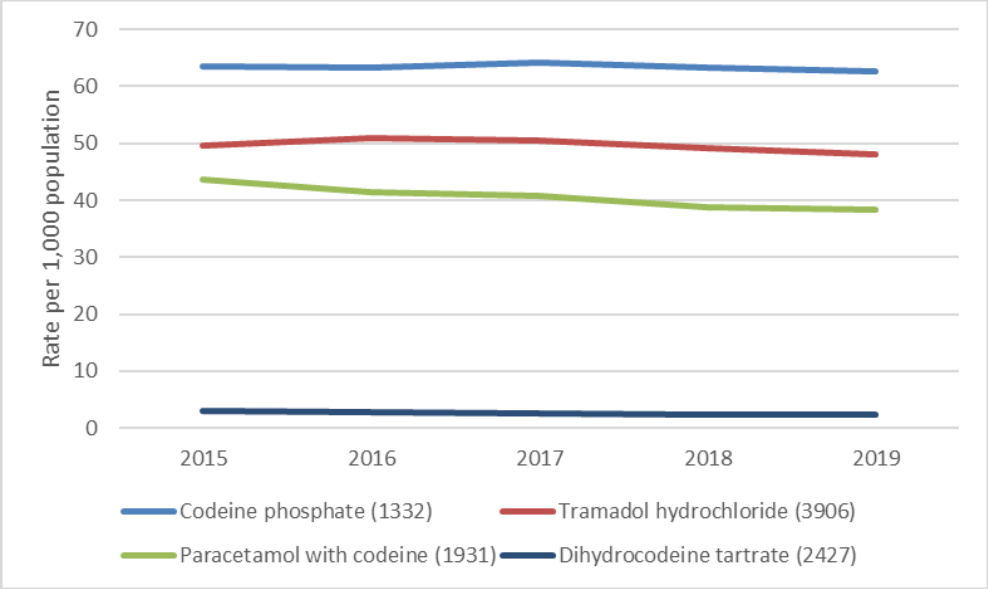


Notes:
The number of people dispensed an opioid is the number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year, as an initial dispensing or all at once (excludes people who only received a repeat dispensing during the year).
The approval for morphine tartrate lapsed in January 2020; there are now no approved morphine tartrate products available in New Zealand.

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).

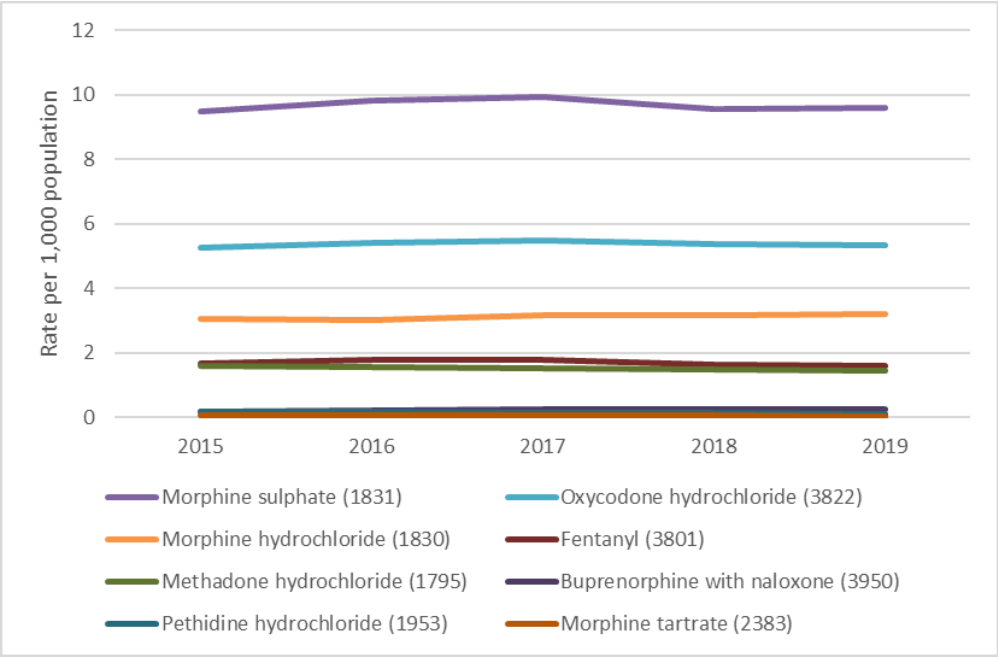
Figure 3 shows the people dispensed a weak opioid and Figure 4 the people dispensed a strong opioid, as rates per 1,000 population, from 2015 to 2019. While the absolute numbers of people dispensed a weak opioid have increased over the time period (Figure 2 above), the rates per 1,000 population have been relatively stable, with a decreasing trend since 2017. The rates per 1,000 population for strong opioids are also stable.

Figure 3: People dispensed a weak opioid (by chemical ID), 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, by age and sex, at 30 June 1996-2020. URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509# (accessed 11 November 2020)..

Figure 4: People dispensed a strong opioid (by chemical ID) – 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, by age and sex, at 30 June 1996-2020. URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509# (accessed 11 November 2020)..

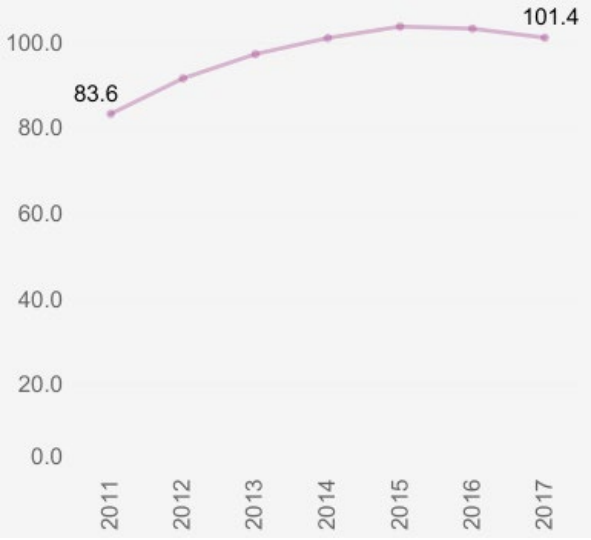
2.5.2 Health Quality and Safety Commission of New Zealand (HQSC)

The opioids domain of the HQSC's Atlas of Healthcare Variation gives an overview on the use of opioids, by district health board (DHB), to identify areas of wide variation.

The most recent data is from 2017, summarised below [28].

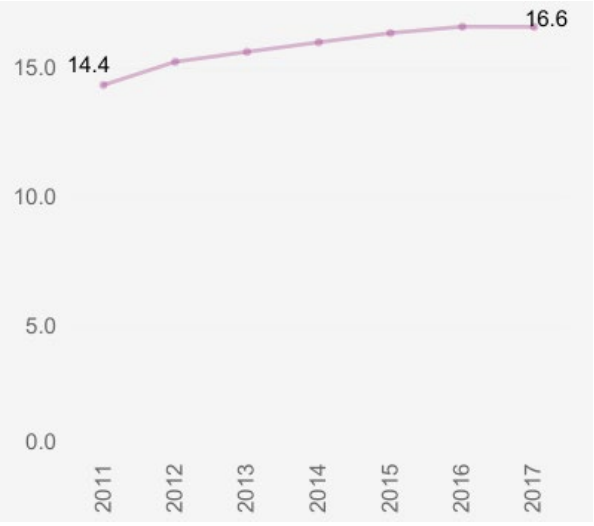
- The overall rate of both weak (Figure 5) and strong opioid (Figure 6) use has not increased since the previous report. However, in those aged 80 and over the rate continues to rise.
- Rates of opioid dispensing is higher in people of European/Other ethnicity, women and people aged 80 and over.
- Morphine use has increased since 2011
- Oxycodone use has remained the same since 2016
- Rates of fentanyl use vary widely, particularly in those aged 80 and over
- Almost 40 percent of those dispensed a strong opioid had a public hospital 'trigger event'

Figure 5: People dispensed a weak opioid, rate per 1,000, 2011 to 2017



Source: HQSC. 2019. *Atlas of Healthcare Variations – Opioids: Opioid single atlas map*. URL: https://public.tableau.com/profile/hqi2803#!/vizhome/Opioidssinglemap/AtlasofHealthcareVariationOpioids (accessed 11 November 2020).

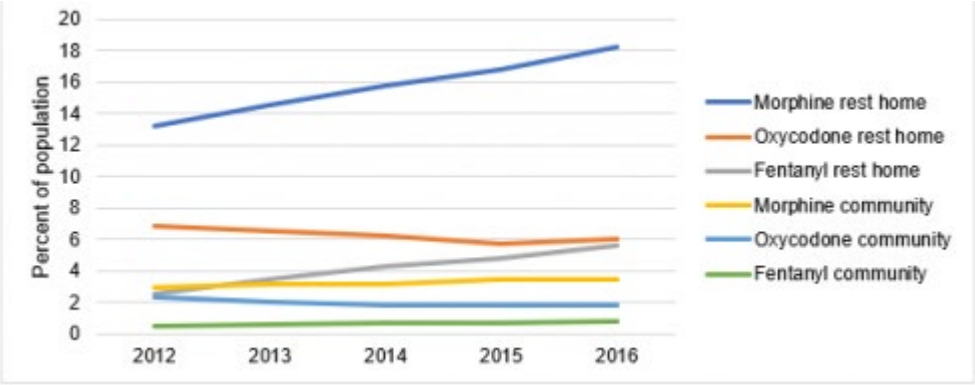
Figure 6: People dispensed a strong opioid, rate per 1,000, 2011 to 2017



Source: HQSC. 2019. *Atlas of Healthcare Variations – Opioids: Opioid single atlas map.* URL: https://public.tableau.com/profile/hqi2803#!/vizhome/Opioidssinglemap/AtlasofHealthcareVariationOpioids (accessed 11 November 2020).

The HQSC also investigated the increasingly high rate of morphine use in people aged 65 years and older living in aged residential care (ARC), compared to those not living in ARC, shown in Figure 7.

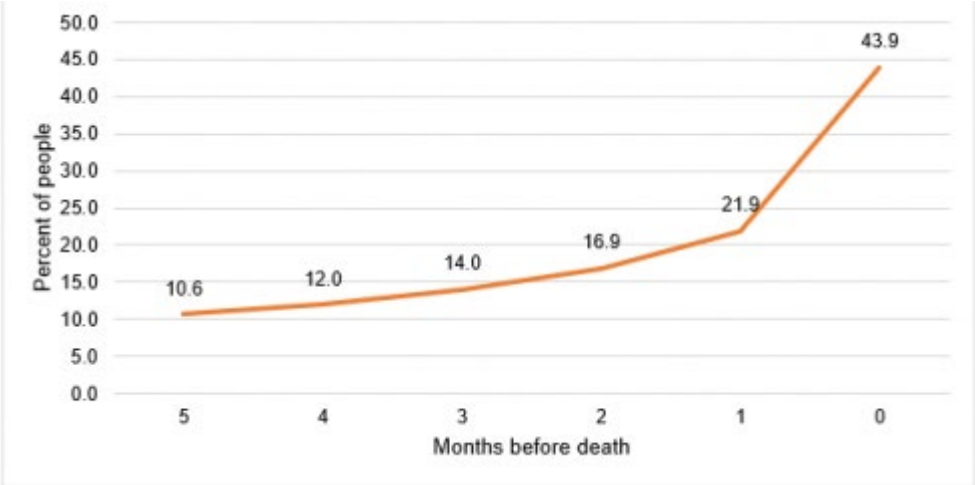
Figure 7: Dispensing of strong opioid by site of residence, 2012 to 2016



Source: HQSC. 2019. *Atlas of Healthcare Variation – Opioids*. URL: https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/opioids/ (accessed 11 November 2020).

One of the most likely reasons for the difference in strong opioid use between community and ARC populations could be the use of strong opioids for palliative care. The dispensing of strong opioids by type in the six months prior to death was analysed. Figure 8 below shows strong opioid dispensing rates were highest in the month in which people die, with 48 percent of ARC residents and 38 percent of non-ARC residents dispensed a strong opioid in their last month of life. Overall, in 2015, 54 percent of those in ARC and 43 percent of those in non-ARC were dispensed a strong opioid at some point in their last six of months of life.

Figure 8: Percent of people dispensed a strong opioid in the months before death, 2017



The HQSC concluded that much of the difference of strong opioid dispensing observed between ARC and non-ARC populations can be explained by strong opioid dispensing to people in their last six months of life.

Comments
The HQSC data uses different inclusion criteria for calculating rates per 1,000 population compared to the data shown in the Pharmaceutical Collections section above. For example, morphine includes morphine hydrochloride (1830), morphine sulphate (1831) and morphine tartrate (2383) combined; weak opioids include tramadol (1229), codeine phosphate (1332), dihydrocodeine tartrate (2427) and tramadol hydrochloride (3906) and excludes paracetamol with codeine (1931). Therefore, the rates are different, but the overall trends are the same (when comparing against the same years) – with stable dispensing rates for the past five years.

3 INTERNATIONAL REGULATORY ACTION

Table 4: Summary of recent international regulator actions for opioids

Medicine Regulator/Country	Action
Food and Drug Administration (FDA) - USA	Manufacturers required to submit Risk Evaluation and Mitigation Strategy (REMS) for all opioids. Updates to prescribing information (labels) for all opioids to include information about naloxone, tapering, central sleep apnoea, drug interactions, REMS. Limit prescription cough and cold medicines containing codeine or hydrocodone to adults only and include information in the Boxed Warnings for misuse, abuse, addiction, overdose, death, and slowed or difficult breathing. Considering safety-packaging (blister packs) for immediate-release opioids.
Medicines and Healthcare products Regulatory Agency (MHRA) – UK	Warnings on package labelling Updates to prescribing information Safety leaflet for patients
Therapeutic Goods Administration (TGA) - Australia	Smaller pack sizes Indication review Review labels and CMI Increase health professional awareness of alternatives to opioids for chronic pain management
Health Canada - Canada	Mandatory risk management plans for prescription opioids Warning sticker and patient information handout to be provided at time of dispensing Restricted advertising to healthcare professionals – must be pre-cleared by an advertising preclearance agency and can only contain information from the product monograph as authorised by Health Canada Considering re-scheduling low-dose codeine and tramadol Removed indication for children from cough and cold products containing opioids

3.1 United States of America (USA)

3.1.1 Classification

In the USA, drugs, substances, and certain chemicals used to make drugs are classified under the Controlled Substances Act (CSA) into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [29]. Schedule I drugs have a high potential for abuse and the potential to create severe psychological and/or physical dependence. As the drug schedule changes -- Schedule II, Schedule III, etc, so does the abuse potential -- Schedule V drugs represent the least potential for abuse. Schedule II drugs include the opioids methadone, oxycodone, fentanyl, pethidine and morphine, and tramadol is a schedule IV drug. Depending on its strength, codeine is a schedule II, III or V drug. Scheduling status affects prescribing authority (eg, manner of prescribing and limits on refills), triggers requirements for

supply chain record keeping, and determines the degree of criminal punishment for illicit trafficking [21]. Both the Drug Enforcement Agency and the Food and Drug Administration have regulatory roles under the CSA.

Medicines are also regulated under the Food, Drug and Cosmetics Act, which is enforced by the Food and Drug Administration (FDA).

3.1.2 Background

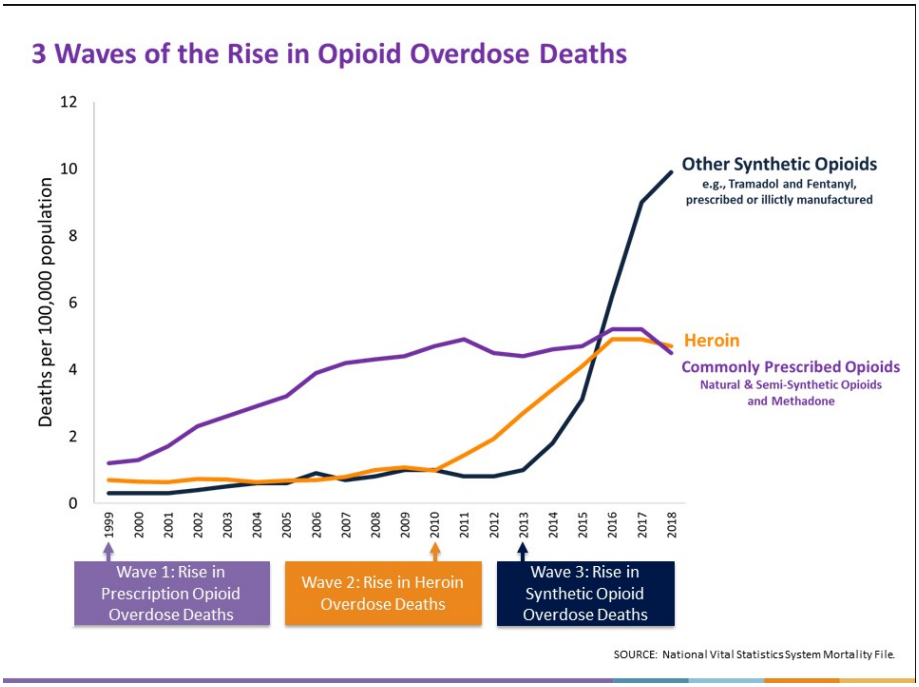
The misuse and abuse of illicit and prescription opioids and the risks of addiction, overdose, and death are a public health crisis in the United States [30]. In 2018, an estimated 1.7 million Americans had a substance use disorder involving prescription pain relievers and 0.5 million had a substance use disorder involving heroin. From 1999 to 2018, nearly 450,000 people died from an overdose involving any opioid, including prescription and illicit opioids. Opioids were involved in 46,802 deaths in 2018.

Opioid prescribing increased steadily from 1999 to 2010 but has decreased since 2012 [31]. However, the amount of opioids in morphine milligram equivalents (MMEs1) prescribed per person in 2017 was still around 3 times higher than it was in 1999. Opioid prescribing in the United States is much higher than in other countries. In 2017, 17% of the U.S. population received at least one opioid prescription.

The number of opioid deaths has also increased, and as a result have reduced the life expectancy in the USA [32]. Overdose deaths involving opioids, including prescription opioids, heroin, and synthetic opioids (like fentanyl), have increased almost six times since 1999 [33]. This rise in opioid overdose deaths can be outlined in three distinct waves – Figure 9 [34].

1. The first wave began with increased prescribing of opioids in the 1990s, with overdose deaths involving prescription opioids (natural and semi-synthetic opioids and methadone) increasing since at least 1999.
2. The second wave began in 2010, with rapid increases in overdose deaths involving heroin.
3. The third wave began in 2013, with significant increases in overdose deaths involving synthetic opioids, particularly those involving illicitly manufactured fentanyl. The market for illicitly manufactured fentanyl continues to change, and it can be found in combination with heroin, counterfeit pills, and cocaine.

Figure 9: 3 Waves of the rise in opioid overdose deaths, USA, 1999 to 2018



Source: Centers for Disease Control and Prevention (CDC). 2020. *Understanding the epidemic* 19 March 2020. URL: https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed 22 September 2020).

Of the 46,000 opioid overdose deaths in 2018, almost 15,000 (32%) involved prescription opioids and 31,000 (67%) involved synthetic opioids (excluding methadone) [35, 36]. Prescription opioid-involved death rates decreased by 13.5% from 2017 to 2018 but synthetic opioid-involved deaths increased by 10%. These increases in synthetic opioid-involved deaths are being driven by increases in fentanyl-involved overdose deaths, and the source of the fentanyl is more likely to be illicitly manufactured than pharmaceutical.

3.1.3 Regulatory actions

The USA response to the opioid crisis is complex and involves multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics.

Addressing the opioid crisis is one of the FDA's highest priorities [32]. The FDA has compiled a timeline to provide chronological information about its activities and significant events related to opioids, including misuse and abuse.

Selected legislative changes and regulatory actions are summarised below.

Risk evaluation and mitigation strategies (REMS)

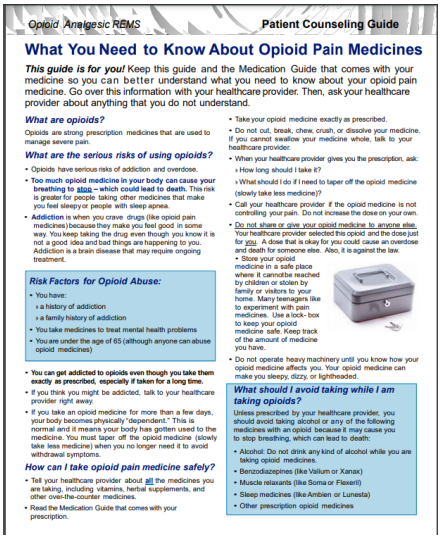
The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks [37].

The FDA has determined that a REMS is necessary for all opioid analgesics intended for outpatient use to ensure that the benefits of these drugs continue to outweigh the risks [38]. The first of the Opioid Analgesic REMS was published in 2012 for extended release (ER) and long-acting (LA) opioids. The Opioid Analgesic REMS was updated in September 2018 to include immediate-release (IR) opioid analgesics [39].

All opioid analgesic companies must provide the following [40]:

- Education for health care providers (HCPs) who participate in the treatment and monitoring of pain. For the purpose of the Opioid Analgesic REMS, HCPs will include not only prescribers, but also HCPs who participate in the treatment and monitoring of patients who receive opioid analgesics, including pharmacists and nurses. Education will be offered through accredited continuing education (CE) activities. These activities will be supported by unrestricted educational grants from opioid analgesic companies.
- Information for HCPs to use when counselling patients about the risks of ER, LA, and IR opioid analgesic use (Figure 10).

Figure 10: Page 1 of the Opioid Analgesic Risk Evaluation and Mitigation Strategies (REMS) Patient counselling guide



Opioid Analgesic REMS — Patient Counseling Guide

What You Need to Know About Opioid Pain Medicines

This guide is for you! Keep this guide and the Medication Guide that comes with your medicine so you can better understand what you need to know about your opioid pain medicine. Go over this information with your healthcare provider. Then, ask your healthcare provider about anything that you do not understand.

What are opioids?

Opioids are strong prescription medicines that are used to manage severe pain.

What are the serious risks of using opioids?

- Opioids have serious risks of addiction and overdose.
- Too much opioid medicine in your body can cause your breathing to slow – which could lead to death. This risk is greater for people taking other medicines that make you feel sleepy or people with sleep apnea.
- Addiction is when you crave drugs (like opioid pain medicines) because they make you feel good in some way. You keep taking the drug even though you know it is not a good idea and bad things are happening to you. Addiction is a brain disease that may require ongoing treatment.

Risk Factors for Opioid Abuse:

- You have:
  - a history of addiction
  - a family history of addiction
- You take medicines to treat mental health problems
- You are under the age of 65 (although anyone can abuse opioid medicines)

- **You can get addicted to opioids even though you take them exactly as prescribed, especially if taken for a long time.**
- If you think you might be addicted, talk to your healthcare provider right away.
- If you take an opioid medicine for more than a few days, your body becomes physically "dependent." This is normal and it means your body has gotten used to the medicine. You must taper off the opioid medicine (slowly take less medicine) when you no longer need it to avoid withdrawal symptoms.

How can I take opioid pain medicine safely?

- Tell your healthcare provider about all the medicines you are taking, including vitamins, herbal supplements, and other over-the-counter medicines.
- Read the Medication Guide that comes with your prescription.
- Take your opioid medicine exactly as prescribed.
- Do not cut, break, chew, crush, or dissolve your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- When your healthcare provider gives you the prescription, ask:
  - How long should I take it?
  - What should I do if I need to taper off the opioid medicine (slowly take less medicine)?
- Call your healthcare provider if the opioid medicine is not controlling your pain. Do not increase the dose on your own.
- Do not share or give your opioid medicine to anyone else. Your healthcare provider selected this opioid and the dose just for you. A dose that is okay for you could cause an overdose and death for someone else. Also, it is against the law.
- Store your opioid medicine in a safe place where it cannotbe reached by children or stolen by family or visitors to your home. Many teenagers like to experiment with pain medicines. Use a lock- box to keep your opioid medicine safe. Keep track of the amount of medicine you have.
- Do not operate heavy machinery until you know how your opioid medicine affects you. Your opioid medicine can make you sleepy, dizzy, or lightheaded.

What should I avoid taking while I am taking opioids?

Unless prescribed by your healthcare provider, you should avoid taking alcohol or any of the following medicines with an opioid because it may cause you to stop breathing, which can lead to death:

- Alcohol: Do not drink any kind of alcohol while you are taking opioid medicines.
- Benzodiazepines (like Valium or Xanax)
- Muscle relaxants (like Soma or Flexeril)
- Sleep medicines (like Ambien or Lunesta)
- Other prescription opioid medicines

Source: FDA. 2019. Opioid Analgesic REMS – REMS Materials: Patient Counselling Guide. URL: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17 (accessed 15 November 2020).

Note that there is no mandatory federal requirement that prescribers or other HCPs take the training and no precondition to prescribing or dispensing opioid analgesics to patients [38].

Strategic Policy Roadmap

As outlined in its 2018 Strategic Policy Roadmap, the FDA's goal is to reduce the opportunities for opioid misuse and abuse while ensuring that its actions are properly targeted, evidence-based, and serve the medical needs of patients. Actions to achieve this goal include the following [32].

- Decrease exposure and prevent new addiction – ensuring that only appropriately indicated patients are prescribed opioids and that the prescriptions are for durations and doses that properly match the clinical reason for which the drug is being prescribed in the first place. (See the REMS and SUPPORT Act sections below.)
- Support treatment of those with opioid use disorder – enabling more people to secure medication-assisted treatment (MAT), which is the use of medications in combination with counselling and behavioural therapies [41]. The FDA has approved buprenorphine, methadone, and naltrexone products for the treatment of opioid use disorder (OUD), and recommends that health care professional discuss naloxone with all patients when prescribing opioids for pain or to treat OUD [30].
- Foster development of novel pain treatment therapies – including supporting the development of abuse-deterrent formulations which target the known or expected routes of abuse, such as crushing in order to snort or dissolving in order to inject, for the specific opioid drug substance [42]. In 2015, the FDA published guidance for industry in developing products with potentially abuse-deterrent properties. The FDA has since approved several products with labelling describing abuse-deterrent properties: Oxycontin, Xtampa ER and RoxyBond (oxycodone); Hysingla ER (hydrocodone); and MorphaBond ER (morphine sulphate). None of these products are generics.
- Improve enforcement and assess benefit/risk – the FDA has an enforcement role for the illicit market of diverted opioids and illegal drugs and collaborates with Customs and Border Protection to intercept drugs being shipped through the mail. It also takes legal action against websites marketing unapproved opioids. The FDA ensures that drug approval and removal decisions are made within a benefit/risk framework that evaluates not only the outcomes of opioids when used a prescribed, but also the public health effects of inappropriate use of these drugs (the draft guidance for industry was published in 2019, and summarises the information that should be included in a new drug application).

Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act

The SUPPORT Act was passed on 24 October 2018. It provides the FDA with new authorities to address the opioid crisis. FDA activities under this Act include the following [43].

- Safety-enhancing packaging and disposal - the FDA opened a public docket to solicit feedback on potentially requiring that certain immediate-release opioid analgesics be made available in fixed-quantity, unit-of-use blister packaging. This is still being evaluated.
- Evidence-based opioid analgesic prescribing guidelines for indication-specific treatment of acute pain where such guidelines do not exist. This is a multi-phase, multi-year project. The FDA has contracted National Academies of Science, Engineering and Medicine (NASEM) to help advance the development of the guidelines. The NASEM report was published in January 2020.
- Clarifying FDA postmarket authorities. The SUPPORT Act required the issuance of guidance regarding the circumstances under which the FDA may require postmarket studies or clinical trials to assess the potential reduction in effectiveness of a drug and how such reduction in effectiveness could result in a change to the benefits of the drug and the risks to the patient.

Labelling changes (updates to prescribing information)

Recent FDA requirements for labelling changes are as follows.

- July 2020 – Drug manufacturers for all opioid pain relievers and medicines to treat opioid use disorder are required to add new recommendations about naloxone to the prescribing information [30]. The patient Medication Guides will also be updated.
- April 2019 – label changes to guide prescribers on gradual, individualised tapering based on reports of harm following sudden discontinuation of opioid medicines [44]. There is also a requirement to include information on other side effects including central sleep apnoea and drug interactions.
- September 2018 – Opioid Analgesic REMS in the Boxed Warning and Warnings and Precautions sections of prescribing information [45].
- January 2018 – labelling changes required for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18 years [46]. Also required for these medicines was the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning section of the label.

3.2 United Kingdom (UK)

3.2.1 Classification

Controlled drugs have the potential to be misused and are classified under the Misuse of Drugs Act 1971 according to their harmfulness [47]. The Act imposes restrictions on possession, supply, manufacture, import and export of controlled drugs. Many controlled drugs are also used as medicines and are categorised into five schedules based on their therapeutic usefulness and potential harms under the Misuse of Drugs Regulations 2001. Depending on the scheduling, there are restrictions as to which group of health care professionals can administer these medicines to patients.

Under the UK Human Medicines Regulations (2012), most opioids are classified as prescription medicines. However, some opioids medicines are available for purchase without prescription as pharmacy only or general sales medicines: low-dose codeine and dihydrocodeine (in combination with paracetamol; co-codamol and codydramol) and low-dose morphine.

3.2.2 Background

In 2019, an expert working group of the UK's Commission on Human Medicines, a committee within the Medicines and Healthcare products Regulatory Agency (MHRA), began a review of dependence and addiction to the opioids as a class [48]. This was initiated in response to the growing concern, both in the UK and internationally, of the increased prescribing and the growing numbers of reports of addiction, dependence and fatalities in association with the use of the opioids in the USA.

The review [48]:

- considered the current data on the utilisation of opioid-containing medicines in the UK, both prescribed and over the counter
- examined whether the risk minimisation measures implemented for over the counter and prescription opioids have been effective or whether further measures are required
- considered the benefit/risk of opioid-containing medicines in particular for non-cancer indications, taking into account alternatives
- made recommendations for regulatory action to better support appropriate use of prescription opioids, including changes to the Summary of Product Characteristics and Patient Information Leaflet and product labelling and packaging.

3.2.3 Regulatory actions [49, 50]

The changes apply to the following opioids:

Alfentanil	Dihydrocodeine	Meptazinol	Oxycodone	Remifentanil
Buprenorphine	Dipipanone	Methadone	Papaveretum	Tapentadol
Codeine	Fentanyl	Morphine	Pentazocine	Tramadol
Diamorphine	Hydromorphone	Opium	Pethidine	

Package labelling

To make it clear that a medicine contains an opioid and that there is a risk of addiction (a recognised term by patients) with prolonged use, the packaging for all opioid medicines in the UK must have the warnings 'Can cause addiction' and 'Contains opioid'.

Updates to the Summary of Product Characteristics (SmPCs)

All opioids

Product information for all opioids in the UK will include consistent warnings of the risks of tolerance and dependence and addiction. The changes apply to sections 4.2 Posology, 4.4 Special Warnings and precautions, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects, and 4.9 Overdose – as follows.

4.2 Posology and method of administration
Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with <active> in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

4.4 Special warnings and precautions for use
Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with <active>.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms

may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

4.6 Fertility, pregnancy and lactation
Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available. Breast feeding Administration to nursing women is not recommended as <active> may be secreted in breast milk and may cause respiratory depression in the infant.

4.8 Undesirable effects
Psychiatric disorders: Frequency unknown: Drug dependence (see section 4.4) General disorders and administration site conditions: Uncommon: drug withdrawal syndrome

4.9 Overdose
Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

For Fentanyl-containing products

There is an additional change required:

4.3 Contraindications
Contraindicated in opioid naive patients

Safety leaflet for patients

The MHRA developed an opioids safety information leaflet on the risks of dependence and addiction. The MHRA encourages health care professionals to use this information alongside the statutory patient information leaflet supplied with opioid medicines.

3.3 Australia

3.3.1 Classification

In Australia, the classification of drugs and poisons is set out in the Schedules of the Poisons Standard [51]. The Poisons Standard also includes model provisions about containers and labels, a list of products recommended to be exempt from these provisions, and recommendations about other controls on drugs and poisons [51]. Opioids are classified as Schedule 4 (prescription) or 8 (controlled drugs).

Codeine was up-scheduled from OTC to Schedule 4 in 2018. An evaluation of evidence 12 months after the change to prescription-only supply of codeine concluded that codeine reclassification successfully reduced harm from codeine, and the amount of codeine used [25]. There was a reduction in calls to the poisons centre involving codeine overdose (for the formulations containing ≤15 mg of codeine affected by the reclassification). Sales of products containing ≤15 mg of codeine rom suppliers to community pharmacies and hospitals dropped approximately ten-fold, with no significant change in sales of higher strength codeine.

3.3.2 Background

The usage of and harm from prescription opioids has been increasing in Australia since 2007 [4].

- From 2007 to 2016, the age-adjusted opioid death rate increased by 62 percent, from 2.9 to 4.7 deaths per 100,000 population. The increase was driven by an increase in accidental opioid deaths and in pharmaceutical opioid deaths.
- From 2007/08 to 2016/17, the age-adjusted rate of hospitalisations per 100,00 population with a principle diagnosis of opioid poisoning increased by 25 percent.

3.3.3 Regulatory actions [52-54]

Public consultation

The Australian Government asked the Therapeutic Goods Administration (TGA) to play a role in tackling the prescription opioid problem. The TGA conducted a public consultation in 2018, seeking comments on options for a regulatory response to misuse of prescribed opioids in Australia. The consultation focused on the higher-risk schedule 8 (controlled drugs) opioids, including, but not limited to: buprenorphine, fentanyl, hydromorphone, methadone, morphone, oxycodone, talpentadol and pethidine. Some schedule 4 (prescription) opioids, such as tramadol, were also considered. The consultation was framed around the level of prescription opioid overdose, and concern over indication creep towards use in chronic non cancer pain, despite limited evidence for efficacy or safety in these patients.

There were eight options presented in the consultation (listed below). A total of 98 submissions were received, with feedback indicating strong and consistent support from all stakeholders for a regulatory response. The favoured options are highlighted in bold.

- **Option 1: Consider the pack sizes for strong (S8) opioids**
- **Option 2: Consider a review of the indications for strong (S8) opioids**
- Option 3: Consider whether the highest dose products should remain on the market, or be restricted to specialist/ authority prescribing
- Option 4: Strengthening of the Risk Management Plans for opioid products
- **Option 5: Review of label warnings and revision to Consumer Medicines Information (CMI)**
- Option 6: Consider incentives for expedited TGA review of improved products for pain relief and opioid antidotes
- Option 7: Potential changes to use of appendices in the Poisons Standard to provide additional regulatory controls for strong S8 opioids
- **Option 8: Increase health professional awareness of alternatives to opioids (both S4 and S8 opioids) in the management of chronic pain.**

Following the initial consultation, the TGA established the Opioid Regulatory Advisory Group (ORAG) to provide independent, expert advice. ORAG strongly supported the proposed options and provided advice on how best to implement them.

Health care professional and consumer organisations represented on ORAG included: Australian and New Zealand Society of Palliative Medicine, Pain Australia, the Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine, Royal Melbourne Hospital, the Australian Medical Association, Palliative Care Australia, University of Western Australia, the Royal Australasian College of Physicians, Australian Commission on Safety and Quality in Health Care, Tasmanian Health Services, Society of Hospital Pharmacists of Australia, Pharmaceutical Society of Australia, and the Royal Australian College of General Practitioners.

Outcome

The regulatory measures described below were considered to ensure that they support and maintain the safe and clinically appropriate use of opioids without restricting prescribers from accessing them for their patients when needed.

- Smaller pack sizes will be available for immediate-release prescription opioid products.

- Boxed warnings and class statements will be required in the Product Information (PI) documents for all prescription opioids in relation to their potential for harmful and hazardous use – see Annex 3.
- The TGA will work with sponsors to ensure that safety information, including the relevant warnings, is prominently displayed in the CMI to ensure consistency of language and information across all classes of prescription opioids.
- The indications in the prescribing information for immediate release products will reinforce that they should only be used when other products are not suitable or effective:

  [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.

- The indications in the prescribing information for modified release products will reinforce that they should only be used when other products are not suitable or effective, and only used where the pain is opioid-responsive and the patient requires continuous long-term treatment:

  [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.

  Not for use in opioid naïve patients. (Hydromorphone and fentanyl patches only)

- The indication for fentanyl patches will be updated to state they should only be prescribed to treat pain in patients with cancer, patients in palliative care and those with exceptional circumstances.

  For the management of pain associated with cancer, palliative care, and other conditions 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*
  - *severe enough to require daily, continuous, long term opioid treatment.*

  Not for use in opioid-naïve patients.

- The TGA will be communicating the changes to both prescribers and consumers using a range of channels to ensure health professionals follow best prescribing practice and consumers are fully informed how best to use opioids. Consumers are also being encouraged to return unwanted opioids to pharmacies for destruction by distributing prescription covers with relevant messaging to every pharmacy in Australia as well as via various social media activities.

These measures align with broader Australian Government initiatives to improve appropriate pain management, particularly the National Strategic Action Plan for Pain Management. This strategic plan will address issues of pain management holistically and will ensure the appropriate support is available for areas of need. The need to maintain appropriate access to opioids, particularly in regional and remote areas, was a consideration at all times in the TGA's regulatory response.

The first of the smaller pack sizes were registered from January 2020. The fentanyl indication changes came into effect in the first half of 2020. Due to the large number of opioid products on the Australian market, the other changes are being phased in.

3.4 Canada

3.4.1 Classification

Canada's Controlled Drugs and Substances Act (CSDA) provides for the control of substances that can alter mental processes, and that may produce harm to health and to society when diverted or misused, and of chemical precursors that can be used to synthesize these substances [55]. The CDSA prohibits certain activities with the substances listed in its schedules, unless they are authorized by the CDSA regulations, or through an exemption pursuant to subsection 56(1) of the Act.

Opioid analgesics are generally scheduled under the Narcotic Control Regulations (NCR; under the CSDA) and are subject to the corresponding requirements. Most codeine products are regulated under the NCR as prescription only. However, section 36 exempts products containing low doses of codeine (8 mg or less per pill, or 20 mg or less per 30 mL of liquid medications) from the requirement to be sold by prescription, as long as certain conditions are met [56].

Tramadol is currently only regulated under the Food and Drugs Act, and is available by prescription [55].

3.4.2 Background

In 2016, there were more than 2,800 suspected opioid-related deaths in Canada and preliminary data for 2017 suggested that there were 3,000 opioid-related deaths [57]. British Colombia was at the forefront of Canada's opioid crisis and declared a public health emergency in April 2016. While problematic substance use was historically viewed as a problem for a certain segment society, the crisis had spread to many communities across the country, affecting all socioeconomic, gender and age groups.

Canadians are second highest users per capita of prescription opioids in the world, after the USA [57].Opioid prescribing increased dramatically following the approval of OxyContin, a controlled-release formulation of oxycodone, in 1996 [58]. This was attributed to an intense marketing campaign by OxyContin's manufacturer, which promoted the use of controlled release opioids for the treatment of chronic non-cancer pain, with claims of minimal risk of addiction. However, it soon became evident that the controlled-release characteristics of this formulation of oxycodone could be overcome by chewing or crushing the tablet, therefore making it an attractive medicine to misuse [27]. Between 2005 and 2011, there was a strong and significant correlation between prescription oxycodone dispensing levels and opioid-related mortality in Ontario. The number of oxycodone-related deaths increased from 0.54 deaths per 100 000 people in 2005 to 1.24 deaths per 100 000 in 2011.

Fentanyl (legal and illegal) has also significantly contributed to the overdose epidemic [57]. In 2016, fentanyl and its analogues were responsible for just over half of all overdose deaths in Canada.

In addition, use of low-dose codeine products is high. In 2015 over 600 million low-dose codeine tablets were sold in Canada, the equivalent of 20 tablets for every person living in Canada that year [56]. In Ontario alone, from 2007 to 2015, an average of 880 individuals per year (representing approximately 2.0% of total admissions per year) who were newly admitted into publicly funded addiction treatment centres indicated non-prescription codeine products as one of their five problem substances. In that same nine-year period, over 500 individuals admitted to these treatment centres stated that non-prescription codeine was their only problem substance.

Tramadol is available in Canada by prescription only [55]. It is indicated for the treatment of moderate to moderately severe pain but is also known to be prescribed "off-label" as a treatment for other conditions, most commonly for ejaculation dysfunction. Tramadol was one of six opioids that accounted for over 96% of opioid prescriptions in Canada between 2012 and 2016. Between 2006 and 2017, tramadol is suspected to have contributed to 71 adverse events related to problematic use, dependence or withdrawal reported in Canada, including 18 deaths.

3.4.3 Regulatory actions

In 2016, the government announced the Canadian Drugs and Substances Strategy (CDSS), and allocated $100 million over five years and $22.7 million ongoing to address drugs and opioids [57]. Key regulatory actions are described below.

Changes to the Controlled Drugs and Substances Act (CSDA), the Customs Act and other related Acts to better equip both health and law enforcement officials to reduce the harms associated with drug and substance use in Canada [59]:

- Streamlines and simplifies the application process for communities who wish to open supervised consumption sites, while ensuring that community consultation continues to be an integral part of the process.
- Prohibits unregistered importation of designated devices that may be used in the illicit manufacture of controlled substances, such as pill presses and encapsulators;
- Amends the Customs Act to remove the exception that prevents border officers from opening mail weighing 30 grams or less, in order to stop drugs, like fentanyl, from entering Canada illicitly through the mail system; and
- Makes a number of amendments to the CDSA, such as allowing temporary scheduling of controlled substances and faster disposition of drugs and substances by law enforcement, which would allow the government and law enforcement greater flexibility in addressing emerging risks.

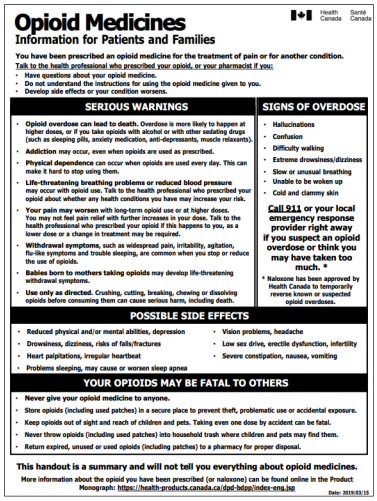
Enforcement of the CSDA Regulations and amendment of the Food and Drug Regulations, Narcotic Control Regulations and New Classes of Practitioners Regulations (Diacetylmorphine (Heroin) and Methadone) [57, 60]:

- Naloxone available without a prescription
- Expedited approval of nasal spray version of naloxone
- Physicians able to apply to Health Canada to request access to medical grade heroin (diacetylmorphine) and methadone for their patients
- Import of medications approved elsewhere for urgent public health needs, including specific diacetyl morphine, naltrexone and buprenorphine formulations
- Made it harder to access six fentanyl precursor chemicals
- Requirement for mandatory Canadian Specific Opioid-targeted Risk Management Plan (CSO-tRMP) for prescription opioids – described further below
- Requirement for a warning sticker and patient information handout to be provided with prescription opioids at time of dispensing – described further below

Mandatory handouts and stickers

Mandatory handouts and stickers (Figure 11) are required for any marketed product containing an active ingredient as included on Part A of the List of Opioids. This includes any prescription opioid that could be dispensed by a retail pharmacy, with the exception of those authorised and indicated for the treatment of an opioid use disorder. Health Canada produced a Questions and Answers document for pharmacists and practitioners to explain the handout and sticker requirements.

Figure 11: Mandatory handout and sticker required in Canada for any marketed product containing an active ingredient as included on Part A of the List of Opioids*



Opioid Medicines
Information for Patients and Families

Health Canada / Santé Canada

You have been prescribed an opioid medicine for the treatment of pain or for another condition.
Talk to the health professional who prescribed your opioid, or your pharmacist if you:
- Have questions about your opioid medicine.
- Do not understand the instructions for using the opioid medicine given to you.
- Develop side effects or your condition worsens.

SERIOUS WARNINGS
- Opioid overdose can lead to death. Overdose is more likely to happen at higher doses, or if you take opioids with alcohol or with other sedating drugs (such as sleeping pills, anxiety medication, anti-depressants, muscle relaxants).
- Addiction may occur, even when opioids are used as prescribed.
- Physical dependence can occur when opioids are used every day. This can make it hard to stop using them.
- Life-threatening breathing problems or reduced blood pressure may occur with opioid use. Talk to the health professional who prescribed your opioid about whether any health conditions you have may increase your risk.
- Your pain may worsen with long-term opioid use or at higher doses. You may not feel pain relief with further increases in your dose. Talk to the health professional who prescribed your opioid if this happens to you, as a lower dose or a change in treatment may be required.
- Withdrawal symptoms, such as widespread pain, irritability, agitation, flu-like symptoms and trouble sleeping, are common when you stop or reduce the use of opioids.
- Babies born to mothers taking opioids may develop life-threatening withdrawal symptoms.
- Use only as directed. Crushing, cutting, breaking, chewing or dissolving opioids before consuming them can cause serious harm, including death.

SIGNS OF OVERDOSE
- Hallucinations
- Confusion
- Difficulty walking
- Extreme drowsiness/dizziness
- Slow or unusual breathing
- Unable to be woken up
- Cold and clammy skin

Call 911 or your local emergency response provider right away if you suspect an opioid overdose or think you may have taken too much. *

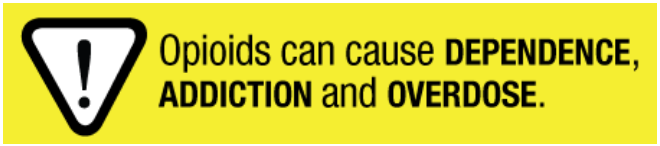
* Naloxone has been approved by Health Canada to temporarily reverse known or suspected opioid overdoses.

POSSIBLE SIDE EFFECTS
- Reduced physical and/or mental abilities, depression
- Drowsiness, dizziness, risks of falls/fractures
- Heart palpitations, irregular heartbeat
- Problems sleeping, may cause or worsen sleep apnea
- Vision problems, headache
- Low sex drive, erectile dysfunction, infertility
- Severe constipation, nausea, vomiting

YOUR OPIOIDS MAY BE FATAL TO OTHERS
- Never give your opioid medicine to anyone.
- Store opioids (including used patches) in a secure place to prevent theft, problematic use or accidental exposure.
- Keep opioids out of sight and reach of children and pets. Taking even one dose by accident can be fatal.
- Never throw opioids (including used patches) into household trash where children and pets may find them.
- Return expired, unused or used opioids (including patches) to a pharmacy for proper disposal.

This handout is a summary and will not tell you everything about opioid medicines.
More information about the opioid you have been prescribed (or naloxone) can be found online in the Product Monograph: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

Date: 2019/03/15



* The list of opioids is available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/list-opioids.html

Available at:
Handout: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/warning-sticker-opioid-patient-information-handout/information-handout.html
Sticker: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/warning-sticker-opioid-patient-information-handout/warning-sticker.html

Mandatory Canadian Specific Opioid-targeted Risk Management Plan (CSO-tRMP)

A mandatory CSO-tRMP is required for any marketed product containing an active ingredient as included on Part B of the List of Opioids. This includes any prescription opioid that could be dispensed by a retail pharmacy or could be administered while not under the direct supervision of a healthcare professional.

In 2018, Health Canada published a Guidance Document for Industry to assist market authorisation holders (MAHs) with the preparation of the RMP. The following is an excerpt from the Guidance Document, outlining the mandatory sections of the CSO-tRMP.

3.2 Mandatory Canadian Specific Opioid targeted Risk Management Plan sections

The Minister of Health, under the authority of section C.01.014.21 of the *Food and Drug Regulations*, imposes the terms and conditions on all prescription opioid products. The following are the terms and conditions relevant to the content of the CSO-tRMP:

1) The CSO-tRMP must contain the following information:
   a) a detailed Safety Specification section that:
      i) describes, quantitatively and qualitatively, the occurrence of opioid-related harms associated with the use of DRUGNAME in Canada; and
      ii) provides detailed information on the evidence gaps and uncertainties related to opioid-related harms that are associated with the use of DRUGNAME in Canada;

b) a detailed Pharmacovigilance Plan section that:
   i) describes routine (passive surveillance) and additional (active surveillance) activities in place or that are to be put in place to monitor and characterize opioid-related harms and address uncertainties associated with the use of DRUGNAME in Canada; and
   ii) provides the timelines for the conducting of those activities;
c) a detailed Risk Minimization Plan section that:
   i) describes risk minimization activities (beyond the approved product label) that are designed to minimize or prevent the occurrence of opioid–related harms in Canadians using DRUGNAME;
   ii) provides the timelines for the conducting of those activities;
   iii) provides all materials that are - or will be - communicated and/or disseminated by the MAH to healthcare professionals with respect to DRUGNAME;
   iv) demonstrates that the materials referred to in (iii) have been submitted to an independent advertising preclearance agency (APA) recognized by Health Canada for a determination as to whether the materials are promotional, and for those that are promotional, a determination as to whether the materials comply with the terms of the marketing authorization. The plan must include:
      - the date the materials were submitted to the APA;
      - the name of the APA;
      - the date of the review; and
      - the outcome of the APA's determinations referred to in (iii), above.
d) a detailed Evaluation of the Risk Minimization section that:
   i) describes the activities that the MAH will carry out to assess the effectiveness of the risk minimization activities on health outcomes in Canadians who are using DRUGNAME; and
   ii) provides the timelines for the conducting of those activities.

2) You must revise and re-submit to Health Canada the CSO-tRMP annually to:
   a) update the Safety Specification section by adding new evidence (quantitative or qualitative) related to opioid-related harms or uncertainties that is generated through the risk-monitoring/characterising activities conducted in Canada or internationally (e.g. pharmacoepidemiological studies or clinical trials undertaken to investigate DRUGNAME); and
   b) update the Pharmacovigilance and Risk Minimization sections to provide the status of the ongoing Pharmacovigilance and Risk Minimization activities and describe any changes to these sections.

Restricting advertising

Direct-to-consumer advertising is not permitted in Canada but MAHs may provide information to health care professionals. As described in CSO-tRMP section c) iv) above, MAHs must submit all materials regarding opioid products they intend to provide to health care professionals for preclearance to an external advertising preclearance agency (APA) recognised by Health Canada [61]. The APA assesses whether the materials are consistent with the terms of the product's market authorisation and determine whether any statements are false or misleading.

Health Canada also imposed additional Terms and Conditions for prescription opioid-containing products restricting all advertising materials of Class B opioids provided to health care professionals to only statements that have been authorised by Health Canada in the Product Monograph (PM) [61]. Specifically, only information contained in the PM would be permitted in such advertising materials and would have to be presented verbatim while meeting fair balance requirements of benefits and risks. Since June 2019 all advertising materials developed are required to comply with the new Terms and Conditions.

In June 2018, the Minister of Health issued a letter to Canadian manufacturers, seeking their commitment to respond to the opioid crisis by immediately ceasing any and all marketing and advertising of opioids to health care professionals. In response to this, Health Canada set up measures to monitor advertising activities and to ensure that any marketing to health care professionals falls within regulatory restrictions. Health Canada launched a web-based platform, Stop Illegal Marketing of Drugs and Devices, to raise awareness about illegal

marketing of drugs and medical devices, educate health care professionals on the rules governing health product advertising in Canada, as well as provide a quick and easy tool to report suspected misleading marketing practices to Health Canada. A page of this platform, Illegal marketing of opioids and other controlled substances, is dedicated to the advertising of controlled substances, including opioids.

Regulation of low-dose codeine

In September 2017, the Government of Canada published its intent to change the Narcotic Control Regulations governing the sale of low-dose codeine formulations such that they would all require a prescription [56]. Currently, codeine formulations containing low-doses (8 mg in solid dosage form, 20 mg/30 ml in liquid formulations) and which are formulated with other active ingredients can be sold by a pharmacist without prescription in most provinces. This regulatory amendment is still under consideration.

Regulation of tramadol

In 2007, the Government of Canada published its intent to add tramadol to Schedule I of the CDSA and to the schedule to the NCR [55]. After considering the review findings and the data available at the time, the Department did not proceed to control tramadol. There is now more evidence that high doses of tramadol could have potential for problematic use comparable to some opioids controlled under Schedule I to the CDSA. In 2019, a pre-publication of regulatory amendments which would re-classify tramadol as a narcotic were published [55]. These are still under consideration.

Cough and cold products containing opioids

In 2019, Health Canada published a summary of a safety review [62] of opioid-containing products indicated for cough and cold, which found limited evidence to support the effectiveness of these products in children and adolescents (under 18 years of age) [63]. The review also found limited evidence to link these products with opioid use disorders and related harms in children and adolescents (under 18 years of age). As a precautionary measure, Health Canada has now limited the use of opioid-containing products indicated for cough and cold for adults only (patients 18 years of age and older) and has notified manufacturers of these products to update the indication and other relevant sections of the Canadian Product Monographs to include this new safety information [63].

Other

Health Canada has also :

- published safety alerts and updates (in Health Product InfoWatch) related to opioids
- supported the development of opioid prescribing guidelines for chronic non-cancer pain [64] and for the clinical management of opioid use disorder [65].

Comments
With the exception of codeine up-scheduling in Australia, It is too soon to tell whether these actions by international regulators have had an impact on opioid harm in their respective countries. Medsafe has asked the regulators for updates as information becomes available.

4 OTHER INFORMATION

4.1 New Zealand information

4.1.1 Data sheets

4.1.1.1 Indications

Table 5 shows indication information from the New Zealand data sheets for opioid products funded in the community.

Table 5: Opioid indications, with current New Zealand data sheet wording (Community-funded products only)

Active ingredient	Product[a]	**Indication(s) from section 4.1 of the data sheet[b]**
Buprenorphine + Naloxone	Buprenorphine Naloxone BNM	Treatment of opioid dependence, within a framework of medical, social and psychological treatment. Naloxone is included in BUPRENORPHINE NALOXONE BNM to deter intravenous misuse of the product.
Codeine	Codeine Phosphate PSM	Codeine phosphate is indicated for: • the relief of mild to moderate pain (including pain associated with terminal illness, post-operative pain, headache), • the relief of symptoms of diarrhoea (except diarrhoea caused by poisoning).
Dihydrocodeine tartrate	DHC Continus Modified release tablet	• DHC CONTINUS tablets are recommended for use in the treatment of post-operative pain, and pain associated with cancer. • DHC CONTINUS tablets are also indicated for the 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
Fentanyl	Fentanyl Sandoz	• Fentanyl Sandoz is indicated in the management of chronic cancer pain. • Fentanyl Sandoz is also indicated in the management of opioid-responsive chronic severe pain of non-malignant origin in opioid tolerant patients, after other conservative methods of analgesia have been tried. It is indicated for use in accordance with NZMA guidelines on chronic pain management and where there is no psychological contraindication, drug seeking behaviour or history of drug misuse
	Fentanyl Solution for injection Boucher & Muir	Fentanyl Injection is indicated in adults and children aged above two years for: • analgesic action of short duration during anaesthetic periods, premedication, induction and maintenance, and in the immediate post-operative period (recovery room) as the need arises • use as an opioid analgesic supplement in general and regional anaesthesia • administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.
Methadone	Biodone Oral solution	Oral Methadone is used in detoxification and maintenance treatment as a substitute for heroin or other morphine-like drugs to suppress the opiate-agonist abstinence syndrome in patients who are dependent on these drugs.
	Methatabs Tablet	Methatabs is indicated for: • The treatment of severe pain Methadone is indicated for relief of severe pain. Methadone is sometimes used as an antitussive when severe pain is present and coughing cannot be relieved by other means. Methadone is not recommended for obstetric analgesia because its long duration of action increases the risk of neonatal respiratory depression. • The treatment of dependence on opioid drugs Methadone is indicated as a suppressant to permit detoxification. Oral Methadone is also indicated as maintenance therapy to discourage addicts from returning to illicit use of other opioid drugs.
	Methadone Injection BP (AFT)	Methadone Injection is used as an analgesic for the relief of moderate to severe pain. Single doses of methadone have a less marked sedative action than morphine.

Morphine hydrochloride	RA Morph	Morphine is an analgesic used for the symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery. Morphine is indicated in adults and children aged 1 year and above. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain.
Morphine sulphate	Arrow – Morphine LA	Arrow – Morphine LA tablets are indicated for the prolonged relief of opioid responsive severe and intractable pain in adults. Use in Non-Malignant Pain The use of Arrow – Morphine LA tablets for the treatment of pain which is not due to malignancy should be restricted to situations where: • All other conservative methods of analgesia have been tried and have failed • The pain is having a significant impact on the patient's quality of life • There is no psychological contraindication, drug seeking behaviour or history of drug misuse
	m-Eslon	For the prolonged relief of chronic, moderate to severe pain in adults. Use in Non-Malignant Pain The use of m-Eslon SR for the treatment of pain which is not due to malignancy should be restricted to situations where: • All other conservative methods of analgesia have been tried and have failed • The pain is having a significant impact on the patient's quality of life • There is no psychological contraindication, drug seeking behaviour or history of drug misuse.
	Sevredol	SEVREDOL tablets are indicated for the relief of both acute and chronic severe pain in adults and children aged three years and above.
	DBL Morphine Sulfate Injection	DBL Morphine Sulfate Injection BP 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. DBL Morphine Sulfate Injection BP may also be used as a pre-operative medication and as an analgesic adjunct in general anaesthesia.
Oxycodone	Oxycodone Sandoz modified release	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.
	OxyNorm (capsules, oral solution)	The management of opioid-responsive moderate to severe pain.
Paracetamol with codeine	Paracetamol + codeine (Relieve)	• For adults and children aged 12 years and above for effective, temporary relief of pain and discomfort associated with headache, migraine headache, tension headache, period pain, back pain, muscle pain, arthritis, toothache, dental procedures, neuralgia, sore throat, cold and flu symptoms in adults only (18 years and older) • Paracetamol + Codeine tablets also help reduce fever. • Paracetamol + Codeine is suitable for asthmatics sensitive to aspirin and NSAIDs.
Pethidine	Pethidine (PSM)	Pethidine Tablets given orally are indicated for the relief of most types of moderate to severe pain. As it has some antispasmodic activity, it may be the analgesic of choice in renal colic, biliary colic and acute pancreatitis.
	DBL™ Pethidine Hydrochloride Injection BP	• DBL Pethidine Hydrochloride Injection BP is indicated for administration as an anaesthetic adjunct and for obstetric analgesia. • DBL Pethidine Hydrochloride Injection BP is also indicated for the short-term (24 to 36 hours) 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. It can be given via the following routes of administration – intramuscular (IM), subcutaneous (SC), slow intravenous (IV) bolus injection, intravenous infusion and patient-controlled analgesia (PCA).

Tramadol	Tramal SR Arrow - Tramadol	Relief of moderate to severe pain.

a. For funded products only.
b. Published data sheet wording as at 16 November 2020.

Comments

There is a wide variation in the data sheets, including the types of pain the opioid is indicated for. Excluding the products used for opioid substitution therapy, only the data sheets for dihydrocodeine, fentanyl and morphine sulphate include information about misuse in the indication section.

4.1.1.2 Comparisons against Australian boxed warnings and class statements

As described in section 3.3 and Annex 3, the TGA now require box warnings and class statements in the prescribing information for all opioids. A comparison of the New Zealand data sheets against the Australian requirements is shown below.

Table 6: Comparison of New Zealand data sheets against the Australian boxed warnings and opioid class statements

Australian boxed warning and Precautions and Warning Class Statement (all opioids)	New Zealand opioid product data sheets - Australian wording[a] included in section 4.3: Special warnings and precautions for use: Yes or No										
	Buprenorphine Naloxone BNM	Codeine Phosphate PSM	DHC Continus Modified release	Fentanyl Sandoz Fentanyl Solution for injection Bo ucher & Muir	Biodone Oral solution Methatabs Methadone Injection BP Solution for injection (AFT)	RA Morph	Arrow – Morphine LA m-Eslon Sevredol DBL Morphine Sulfate Injection	Oxycodone Sandoz modified release OxyNorm	Paracetamol + codeine (Relieve)	Pethidine (PSM) DBL™ Pethidine Hydrochloride Injection BP	Tramal SR Arrow - Tramadol
Boxed warning[b]	No	No	No	No	No	No	DBL only	No	No	DBL only	No
Hazardous and harmful use	No	No	No	No	No	No	DBL only	No	No	DBL only	No
Respiratory depression[c]	Yes	No	Yes	Yes	No	Yes	Yes	OxyNorm only	No	Yes	Yes
Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol	Yes	No	Yes	Yes	Biodone and Methadone Yes	Yes	Yes	Yes	Yes	Yes	Yes
Use of opioids in chronic (long-term) non-cancer pain (CNCP)	No	No	No	No	No	No	DBL only	Sandoz only	No	DBL only	No
Tolerance, dependence and withdrawal	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Accidental ingestion/ exposure	Yes	No	No	Fentanyl Sandoz (patch) only	No	No	DBL only	No	No	DBL only	No
Hyperalgesia	No	No	No	No	No	No	Arrow and DBL Yes	Yes	No	DBL only	No
Ceasing opioids	Yes	No	No	No	No	No	DBL only	No	No	DBL only	No

a. The New Zealand wording may be similar but not identical to the Australian wording.
b. The boxed warning includes: Limitations of use, Hazardous and harmful use, Life threatening respiratory depression, Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol
c. The respiratory sedation warning is separate from the respiratory sedation associated with concomitant use of benzodiazepines and other CNS depressants.

Comments
Very few New Zealand data sheets contain the information now required in the Australian opioid prescribing information.

4.1.2 Opioid dependence [12]

In New Zealand, the *Diagnostic and Statistical Manual of Mental Disorders* (APA 2000 and 2013) and the *International Statistical Classification of Diseases and Related Health Problems* (ICD) (WHO 2010) are the diagnostic tools internationally used to classify mental health and substance-use disorders [12]. Either tool can be used however the World Health Organization requires New Zealand's Ministry of Health to report on opioid use disorders to international data collections under the ICD system.

Opioid dependence in New Zealand primarily involves the use of pharmaceutically sourced products (such as morphine, codeine-based products, methadone and oxycodone), home-bake heroin and opium poppies [12].

New Zealand national drug surveys on recreational drug use between 1996 and 2010 suggest that levels of opioid use, availability and price have remained constant; over this timeframe, approximately 1 percent of New Zealanders reported that they had ever tried opioids, and less than 1 percent reported current use. Estimates of the prevalence of opioid dependence in New Zealand have varied [12]. A 2008 two-arm survey (involving methadone treatment programmes and needle exchange programmes in Auckland, Tauranga and Christchurch) of regular (daily or almost daily) opioid users estimated the number of people with opioid dependence in New Zealand to be 9142; half of these people were reported to be in treatment.

4.1.3 Published literature

4.1.3.1 NZ deaths by opioid overdose – Shipton et al 2017 [66]

Title: Deaths from opioid overdosing: implications of coroners' inquest reports 2008–2012 and annual rise in opioid prescription rates: a population based study.

Method: Population-based cohort study with the main aim of investigating the opioid-related death rate in New Zealand between 1 January 2008 and 31 December 2012. Secondary aims were to: compare the opioid-related death rate per population in New Zealand in 2001/2002 with that in 2011/2012; investigate the number of opioid prescriptions in New Zealand between 2001 and 2012; compare the opioid-related death rate per population in NZ between 2001 and 2012 with the number of opioid prescription in New Zealand between 2001 and 2012. Coronial records from 2008–2012 were reviewed, and opioid prescription data (dose and formulation) was obtained from the Pharmaceutical Collection.

Results: There were 325 deaths primarily ascribed to opioid use from 2008 to 2012 (Table 7). Males had a higher rate of death than females (16.58 vs. 13.43 per 1,000,000 person-years; rate ratio 1.23; 95% CI 0.99–1.54; p = 0.059). The highest incidence rate per 1,000,000 person years was in the 40–49 year age group.

Table 7: [redacted]

[redacted]

There were 179 unintentional opioid overdoses, 110 intentional opioid overdoses and 37 opioid deaths from undetermined or other specified intent. The number of opioid deaths per year and type of opioid (2008–2012) is shown in Table 8. The opioids methadone, morphine, codeine were the most frequent causes of death.

Table 8: [redacted]

There was an increase in opioid prescribing for each type of opioid between 2001 and 2012 (Figure 12), except pethidine and dextropropoxyphene (the latter's approval was revoked in August 2010).

Figure 12: [redacted]

Between 2001 and 2012 there was an approximate linear relationship between the number of prescriptions and the number of deaths by primary opioid contribution: an increase of 100,000 opioid prescriptions was associated with an additional 2.4 (95% CI 1.6–3.2, $p < 0.001$) deaths. Much of the increase in deaths occurred between 2002 and 2008, with only weak evidence of a linear increase by year from 2008 and 2012 ($p = 0.07$).

The mortality rate per prescription for methadone, morphine and codeine have remained stable, however the absolute numbers of prescriptions and deaths has increased (Table 9).

Table 9: [redacted]

[redacted]

Conclusion: A multifaceted national public health approach is needed to bring together the various stakeholders involved with pain management, opioid dependence, opioid availability and opioid diversion. There needs to be a targeted approach to educate current and future medical practitioners regarding the appropriate use of opioid prescriptions for the management of pain, as well as a strengthening of primary, secondary and tertiary resources to support medical practitioners managing their patients who suffer with pain.

Comments
The reclassification of all codeine-containing products to prescription only may result in further increases in codeine prescribing as patients are no longer able to buy it over the counter. However, the requirement for patients to see a medical professional may result in less codeine harm, including deaths.

4.1.3.2 NZ deaths by poisoning – Fountain et al 2019 [67]

Title: Deaths by poisoning in New Zealand, 2008–2013

Methods: Retrospective study reviewing New Zealand's poison-related death findings recorded in the National Coronial Information System database from 1 January 2008 to 31 December 2013. The majority of the cases identified included a police report detailing the circumstances of death, a forensic toxicologist's report including measured levels of exogenous compound(s) and professional interpretation, a pathologist's report, and the coroner's findings. These documents were reviewed by an assessor with medical toxicology experience to confirm whether a poisoning-related death had occurred and, if possible, to identify the substance that was the primary contributor to death. Detailed clinical records relating to those who died in medical care were not available.

Results: There were 1402 poisoning-related deaths recorded in the NCIS database representing a mortality rate of 5.4 deaths/100,000 population per year. The mortality rate due to poisoning was higher in males (6.96/100,000) than females (3.83/100,000). Fatalities peaked in the 40–50-year age group with the highest proportion of intentional deaths occurring in people aged 80–90 years. Pharmaceuticals accounted for 731 fatalities (52%) and chemicals 431 (31%), with multiple exposures occurring in 399 cases (28.5%). There was no statistically significant change in either the opioid-related death rate (Figure 13) or the total number of deaths.

Figure 13: [redacted]

Methadone was the leading pharmaceutical cause of fatality and the third most common cause overall, followed by morphine and codeine, with zopiclone and clozapine equally ranked as the sixth most common cause (Table 10). The authors noted that the escalation in opioid-related deaths experienced by many developed nations was not evident from this New Zealand review.

Table 10: [redacted]

[redacted]

The authors noted that the most common substances primarily contributing to death identified in this study differ from those identified from 2001 New Zealand coronial data. While carbon monoxide, ethanol, morphine, and methadone were the most implicated agents in both studies, dosulepin, diazepam, paracetamol, and dextropropoxyphene were no longer significant based on this current study's findings and had been replaced by codeine, butane, clozapine, and helium. The authors stated that these changes may reflect successful interventions that include the removal of the opioid drug dextropropoxyphene from the New Zealand market, in August 2010, due to toxicity and lack of efficacy.

Comments
This study using data from the coronial database found that opioid-related deaths rates were reasonably stable between 2008 and 2013. The substances causing most poisoning deaths have changed since 2001 - regulatory actions may have contributed to these changes, including removal of the opioid dextropropoxyphene from the New Zealand market in 2010.

4.1.3.3 NZ study on intentional self-poisoning – Kumpula et al 2020 [68]

Title: Prescribers aware: a cross-sectional study from New Zealand emergency departments on the substances used in intentional self-poisoning and their sources

Method: A cross-sectional prospective study, collecting information about the demographics and presentation particulars of intentional self-poisoning patients aged ≥16 years, presenting to three public EDs (Wellington, Dunedin and Invercargill), as well as the substances they used in the self-poisoning event and the sources of these agents. ED clinicians collected the data. Patients excluded from the study were those presenting due to a purely recreational overdose (no self-harming intent evident), patients who were severely unwell and transferred to other wards such as the intensive care unit (ICU) and patients who were in an acute mental health crisis or otherwise not safe to be approached.

Results: A total of 102 patients were recruited from the potentially eligible 1137 intentional self-poisoning patients presenting to the three EDs during the study period. The median age of participants was 21.5 years (interquartile range [IQR]: 18.3–29), and more than two-thirds (68%) were female. Most patients (88%) were NZ European, with 5% Māori and 1% Pasifika. Thirty patients (29%) had pre-existing psychiatric conditions (23 of which had depression) and 30 patients had non-psychiatric pre-existing conditions.

Paracetamol and ethanol were most commonly encountered substances (Table 11). Most participants self-reported that they had used their own medications in the intentional self-poisoning event (Table 12).

Table 11: [redacted]

Table 12: [redacted]

Conclusions: Most people use their own prescribed medicines in intentional self-poisoning. Paracetamol and ethanol are the most common substances involved in hospital presentations due to self-poisoning.

Comments
The total study sample was relatively low and only included eligible patients that were well enough to participate. Therefore, the results may not be generalisable to the population of patients who are dispensed opioids in New Zealand. However, this study has been included as the data is more recent.

4.1.4 National collections

See Annex 4 for an explanation of the data supplied by National Collections.

In summary, the 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).

Limitations of the data

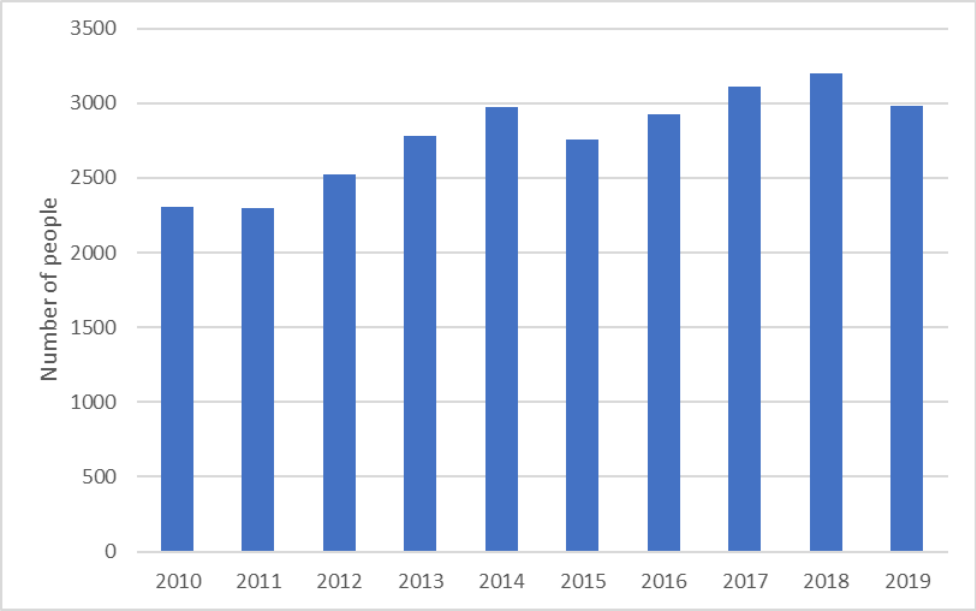
- Only includes information for funded prescription opioids that were dispensed in the community. It does not include non-funded prescription medicines, or codeine-combination medicines that were previously available without prescription. It does not include harm from illicit opioid use.
- The data contains 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.

4.1.4.1 Hospital discharges

Figure 14 shows the number of people who had been dispensed an 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.

The number of people hospitalised rose steadily between 2010 and 2014, then decreased in 2015. From 2016 to 2018 the numbers increased again, and then dropped in 2019. Note this is the number of people hospitalised rather than the number of hospitalisations – it does not include repeat hospitalisations for the same person in the same year.

Figure 14: Number of people who had been dispensed an opioid who were discharged from hospital[a] with substance abuse or poisoning clinical codes[b], 2010 to 2019



a. Excludes repeat discharges in the same calendar 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.

Table 13 shows the number of people who had an initial opioid dispensing in a particular year and who were hospitalised with a substance use or poisoning disorder in that same year. This is to avoid overcounting and duplication. The opioids associated with the greatest number of people being hospitalised in the same year as the initial dispensing are codeine, tramadol and morphine sulphate.

Table 13: Number of people dispensed a particular opioid who were discharged from hospital[a] with substance abuse and poisoning codes[b] during the same year as the initial dispensing, 2010 to 2019

Opioid (Chemical ID)	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
All	1567	908	958	940	933	897	952	968	874	782
Codeine phosphate (1332)	656	333	353	313	287	258	258	248	237	221
Tramadol hydrochloride (3906)	317	368	332	309	297	285	270	249	200	167
Morphine sulphate (1831)	224	101	117	126	170	164	151	162	143	133
Buprenorphine + naloxone (3950)	0	0	34	52	78	95	146	133	97	94
Paracetamol + Codeine (1931)	302	191	170	140	114	103	111	129	112	93
Methadone hydrochloride (1795)	623	77	80	74	83	68	97	78	89	73
Oxycodone hydrochloride (3822)	219	110	113	71	81	68	56	90	88	73
Morphine hydrochloride (1830)	69	30	40	36	54	57	40	48	59	39
Fentanyl (3801)	15	40	27	39	46	43	31	55	33	30
Dihydrocodeine tartrate (2427)	133	50	58	55	45	46	42	35	38	29
Morphine tartrate (2383)	3	3	3	4	2	2	1	2	1	3
Pethidine hydrochloride (1953)	15	3	2	3	1	5	2	2	0	1

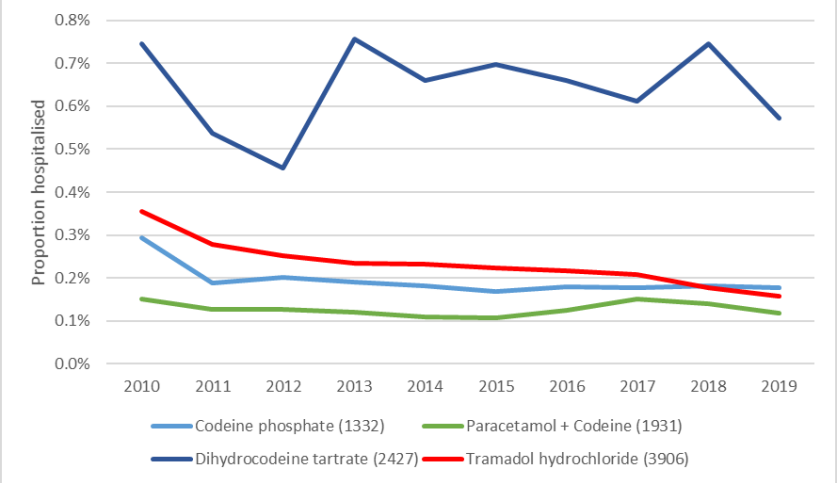
a. Excludes repeat discharges in the same calendar year.

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.

Figure 15 shows the proportion of people hospitalised in the same year as the initial weak opioid dispensing compared to those that were dispensed that opioid and not hospitalised. Figure 16 shows the strong opioids, excluding the opioid substitution treatments (OST), methadone and buprenorphine with naloxone.

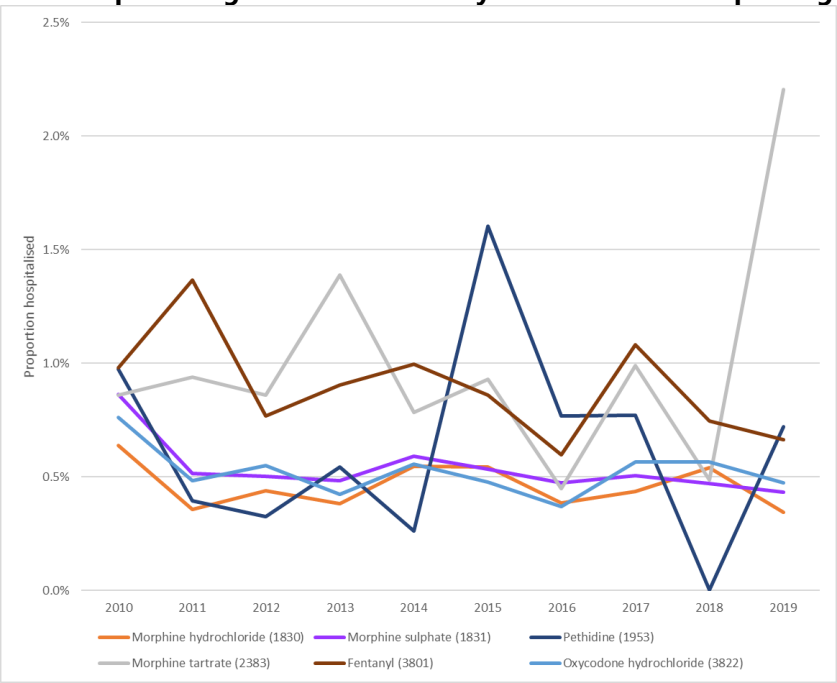
Of the weak opioids, a greater proportion of people were hospitalised with a poisoning or substance abuse code following a dispensing of dihydrocodeine compared to the other opioids. Compared to the weak opioids, the proportions fluctuate more and are higher for the strong opioids. This may be in part due to the lower numbers of people who received strong opioids. Due to their increased potency, strong opioids may also be more likely to contribute to a hospitalisation event within 12 months of dispensing compared to a weak opioid.

Figure 15: 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.

Figure 16: Proportion[a] of people dispensed a strong opioid[b,c] who were hospitalised with a substance abuse or poisoning code[d] in the same year as the initial dispensing[e], 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. Excludes the strong opioids methadone and buprenorphine with naloxone that are used for opioid substitution treatment.
c. As at January 2020, morphine tartrate was no longer approved in New Zealand.
d. 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.
e. Excludes repeat discharges in the same calendar year.

Not shown in Figure 16 are the proportions for the opioid substitution treatments: methadone and buprenorphine with naloxone. The average proportions for these two medicines were much higher than the other strong opioids. Across the 10-year period, on average, 5.8% of people were hospitalised with a poisoning or substance abuse code in the same year as a dispensing of methadone and 26.4% for buprenorphine with naloxone – likely reflecting the indications that these products are used for.

4.1.4.2 Mortality

Between 2010 and 2016, there were 327 deaths in patients who had been dispensed an opioid and the cause of death was due to poisoning or substance abuse (Table 14). Accidental poisoning (X42) was the most common cause of death, followed by intentional self-poisoning.

Table 14: Number of deaths per year in patients who had been dispensed an opioid, with underlying cause of death attributed to a substance abuse or poisoning code[a], 2010 to 2016

Code	2010	2011	2012	2013	2014	2015	2016	Year Unknown	Total
F11.2	3	2	0	0	2	0	0	0	7
F19.2	0	1	0	0	0	0	0	0	1
X42	22	25	27	33	34	28	24	1	194
X62	10	13	17	19	12	11	12	3	97
Y12	2	2	7	5	4	3	5	0	28
Total	37	43	51	57	52	42	41	4	327

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.

With the exception of the patients noted below, all deaths shown in Table 14 had an accompanying T40.2, T40.3, T40.4 or T40.6 nature of injury code.

- F11.2 – includes 3 patients in 2010, 2 in 2011 and 1 in 2014 who did not have an accompanying T40 (poisoning by narcotics and psychodysleptics) nature of injury code.
- F19.2 – includes 1 patient in 2011 who do not have an accompanying T40 nature of injury code.
- X42 – includes 2 patients in 2011, and 1 each in 2013, 2014 and 2016 who had an accompanying T40.1 (heroin) nature of injury code.
- Y12 – includes 1 patient in 2012 and 2014 who had an accompanying T40.1 (heroin) injury code.

Codeine, tramadol, paracetamol + codeine and methadone were the dispensed opioids associated with the greatest number of deaths per year (Table 15).

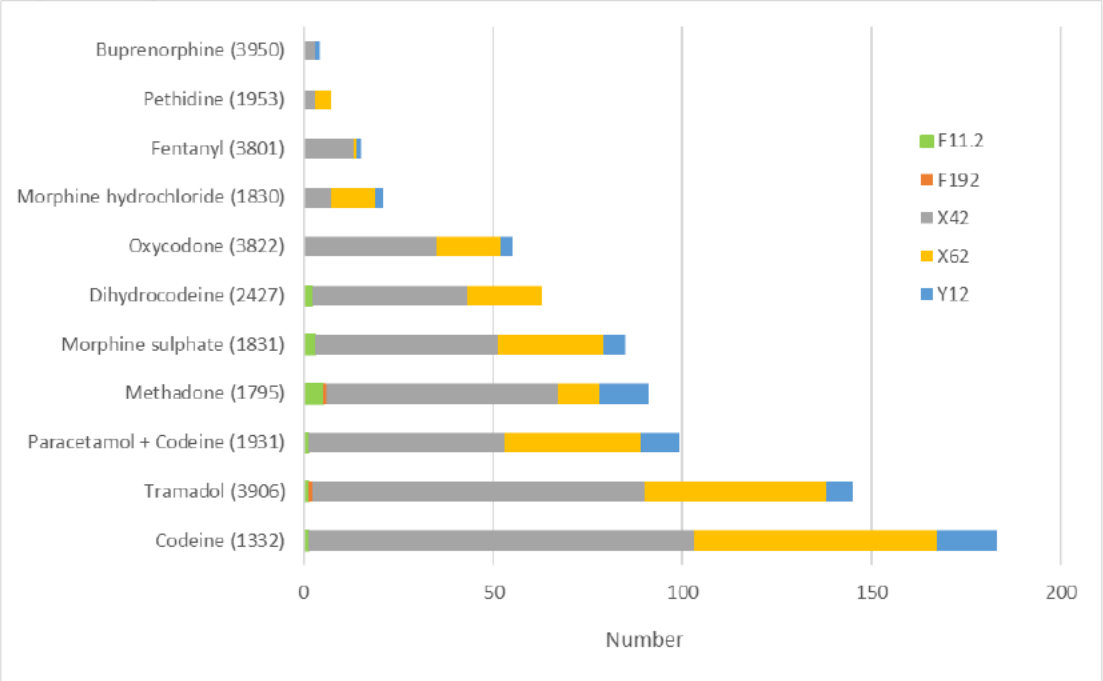
Table 15: Number of deaths per year due substance abuse or poisoning codes[a], by dispensed opioid, 2010 to 2016

Opioid (Chemical ID)	2010	2011	2012	2013	2014	2015	2016	Unknown[b]	Total
All	37	43	51	57	52	42	41	4	327
Codeine (1332)	18	17	31	34	27	24	28	3	182
Tramadol (3906)	5	15	22	27	26	25	23	2	145
Paracetamol + Codeine (1931)	7	9	16	14	15	17	21		99
Methadone (1795)	6	16	14	15	17	12	11		91
Morphine sulphate (1831)	7	9	16	14	12	12	14	1	85
Dihydrocodeine (2427)	6	3	9	12	11	15	6	1	63
Oxycodone (3822)	6	7	12	11	8	5	7		56
Morphine hydrochloride (1830)	2	3	9	3	2	1	1		21
Fentanyl (3801)	0	1	3	1	1	3	6		15
Pethidine (1953)	0	0	1	2	2	2	0		7
Buprenorphine (3950)	0	0	1	1	0	0	2		4
Morphine tartrate (2383)	0	0	0	0	0	0	0		0

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.

With the exception of morphine hydrochloride, accidental poisoning (X42) was most frequently recorded as the primary cause of death for the dispensed opioids, followed by intentional self-poisoning (Figure 17).

Figure 17: Total deaths between 2010 and 2016 due to substance abuse or poisoning clinical codes[a], by dispensed 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.

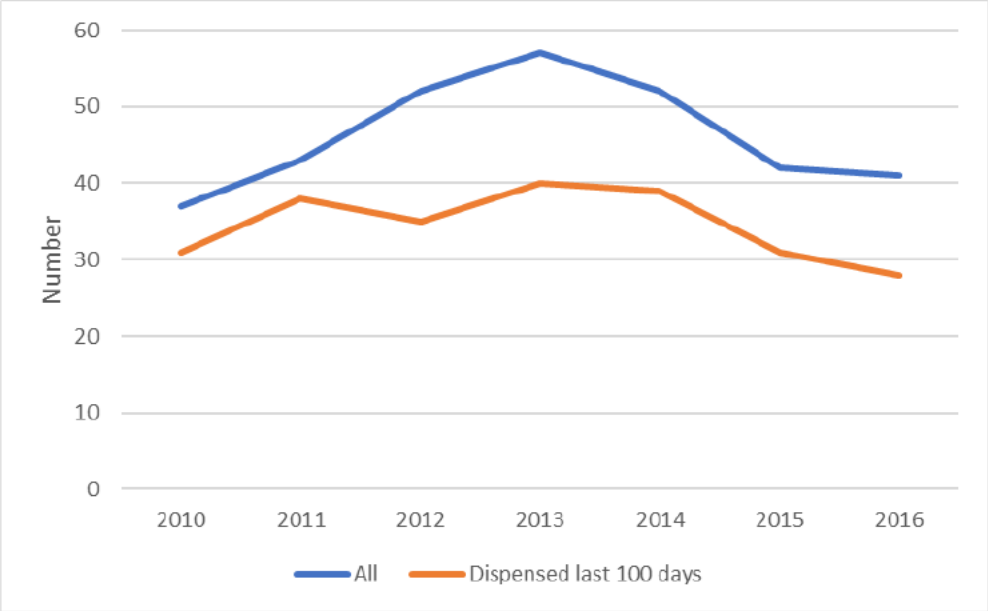
Table 16 below shows the number of deaths due to poisoning or substance abuse within 100 days of the final dispensing, by opioid. This cut-off was chosen to try and focus the data to cases more likely to be related to the prescribing. The number of deaths is lower than in Table 15 above, but the overall trend from 2010 to 2016 is the same (Figure 18).

Table 16: Number of deaths per year due to substance abuse or poisoning clinical codes*, within 100 days of last opioid dispensing, 2010 to 2016

Opioid (Chemical ID)	2010	2011	2012	2013	2014	2015	2016	Total
All	31	38	35	40	39	31	28	242
Codeine (1332)	12	11	6	14	14	6	11	74
Methadone (1795)	4	14	9	11	11	10	6	65
Tramadol (3906)	4	8	9	11	12	8	7	59
Morphine sulphate (1831)	7	5	10	7	7	5	7	48
Dihydrocodeine (2427)	5	3	5	9	6	5	2	35
Oxycodone (3822)	5	4	8	2	3	2	1	25
Paracetamol + Codeine (1931)	5	6	2	2	3	3	1	22
Morphine hydrochloride (1830)	1	3	5	1	2	1	1	14
Fentanyl (3801)	0	1	2	0	0	1	3	7
Pethidine (1953)	0	0	0	0	1	0	0	1
Buprenorphine (3950)	0	0	1	0	0	0	0	1
Morphine tartrate (2383)	0	0	0	0	0	0	0	0

* 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.

Figure 18: Number of deaths due to poisoning or mental and behavioural disorders: opioids dispensed at any time and deaths within 100 days of last opioid dispensing, 2010 to 2016



4.1.5 CARM data

Serious reports

[redacted]

Abuse, misuse or dependence

The search terms for abuse, misuse or dependence were:

- Drug dependence (Non-narcotic)
- Drug dependence (Narcotic)
- Drug abuse
- Drug alcohol interaction
- Drug withdrawal syndrome
- Withdrawal syndrome
- Coma
- Intentional overdose
- Accidental overdose
- Sudden death

Since the year 2000, there have 51 cases reported to CARM where the suspect medicine was an opioid and the reported reactions were assessed as abuse, misuse or dependence terms.

Of the 51 case reports:

- 44 were associated with 1 opioid medicine and 7 were associated with two or more opioids
- 27 were for women, 23 for men and gender was not reported in 1 case
- 43 had a reported age, which ranged from 17 months to 82 years (mean age 47.2 years):
  - 2 were in children aged under 2 years, [redacted]
  - 6 in adults aged 20–29 years

- 4 in adults aged 30–39 years
- 10 in adults aged 40–49 years
- 10 in adults aged 50–59 years
- 8 in adults aged 60–69 years

[redacted]

Table 17: [redacted]

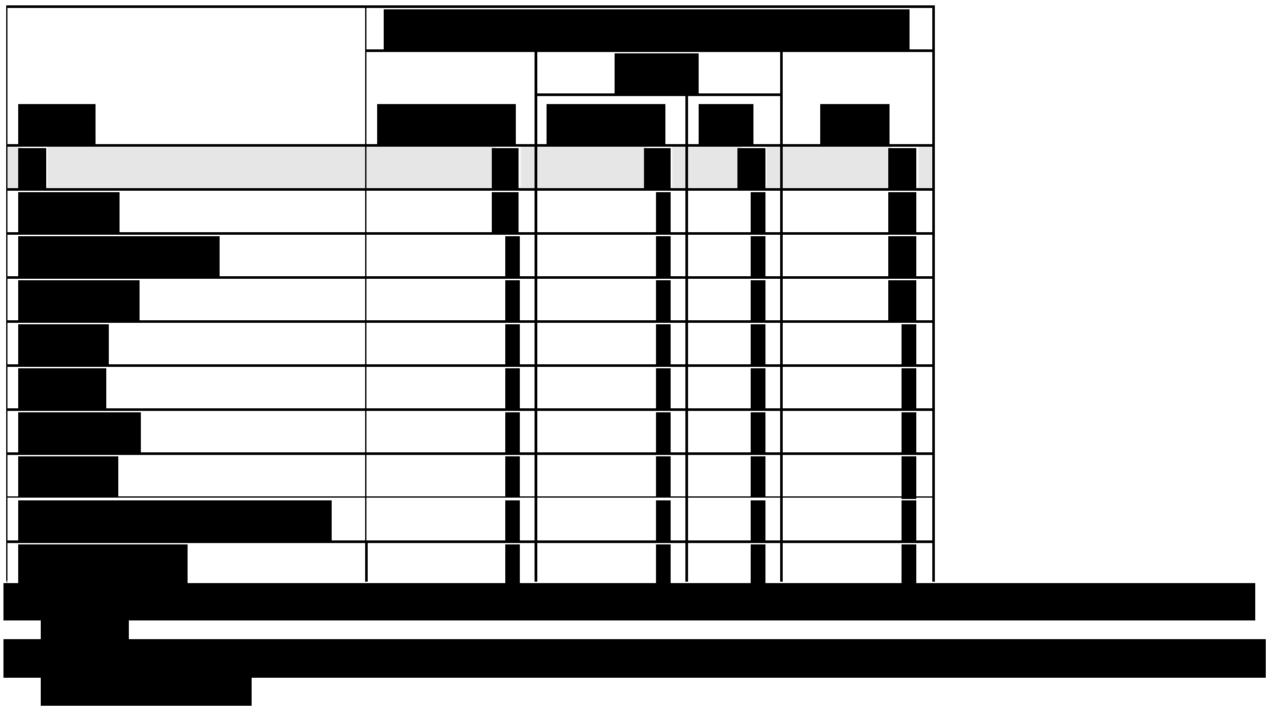
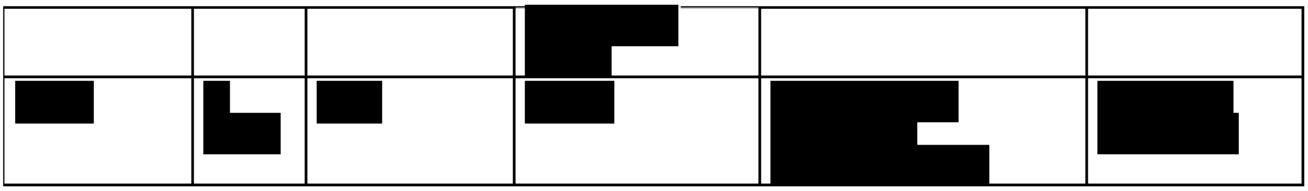


Table 18: [redacted]



4.1.6 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. See Annex 5 for the full information received from the NPC.

There were 1,889 calls to the NPC for opioid exposures during the time period (Table 19). 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.

Table 19: 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.

There is a high rate of polysubstance exposures involving opioids (Table 20). Among opioid exposures, 65% involved a single substance. For comparison purposes, 92% of all exposures reported to the NPC during this period involved a single substance.

Table 20: Number of substances in exposure, selected opioids, 1 January 2017 to 30 June 2020

Number of substances in exposure	Patients	% of total
1	1,232	65.2%
2	324	17.2%
3	174	9.2%
4	80	4.2%
5	34	1.8%
6	22	1.2%
7	13	0.7%
8	8	0.4%
9	2	0.1%
Grand Total	1,889	100.0%

Patient demographics (age, gender, ethnicity) are shown in Table 21. Most patients were aged 20 and over, female and European. However, 28.7% of the patients were children aged 12 years and under.

Table 21: Patient demographics for opioid exposure, 1 January 2017 to 30 June 2020

	Patients	% of total
Age		
0–12 years	542	28.7
13–19 years	239	12.7
20 years and older	1,069	56.6
Unknown	39	2.1
Total	1,889	100
Gender		
Female	1,118	59.2
Male	679	35.9
Unspecified or unknown	92	4.9
Total	1,889	100
Ethnicity		
NZ Maori	208	11.0
Pacific peoples	35	1.9
Asian	19	1.0
MELAA	7	0.4
Other	25	1.3
European	521	27.6
Don't know/Not stated/Refused to say	1,074	56.9
Total	1,889	100

Reasons for the exposure event are shown in Table 22. Intentional exposure (29.3%), child exploratory (26.5%) and therapeutic error (21.2%) were the main reasons given. Abuse exposures were just under 4% of the total.

When compared to all exposures reported to the NPC during the same period, 6% of exposures were categorised as intentional, 14% categorised as therapeutic error and 1.1% of opioid exposures were categorised as abuse. The NPC notes that they are not likely to be called in the context of opioid abuse by the general populations, although the proportion of exposures categorised as abuse and involving opioids is higher compared to all exposures.

Table 22: Reason for exposure event, selected opioids, 1 January 2017 to 30 June 2020

Reason for exposure event	Patients	% of total
Abuse	70	3.7%
Child Exploratory	500	26.5%
Intentional	553	29.3%
Other	7	0.4%
Therapeutic error	400	21.2%
Unintentional	276	14.6%
Unknown	83	4.4%
Grand Total	1,889	100.0%

Where the NPC was able to give advice on management of the exposure, 59.3% of the 1,889 patients exposed to opioids were advised to seek medical referral. For comparison purposes, 25% of all exposures reported to the NPC for the same period were categorised as medical referrals.

4.1.7 New Zealand Drug Harm Index [69]

The New Zealand Drug Harm Index 2016 estimated the social cost of drug-related harms and intervention costs in New Zealand in 2014/15 as $1.8 billion [69]. Of this, opioids and sedative drugs contributed $175.9 million: $80.1 million for personal harm; $72 million for community harm; $23.8 million for intervention costs (with $5.3 million attributed to health costs, $7 million to police/customs and $6.3 million to courts/corrections).

Based on figures derived from the New Zealand Health Survey, there were an estimated 388,000 illicit drug users in 2012/13. Of this population, there were estimated to be 29,200 opioid and sedative drug users: 2,000 dependent users and 27,200 casual users.

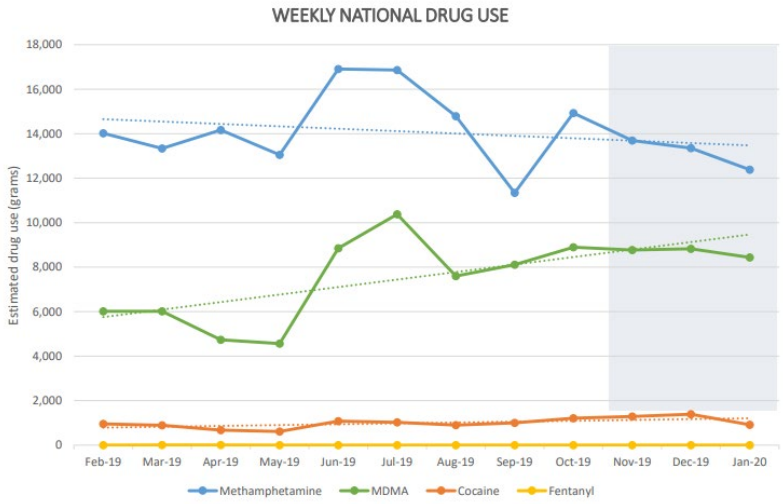
4.1.8 National wastewater testing programme [70, 71]

Nationwide wastewater testing started in November 2018, and testing sites cover approximately 75 percent of the total New Zealand population. Wastewater testing occurs during one week per month, however the frequency of testing varies between sites. The drugs being tested for are: methamphetamine, cocaine, heroin, MDMA and fentanyl.

The quarter 1 2020 (November 2019 to January 2020) results were published in August 2020. Methamphetamine is the most commonly detected illicit drug nationwide – the average national weekly use for quarter 1 of 2020 was 13.1 kg (Figure 19. In comparison, fentanyl was rarely detected above the limit of quantification, and no patterns of use were apparent. Heroin was not detected at any of the testing sites. Figure 20 shows the per capita drug use (mg/day/1,000 people) by Police district per testing quarter (from Q2 2019 to Q1 2020).

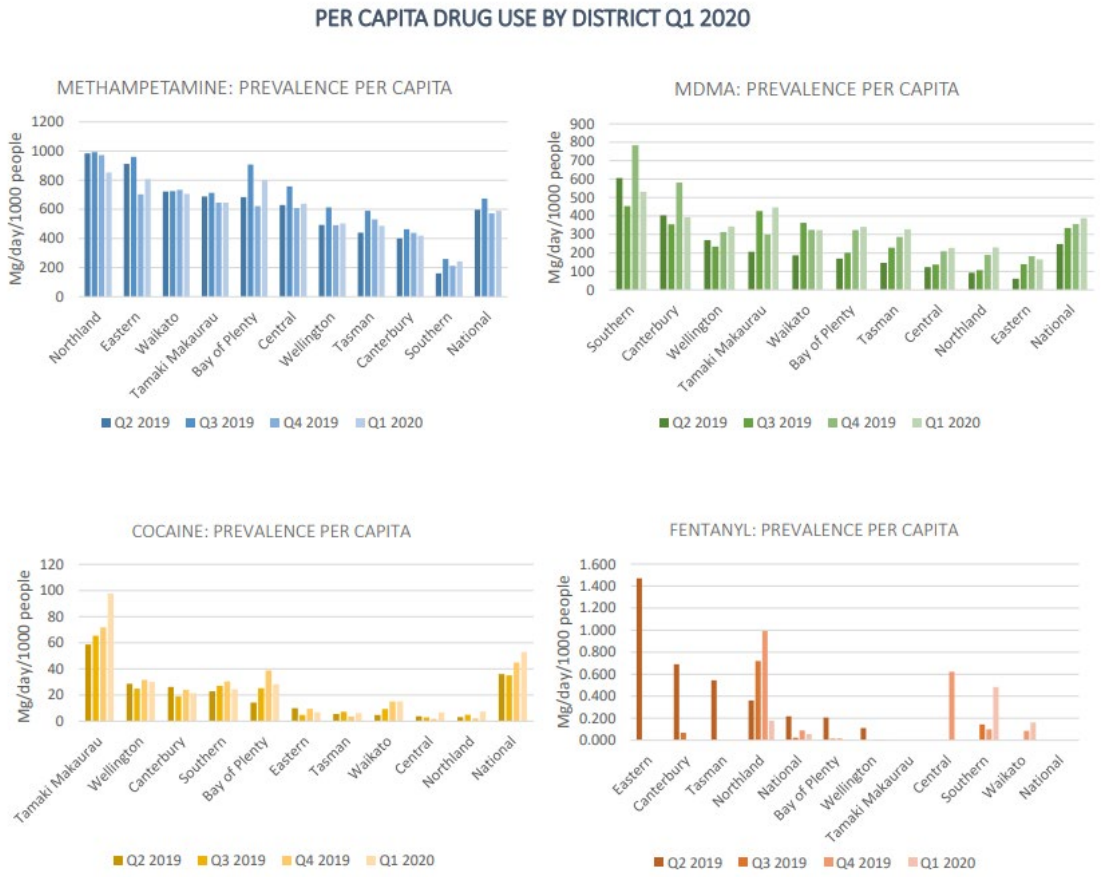
The aim of testing for fentanyl is to establish a baseline of consumption so, over time, Police and the Ministry of Health can determine any fluctuations in the consumption. A baseline for consumption remains unclear at present. As fentanyl has only been tested for very recently, it is too early to draw conclusions about what proportion of the fentanyl in wastewater is illicit.

Figure 19: National wastewater testing programme: Weekly national drug use, Feb 2019 to Jan 2020



Source: New Zealand Police. 2020. *National Wastewater Testing Programme - Quarter 1 2020* August 2020. URL: https://www.police.govt.nz/about-us/publication/national-wastewater-testing-programme-quarter-1-2020 (accessed 28 September 2020).

Figure 20: National wastewater testing programme: Per capita drug use by district,* by quarter



* Per capita graphs are not shown on a comparative scale, due to the significant variance across different drug types. Drug use is shown as milligrams consumed per day, per 1,000 people.

Source: New Zealand Police. 2020. *National Wastewater Testing Programme - Quarter 1 2020* August 2020. URL: https://www.police.govt.nz/about-us/publication/national-wastewater-testing-programme-quarter-1-2020 (accessed 28 September 2020).

Sample sites in each police district are shown in Table 23 below. Note that regions covered by police districts and district health boards do not always align. For example, the Central police district includes Whanganui, New Plymouth, Palmerston North and Levin, whereas these regions are covered by the Whanganui, Taranaki and MidCentral DHBs, respectively.

Table 23: Police districts and wastewater sample testing sites

Police district	Sample sites
Northland	Whangarei, Kerikeri
Eastern	Gisborne, Hastings, Napier, Wairoa
Canterbury	Christchurch, Ashburton, Timaru, Rangiora
Tasman	Nelson Bell Island, Nelson city, Greymouth, Blenheim, Westport
Central	Whanganui, New Plymouth, Palmerston North, Levin
Bay of Plenty	Tauranga city, Tauranga beach, Whakatane, Rotorua, Taupo, Kawerau, Opotiki, Tokoroa
Southern	Dunedin Green Island, Queenstown, Dunedin Tahuna, Invercargill
Wellington	Paraparaumu, Masterton, Moa Point, Karori, Porirua, Seaview
Waikato	Waikato, Thames, Huntly
Tamaki Makaurau	Rodney, Central, North, West, South

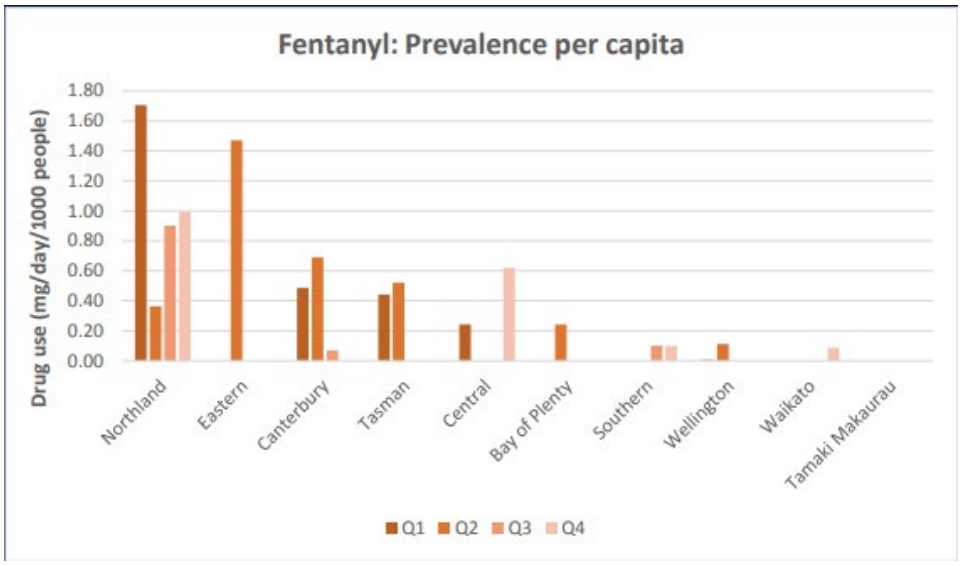
Comparison of fentanyl wastewater prevalence versus dispensings

If fentanyl is detected in wastewater in regions where dispensing is low, that may be an indication that the detected fentanyl is illicit. Fentanyl dispensing data is available up to the end of 2019, so the figures below show data for each quarter of 2019 (testing quarters, rather than calendar quarters).

Figure 21 shows the fentanyl prevalence in use per day (mg/day/1,000 people) for each of the wastewater testing regions, for each testing quarter of 2019. NZ Police state that the identification of fentanyl in Northland Districts, compared to other districts, must be viewed with caution as the detected average usage across all testing sites is extremely low [71].

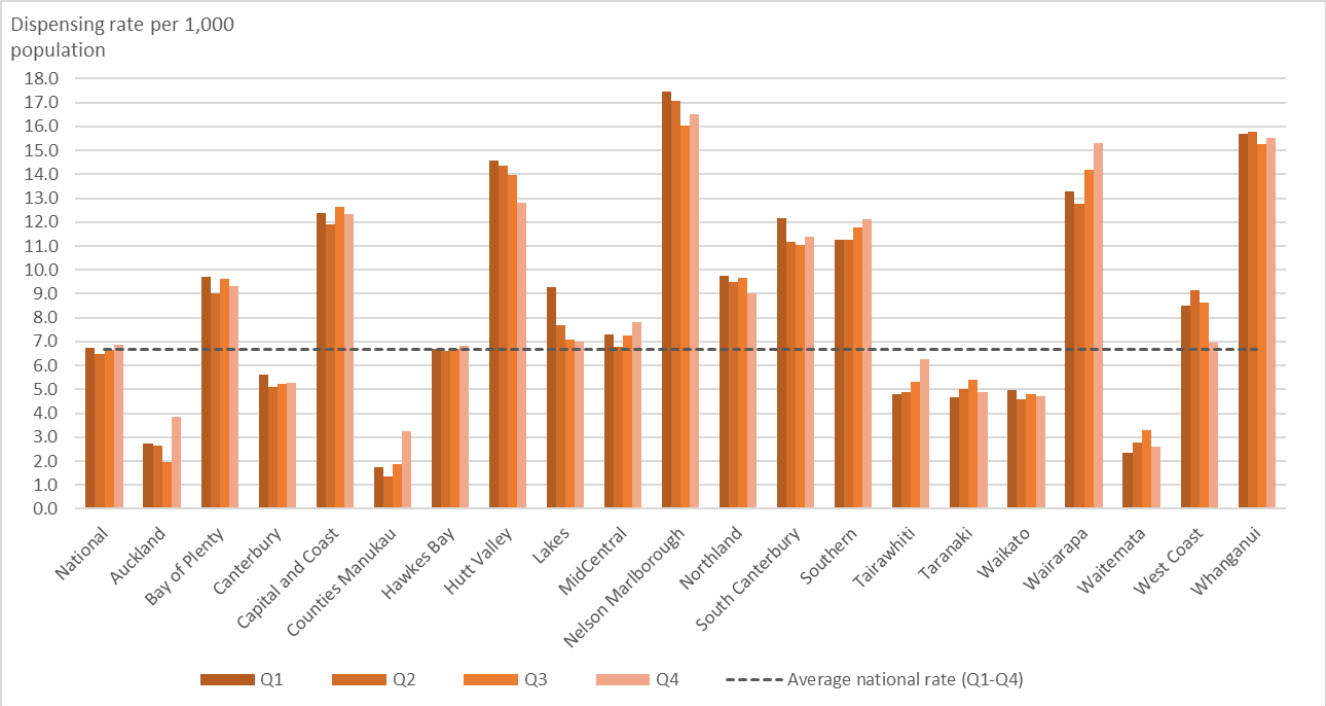
Figure 22 shows the fentanyl dispensing rate per 1,000 population, for the corresponding quarters of 2019. The dotted line is the average national dispensing rate for the year.

Figure 21: Fentanyl prevalence per capita, by testing quarter*



* Testing quarters: Q1 = Nov 2018 to Jan 2019; Q2 = Feb 2019 to Apr 2019; Q3 = May 2019 to Jul 2019; Q4 = Aug 2019 to Oct 2019

Figure 22: Fentanyl dispensing rates per DHB, by testing quarter*



* Testing quarters: Q1 = Nov 2018 to Jan 2019; Q2 = Feb 2019 to Apr 2019; Q3 = May 2019 to Jul 2019; Q4 = Aug 2019 to Oct 2019

Sources:
DHB Populations from Stats NZ. NZ.Stat: Subnational population estimates (DHB, DHB constituency), by age and sex, as at 30 June 1996–2019 (2020 boundaries). URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509.
Quarterly dispensing data from the 'Pharmaceutical dispensings Proof of Concept' Qlik application. The data was published on 4 March 2020 and last loaded on 11 June 2020. The data and methods used have not been tested. These are not official statistics.

4.2 International comparisons

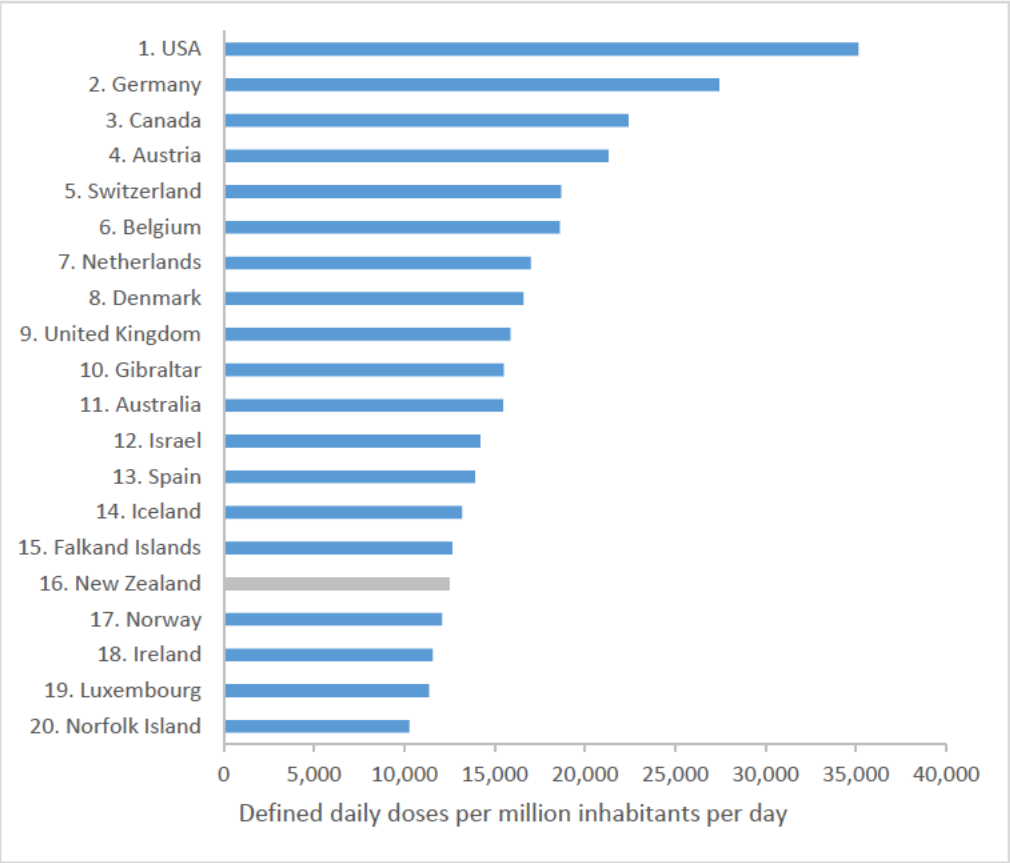
Issues related to opioid use and harm have been reported in several countries [4]. Although complicated by underlying differences in health systems, data definitions, social context, populations and data availability, international comparisons of data are important.

4.2.1 Licit opioid consumption

Licit opioid consumption can be measured using the defined daily dose (DDD) per capita, per day [4]. This is a measure, per capita, of the assumed average doses of opioids for an adult, per day.

Based on data from the International Narcotics Control Board, New Zealand has the 16th highest opioid consumption in DDDs per capita, per day, of 181 countries and territories [72]. The United States ranks first, with around 35,140 DDDs per 1,000,000 population, followed by Germany, with around 27,400 (see Figure 23). New Zealand has around 12,470 DDDs per 1,000,000 population (see grey bar). Note that this data does not include codeine consumption for New Zealand, although it does for some other countries.

Figure 23: Licit opioid consumption[a,b] (excluding preparations in Schedule III), defined daily doses per 1,000,000 population, top 20 countries and territories, 2016–2018



a. This table presents the information on the average consumption by countries/territories and regions of the eight most consumed narcotic drugs (codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, pethidine, others), expressed in S-DDD per million inhabitants per day, excluding preparations listed in Schedule III of the Single Convention on Narcotic Drugs of 1961, in the three-year period 2016–2018.

b. There is no New Zealand data reported for codeine; hydrocodone and hydromorphone were less than 1 DDD per million inhabitants.

Source: International Narcotics Control Board. 2020. Table XIV.1.a: All countries: levels of consumption of narcotic drugs, in defined daily doses for statistical purposes per million inhabitants per day. In: *Narcotic Drugs - Estimated World Requirements for 2020, Statistics for 2018.* URL: https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2019/Narcotic_Drugs_Technical_Publication_2019_web.pdf (accessed 30 September 2020).

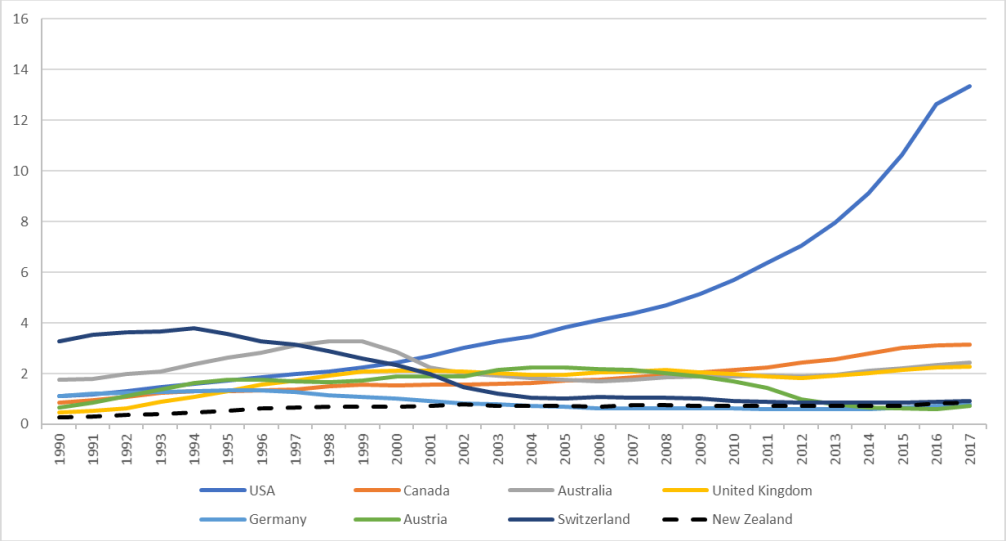
Comments
The data in Figure 23 does not support a problem of opioid overuse in New Zealand.

4.2.2 Mortality

4.2.2.1 Poisoning

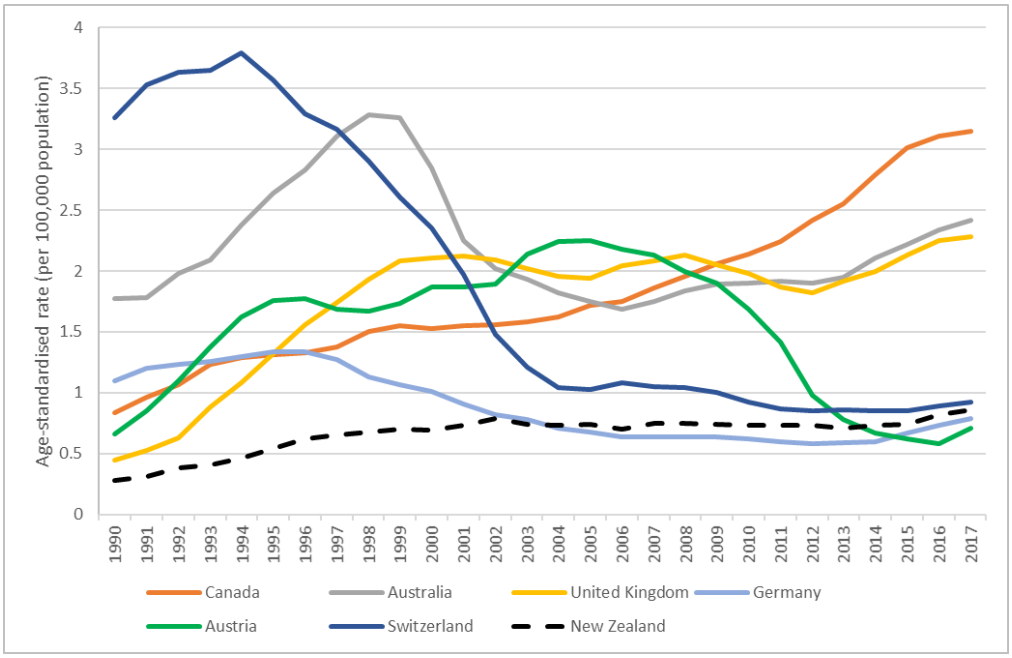
Age standardised rates of death due to opioid-use disorders for selected countries are shown below. Figure 24 includes the USA, and Figure 25 excludes the USA so that death rates for other countries can be more easily seen.

Figure 24: Age-standardised rates of death due to opioid-use disorders (cause B7.2.1), selected countries, 1990 to 2017



Source: Global Health Data Exchange. *GBD Results Tool*. URL: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2017-permalink/569cfab3777a4c822ca0ec07c4a578f9 (accessed 30 September 2020).

Figure 25: Age-standardised rates of death due to opioid-use disorders (cause B7.2.1), selected countries (excluding USA), 1990 to 2017



Source: Global Health Data Exchange. *GBD Results Tool*. URL: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2017-permalink/569cfab3777a4c822ca0ec07c4a578f9 (accessed 30 September 2020).

Comments

Rates of death from opioid-use disorders in New Zealand are low compared to many other Western countries, and much lower than in the USA. The rate of death has also been reasonably stable in NZ, compared to other countries.

4.3 Company data

[redacted]

5 DISCUSSION AND CONCLUSIONS

This paper reviews the available data on opioid use to try and ascertain if there is a problem in New Zealand, or a recent increase in problems as seen elsewhere.

If the MARC conclude that there is a problem that needs addressing, Medsafe will investigate potential actions and bring options back to the Committee for discussion. Medsafe acknowledges that there is a balance between regulating these products to prevent harm, while still allowing patients safe and appropriate access to opioids to manage pain.

6 ADVICE SOUGHT

The Committee is asked to advise:

- Whether there is evidence of an abuse, misuse and dependence problem with opioids in New Zealand?

7 ANNEXES

Annex 1: Opioid products approved in New Zealand

Annex 2: Opioid usage information – 2019

Annex 3: Australian boxed warnings and opioid class statements

Annex 4: Explanation of the linked National Collections data

Annex 5: National Poisons Centre data request

Annex 6: Line listings of NZ tramadol cases for Drug abuse and Drug diversion – Seqirus

8 REFERENCES

1. 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).
2. 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).
3. United Nations Office on Drugs and Crime (UNODC) and World Health Organization (WHO). 2013. *Discussion paper: Opioid overdose: preventing and reducing opioid overdose mortality*. URL: https://www.who.int/substance_abuse/publications/opioid_overdose.pdf (accessed 2 July 2020).
4. 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).
5. Medsafe. 2020. *Reclassification of codeine* 23 October 2020. URL: https://www.medsafe.govt.nz/profs/class/ReclassificationOfCodeine.asp (accessed 10 November 2020).
6. Ministry of Health. 2019. *Controlled drugs* updated 13 February 2019. URL: https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/controlled-drugs (accessed 6 November 2020).
7. Ministry of Health. 2018. *Medicines Control* updated 26 February 2018. URL: https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control (accessed 14 November 2020).
8. Ministry of Health. 2019. *Drug abuse containment* updated 13 February 2019. URL: https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/drug-abuse-containment (accessed 10 November 2020).

9. Berterame S, Erthal J, Thomas J, et al. 2016. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *The Lancet* 387(10028): 1644-56. DOI: https://doi.org/10.1016/S0140-6736(16)00161-6 (accessed 25 June 2020).
10. New Zealand Formulary. 2020. *New Zealand Formulary v101.1: Central nervous system/Opioid analgesics* 5 November 2020. URL: https://nzf.org.nz/nzf_2456 (accessed 29 September 2020).
11. New Zealand Formulary. 2020. *New Zealand Formulary v101.1: Palliative care/Pain - Opioid analgesics* 5 November 2020. URL: https://nzf.org.nz/nzf_70664 (accessed 28 September 2020).
12. Ministry of Health. 2014. *New Zealand Practice Guidelines for Opioid Substitution Treatment.* URL: https://www.health.govt.nz/publication/new-zealand-practice-guidelines-opioid-substitution-treatment-2014 (accessed 11 November 2020).
13. Pathan H and Williams J. 2012. Basic opioid pharmacology: an update. *British Journal of Pain* 6(1): 11-16. DOI: 10.1177/2049463712438493 (accessed 29 September 2020).
14. Snyder B. 2014. Revisiting old friends: update on opioid pharmacology. *Australian Prescriber* 37(2): 56-60. URL: https://www.nps.org.au/australian-prescriber/articles/revisiting-old-friends-update-on-opioid-pharmacology (accessed 9 September 2020).
15. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. 2015. *Acute Pain Management: Scientific Evidence (Fourth edition).* Available at: https://www.anzca.edu.au/safety-advocacy/advocacy/college-publications# (accessed 3 July 2020).
16. Medsafe. 2018. Spotlight on codeine. *Prescriber Update* 39(2): 18-19. URL: https://www.medsafe.govt.nz/profs/PUArticles/June2018/SpotlightOnCodeine.htm (accessed 10 November 2020).
17. Medsafe. 2020. Spotlight on tramadol, including updated advice for use in children. *Prescriber Update* 41(2): 25-6. URL: https://www.medsafe.govt.nz/profs/PUArticles/June2020/Spotlight-on-tramadol.html (accessed 10 November 2020).
18. BPAC NZ. 2018. *Unintentional misuse of prescription medicines* 26 October 2018. URL: https://bpac.org.nz/2018/misuse.aspx (accessed 14 November 2020).
19. 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).
20. 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).
21. National Academies of Sciences E, 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).
22. 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).
23. BPAC NZ. 2018. *When to consider strong opioids for patients with acute pain* 23 February 2018. URL: https://bpac.org.nz/2018/opioids.aspx (accessed 2 July 2020).
24. 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).
25. BPAC NZ. 2020. *Codeine: all formulations prescription only* 9 October 2020. URL: https://bpac.org.nz/2020/codeine.aspx (accessed 10 November 2020).
26. BPAC NZ. 2020. *Codeine reclassified as a prescription-only medicine: a community pharmacist perspective* 9 October 2020. URL: https://bpac.org.nz/2020/codeine-rx.aspx (accessed 16 November 2020).

27. BPAC NZ. 2014. Identifying and managing addiction to opioids. *Best Practice Journal* 64(16-25. URL: https://bpac.org.nz/bpj/2014/october/opioid-addiction.aspx (accessed 2 July 2020).
28. Health Quality and Safety Commission New Zealand. 2019. *Atlas of Healthcare Variation - Opioids* updated 11 October 2019. URL: https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/opioids/ (accessed 11 November 2020).
29. Unites States Drug Enforcement Administration. *Drug Scheduling* URL: https://www.dea.gov/drug-scheduling (accessed 15 November 2020).
30. Food and Drug Administration. 2020. *FDA recommends health care professionals discuss naloxone with all patients when prescribing opioid pain relievers or medicines to treat opioid use disorder* 23 July 2020. URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain (accessed 15 November 2020).
31. National Academies of Sciences Engineering and Medicine. 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence.* URL: https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence (accessed 20 July 2020).
32. Food and Drug Administration. 2020. *Opioid medications* 4 August 2020. URL: https://www.fda.gov/drugs/information-drug-class/opioid-medications (accessed 22 September 2020).
33. Centers for Disease Control and Prevention (CDC). 2020. *Data overview* 19 March 2020. URL: https://www.cdc.gov/drugoverdose/data/index.html (accessed 22 September 2020).
34. Centers for Disease Control and Prevention (CDC). 2020. *Understanding the epidemic* 19 March 2020. URL: https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed 22 September 2020).
35. Centers for Disease Control and Prevention (CDC). 2020. *Overdose death maps* 19 March 2020. URL: https://www.cdc.gov/drugoverdose/data/prescribing/overdose-death-maps.html (accessed 22 September 2020).
36. Centers for Disease Control and Prevention (CDC). 2020. *Synthetic opioid overdose data* 19 March 2020. URL: https://www.cdc.gov/drugoverdose/data/fentanyl.html (accessed 22 September 2020).
37. Food and Drug Administration. *Approved Risk Evaluation and Mitigation Strategies (REMS)* URL: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (accessed 15 November 2020).
38. Food and Drug Administration. 2018. *Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)* 27 September 2020. URL: https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems (accesssed 15 November 2020).
39. Food and Drug Administration. 2018. *FDA takes important steps to encourage appropriate and rational prescribing of opioids through final approval of new safety measures governing the use of immediate-release opioid analgesic medications* 18 September 2020. URL: https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-encourage-appropriate-and-rational-prescribing-opioids-through-final (accessed 11 November 2020).
40. Food and Drug Administration. 2018. *FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain.* URL: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2019_11_14_FDA_Blueprint.pdf (accessed 15 November 2020).
41. Food and Drug Administration. 2019. *Information about Medication-Assisted Treatment (MAT)* 14 February 2019. URL: https://www.fda.gov/drugs/information-drug-class/information-about-medication-assisted-treatment-mat (accessed 15 November 2020).
42. Food and Drug Administration. 2019. *Abuse-Deterrent Opioid Analgesics* 11 June 2019. URL: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics (accessed 15 November 2020).
43. Food and Drug Administration. 2019. *Statement on agency's first year accomplishments implementing SUPPORT Act authorities to address the opioids crisis* 24 October 2019. URL: https://www.fda.gov/news-events/press-announcements/statement-agencys-first-year-accomplishments-implementing-support-act-authorities-address-opioids (15 November 2020).

44. Food and Drug Administration. 2019. *FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering* 9 April 2020. URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes (accessed 15 November 2020).
45. Food and Drug Administration. 2020. *New Safety Measures Announced for Extended-release and Long-acting Opioids* updated 25 August 2020. URL: https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-extended-release-and-long-acting-opioids (accessed 15 November 2020).
46. Food and Drug Administration. 2018. *FDA Drug Safety Communication: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older* 22 January 2018. URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-labeling-changes-prescription-opioid-cough-and-cold (accessed 15 November 2020).
47. Faculty of Pain Medicine of the Royal College of Anaesthetists. *Opioids and the law* URL: https://fpm.ac.uk/opioids-aware-best-professional-practice/opioids-and-law (accessed 15 November 2020).
48. Medicines and Healthcare products Regulatory Agency. 2019. *Opioid Expert Working Group meets at MHRA* 13 February 2019. URL: https://www.gov.uk/government/news/opioid-expert-working-group-meets-at-mhra (accessed 15 November 2020).
49. 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).
50. Medicines and Healthcare products Regulatory Agency (MHRA). 2020. Transdermal fentanyl patches for non-cancer pain: do not use in opioid-naive patients. *Drug Safety Update* 14(2): 2. URL: https://www.gov.uk/drug-safety-update/transdermal-fentanyl-patches-for-non-cancer-pain-do-not-use-in-opioid-naive-patients (accessed 25 September 2020).
51. Therapeutic Goods Administration. *The Therapeutic Goods Act 1989 & the Poisons Standard* URL: https://www.tga.gov.au/therapeutic-goods-act-1989-poisons-standard (accessed 6 July 2020).
52. Therapeutic Goods Administration. 2020. *Prescription opioids: What changes are being made and why* 29 May 2020. URL: https://www.tga.gov.au/prescription-opioids-what-changes-are-being-made-and-why (accessed 24 June 2020).
53. Therapeutic Goods Administration. 2018. *Prescription Strong (Schedule 8) Opioid Use and Misuse in Australia - Options for a Regulatory Response: Consultation paper.* URL: https://www.tga.gov.au/sites/default/files/consultation-prescription-strong-schedule-8-opiod-use-misuse-in-australia-options-for-regulatory-response.pdf (accessed 24 June 2020).
54. Therapeutic Goods Administration. 2018. *Submissions received and next steps: Prescription strong (Schedule 8) opioid use and misuse in Australia - options for a regulatory response* 12 September 2018. URL: https://www.tga.gov.au/submissions-received-and-next-steps-prescription-strong-schedule-8-opioid-use-and-misuse-australia-options-regulatory-response (accessed 6 July 2020).
55. Government of Canada. 2019. Regulations Amending the Narcotic Control Regulations (Tramadol). *Canada Gazette* Part I, Volume 153(16): 1. URL: http://www.gazette.gc.ca/rp-pr/p1/2019/2019-04-20/html/reg2-eng.html (accessed 13 November 2020).
56. Government of Canada. 2017. Controlled Drugs and Substances Act - Notice to interested parties - Non-prescription availability of low-dose codeine products. *Canada Gazette* Part I, Volume 151(36): 1. URL: http://www.gazette.gc.ca/rp-pr/p1/2017/2017-09-09/html/notice-avis-eng.html (accessed 13 November 2020).
57. Health Canada. 2017. *Government of Canada: Actions on Opioids.* URL: https://www.canada.ca/en/health-canada/services/publications/healthy-living/actions-opioids-2016-2017.html (accessed 12 November 2020).

58. Gomes T, Jain S, Paterson JM, et al. 2018. Trends and uptake of new formulations of controlled-release oxycodone in Canada. *Pharmacoepidemiology and Drug Safety* 27(5): 520-25. DOI: https://doi.org/10.1002/pds.4390 (accessed 25 June 2020).
59. Health Canada. 2017. *Royal Assent of Bill C-37 - An Act to amend the Controlled Drugs and Substances Act and to make related amendments to other Acts* 18 May 2017. URL: https://www.canada.ca/en/health-canada/news/2017/05/royal_assent_of_billc-37anacttoamendthecontrolleddrugsandsubstan.html (accessed 12 November 2020).
60. Government of Canada. 2017. Regulations Amending the Food and Drug Regulations (Opioids). *Canada Gazette* Part I, Volume 151(24): 1. URL: http://www.gazette.gc.ca/rp-pr/p1/2017/2017-06-17/html/reg8-eng.html (accessed 12 November 2020).
61. Health Canada. 2019. *Notice to Stakeholders: Further Restrictions to the Marketing and Advertising of Opioids* updated 27 March 2019. URL: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/additional-restrictions-advertising-opioids.html (accessed 12 November 2020).
62. Health Canada. 2019. *Summary Safety Review - Cough and cold products containing opioids (including codeine, hydrocodone or normethadone) - Health Canada* 18 February 2019. URL: https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00216 (accessed 14 November 2020).
63. Health Canada. 2020. *Prescription Cough and Cold Products Containing Opioids and the Risk of Opioid Use Disorder in Children and Adolescents (< 18 years of age)* 24 August 2020. URL: https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/73741a-eng.php (accessed 14 November 2020).
64. National Pain Center. 2017. *The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain* URL: https://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf (accessed 14 November 2020).
65. Canadian Research Initiative on Substance Misuse (CRISM). 2018. *CRISM National Guideline for the Clinical Management of Opioid Use Disorder.* URL: https://crism.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf (accessed 14 November 2020).
66. Shipton E, Shipton A, Williman J, et al. 2017. Deaths from opioid overdosing: implications of coroners' inquest reports 2008–2012 and annual rise in opioid prescription rates: A population-based cohort study. *Pain Therapy* 6(2): 203-15. DOI: 10.1007/s40122-017-0080-7 (accessed 15 November 2020).
67. Fountain J, Reith D, Tomlin A, et al. 2019. Deaths by poisoning in New Zealand, 2008-2013. *Clinical Toxicology* 57(11): 1087-94. DOI: https://doi.org/10.1080/15563650.2019.1582777 (accessed 23 September 2020).
68. Kumpula E-E, Lambie B, Quigley P, et al. 2020. Prescribers aware: a cross-sectional study from New Zealand emergency departments on the substances used in intentional self-poisoning and their sources. *Journal of Primary Health Care* 12(3): 235-43. DOI:10.1071/HC20017 (accessed 15 November 2020).
69. McFadden Consultancy. 2016. *Research Report: The New Zealand Drug Harm Index 2016.* URL: https://www.health.govt.nz/publication/research-report-new-zealand-drug-harm-index-2016 (accessed 13 November 2020).
70. New Zealand Police. 2020. *National Wastewater Testing Programme - Quarter 1 2020* August 2020. URL: https://www.police.govt.nz/about-us/publication/national-wastewater-testing-programme-quarter-1-2020 (accessed 28 September 2020).
71. New Zealand Police. 2020. *National Wastewater Testing Programme - Quarter 4 2019* February 2020. URL: https://www.police.govt.nz/about-us/publication/national-wastewater-testing-programme-quarter-4-2019 (accessed 28 September 2020).
72. International Narcotics Control Board. 2020. *Narcotic Drugs - Estimated World Requirements for 2020, Statistics for 2018.* URL: https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2019/Narcotic_Drugs_Technical_Publication_2019_web.pdf (accessed 30 September 2020).