Medicines Adverse Reactions Committee

Meeting date	9/06/2022	Agenda item	3.2.1
Title	**Opioids and Serotonin Syndrome**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Sponsor(s)**		
Alfentanil	Medicianz Healthcare Limited, Max Health Limited		
Buprenorphine	Mundipharma New Zealand Ltd, Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics		
Buprenorphine (combination products)	Boucher & Muir (New Zealand) Limited t/a BNM Group, Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics		
Codeine	PSM Healthcare Ltd trading as API Consumer Brands		
Codeine (combination products)	Sanofi-aventis New Zealand limited, Reckitt Benckiser (New Zealand) Limited, GlaxoSmithKline Consumer Healthcare New Zealand ULC, Viatris Limited.		
Dextromethorphan	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics, GlaxoSmithKline Consumer Healthcare New Zealand ULC		
Dextromethorphan (combination products)	GlaxoSmithKline Consumer Healthcare New Zealand ULC		
Dihydrocodeine	Mundipharma New Zealand Ltd		
Fentanyl	Pfizer New Zealand Limited, Boucher & Muir (NZ) Ltd t/a Mercury Pharma (NZ), Juno Pharmaceuticals NZ Limited, Novartis New Zealand Ltd, Biomed Limited		
Fentanyl (combination products)	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics, Biomed Limited		
Methadone	Biomed Limited, AFT Pharmaceuticals Ltd, PSM Healthcare Ltd trading as API Consumer Brands		
Morphine	Teva Pharma (New Zealand) Limited, Pfizer New Zealand Limited, Multichem NZ Limited, Juno Pharmaceuticals NZ Limited, Medicianz Healthcare Limited, Biomed Limited, Mundipharma New Zealand Ltd		
Oxycodone	Boucher & Muir (New Zealand) Limited t/a BNM Group, Max Health Limited, Novartis New Zealand Ltd, Mundipharma New Zealand Ltd		
Pethidine	PSM Healthcare Ltd trading as API Consumer Brands, Pfizer New Zealand Limited		
Remifentanil	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics, AFT Pharmaceuticals Ltd		
Tramadol	Teva Pharma (New Zealand) Limited, Seqirus (NZ) Ltd		
PHARMAC funding	All opioids listed above (except buprenorphine-only products) have at least one product funded on the Hospital and/or Community Schedules.		

Previous MARC meetings	None
International action	• FDA – Label changes in the warning and precaution section of opioid agonists labels to include serotonin syndrome with serotonergic medicines (2016). • EMA: Updates to oxycodone SmPC section 4.5 to include serotonin syndrome (2018). • EMA: Updates to methadone SmPC section 4.5 to include serotonin syndrome (2020) • EMA: Updates to buprenorphine (including combination with naloxone) SmPC section 4.4 and 4.5 to included serotonin syndrome (2020).
Prescriber Update	Articles in relation to serotonin syndrome/toxicity in general: • Serotonin syndrome/toxicity – reminder (Dec 2010) • Neuroleptic Malignant Syndrome or Serotonin Syndrome (Dec 2012) • Tramadol – the Highs and Lows (Dec 2014) • Serotonin Syndrome: Short Time to Onset, Even with the First Dose (March 2016) • Reminder: Interactions Resulting in Serotonin Syndrome (Sep 2015)
Classification	Prescription medicine
Usage data	See section 4
Advice sought	**The Committee is asked to advise:** • If the information in the opioid data sheets about the risk of a drug-drug interaction with serotonergic medicines increasing the risk of serotonin syndrome is sufficient or are data sheet updates required for codeine, dihydrocodeine, oxycodone, buprenorphine, dextromethorphan, morphine, methadone, tramadol, pethidine, fentanyl, alfentanil and remifentanil? • If the information in the serotonergic medicine data sheets about the risk of a drug-drug interaction with opioid medicines increasing the risk of serotonin syndrome is sufficient or are data sheet updates required for SSRIs (sertraline, citalopram, escitalopram, paroxetine, fluoxetine), SNRIs (venlafaxine), MAOIs (tranylcypromine, moclobemide, linezolid, methylene blue) and TCAs (imipramine, clomipramine, amitriptyline, nortriptyline, dosulepin) or other serotonergic medicines? • Does the topic require further communication, other than MARC's Remarks in *Prescriber Update*?

Table of Contents

1 PURPOSE

In December 2020, two sponsors notified Medsafe of the signal of buprenorphine drug-drug interaction with serotonergic medicines leading to serotonin syndrome (SS) in response to the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA's PRAC) recommendation [1].

The PRAC recommended that the summary of product characteristics (SmPC) and patient information sheet (PIL) of buprenorphine-containing products should be updated, based on their review of the available evidence for the signal. The PRAC also recommended that the sponsors of serotonergic medicines products should ensure that this possible interaction with buprenorphine is reflected in their product information [1].

The purpose of this paper is to review the information on serotonin syndrome (SS) caused by an interaction between opioids and serotonergic medicines.

2 BACKGROUND

2.1 Opioids

Opioids are a group of medicines that act on opioid receptors [2].

DOP, KOP, and MOP (previously known as delta, kappa and mu) are opioid receptors. A fourth novel receptor, nociception (NOP), was discovered more recently, and is considered 'opioid-like' [3].

Stimulation of differing opioid receptors produces a range of effects including analgesia, sedation, respiratory depression, and constipation. All the opioid analgesics act as agonists at the mu receptor, leading to inhibition of the ascending pain pathway. Certain opioids also have additional activity at other opioid receptor(s) or non-opioid receptors, such as serotonin and noradrenaline reuptake transporters [2, 3].

Morphine and codeine (a prodrug of morphine) are naturally occurring opioids, produced from the opium poppy. Semi-synthetic opioids, such as oxycodone, buprenorphine and dihydrocodeine, have been produced from natural opioids. Opioids such as pethidine (meperidine), fentanyl (and its analogues alfentanil and remifentanil), methadone, tramadol, dextromethorphan are devoid from natural opioids, and are classified as synthetic opioids. Synthetic opioids can be further categorised into four groups, of which pethidine and fentanyl (and its analogues) are referred to as phenylpiperidine derivatives [3].

2.1.1 Indication

Opioids are commonly prescribed in clinical practice, most often for their analgesic properties [4]. The extent of pain relief required, onset of action and individual variability, coupled with the context of the clinical situation, will influence the opioid of choice [5].

Information on the opioids that are currently approved in New Zealand is outlined in Table 1. All these medicines, except dextromethorphan, are prescription only. Most opioids are funded in both the community and hospitals.

Table 1: Summary of approved opioids in New Zealand, by route, classification, and funding status

Opioid	Route	Classification[a]	Funding status	
			Community[b]	Hospital[c]
Codeine	Oral	Prescription	Yes	Yes
Codeine combination products	Oral	Prescription	Yes	Yes
Dihydrocodeine	Oral	Prescription	Yes	Yes
Tramadol	Oral, oral liquid, injection	Prescription	Yes[d]	Yes
Morphine	Oral, injection	Prescription	Yes	Yes
Oxycodone	Oral, injection	Prescription	Yes	Yes
Fentanyl	Oral, injection, transdermal	Prescription	Yes	Yes
Fentanyl combination products	Injection	Prescription	No	Yes
Methadone	Oral, injection	Prescription	Yes	Yes
Buprenorphine	Oral, transdermal, injection	Prescription	No[e]	No[e]
Buprenorphine combination products	Oral	Prescription	Yes	Yes
Pethidine	Oral, injection	Prescription	Yes	Yes
Remifentanil	Injection	Prescription	No	Yes
Alfentanil	Injection	Prescription	No	Yes
Dextromethorphan	Capsule, oral liquid, pastille	Prescription, restricted	No	No

a. Medsafe. 2021. Classification database. updated 8 December 2021. URL: https://www.medsafe.govt.nz/profs/class/classintro.asp (accessed 6 May 2022).
b. PHARMAC. 2022. Online Pharmaceutical Schedule – May 2022. URL: https://pharmac.govt.nz/pharmaceutical-schedule/community-section-b/ (accessed 6 May 2022).
c. PHARMAC. 2022. Online Hospital Medicines List (HML) – May 2022. https://pharmac.govt.nz/pharmaceutical-schedule/hml-online-section-h/ (accessed 6 May 2022).
d. Tramadol injection and oral liquid not funded in community.
e. Buprenorphine-only products are not funded.
f. Dextromethorphan is a prescription medicine exception when sold in liquid form when in packs containing not more than 600 milligrams and with a recommended daily dose of not more than 120 milligrams; in medicines for the treatment of cough and cold in adults and children aged 6 years and older.

Opioids vary in potency and can be defined as 'weak' or 'strong', usually in comparison with the potency of morphine. The World Health Organization (WHO) developed a simple stepwise approach, often referred to as the WHO analgesic 'ladder' for cancer pain. Step 1 of the ladder is 'mild pain', with non-opioid options such as paracetamol and/or non-steroidal anti-inflammatory. Weak opioids are recommended at step 2 'mild to moderate pain' and strong opioids at step 3 for 'moderate to severe pain' [6].

There are three commonly recognised types of pain: acute pain, cancer pain and chronic non-cancer pain [5, 7, 8]. Although the WHO ladder was developed for cancer pain, it has been used when treating other pain states such as acute pain, however its application in chronic non-cancer pain is controversial [6].

Weak opioids, such as codeine and tramadol, may be prescribed for pain when further relief is needed on top of non-opioid pain options. These medicines are often prescribed in primary care for short periods of time, and subsequently discontinued on resolution of the acute pain [5, 6].

Stronger opioids, such as morphine, oxycodone, and fentanyl, are more likely to be prescribed in acute pain resulting from more serious presentations, such as trauma or after an operation [6]. These opioids are more commonly seen in the hospital setting, as they can be given intravenously to provide rapid pain relief [6].

Intermittent use of stronger oral opioids may be used by individuals; however, it is recommended that they are used at the lowest effective potency and for the shortest possible time [5, 8]. Oxycodone is often used second line to morphine [8].

Alfentanil and remifentanil are used intravenously and are usually used in anaesthesia or intensive care setting [6]. In hospital, fentanyl in combination with bupivacaine or ropivacaine are used for epidural infusion for acute pain management [9].

Individuals who have terminal illnesses, such as cancer and palliative care, may require regular strong opioids to control their pain. This may include methadone tablets/liquid, or long-acting preparations of morphine, oxycodone, or a fentanyl patch. However, the effectiveness of opioids for chronic non-malignant pain is unproven [7].

Lesser used opioids in pain management include pethidine. It is no more effective than morphine, however is associated with an increased risk of adverse effects, such as vomiting and seizures [8].

Opioids are also used for other indications than analgesia. Methadone and buprenorphine (in combination with naloxone) are used in opioid substitution therapy [6].

Further information on the indication of approved opioids in NZ can be found in section 4.1 in the relevant data sheet.

Comment

There are a range of different opioids available in NZ that may be prescribed both in hospital and/or the community.

The clinical situation will determine the type of opioid that is prescribed.

Conditions were imposed on the use of dihydrocodeine following a section 36 risk-benefit review. The indication was changed so that the medicine could only be used for severe pain where other treatment options have failed, the pain is opioid-responsive and requires daily, continuous long-term treatment. The medicine is not indicated for use in chronic non-cancer pain or as an as-needed analgesia.

2.2 Serotonin Syndrome

Serotonin toxicity/syndrome is a potentially life-threatening drug-induced condition caused by an excess of the neurotransmitter serotonin (5-hydroxytrptamine, 5-HT) in the synapses of the brain [10].

The terms ‘syndrome’ and ‘toxicity’ are used interchangeably [10]. For this report, serotonin syndrome (SS) will be referred to.

The number of pro-serotonergic agents being prescribed in clinical practice is increasing [11]. However, the exact incidence of SS is difficult to estimate, which may be due to lack of recognition and awareness of the condition [12]. In a retrospective cohort study from US insurance claims in 2013, of 15 million patients exposed to at least one serotonergic medicine, the incidence of SS was between 0.9 and 2.3/1000 individuals exposed [13].

2.2.1 Serotonin signalling pathway

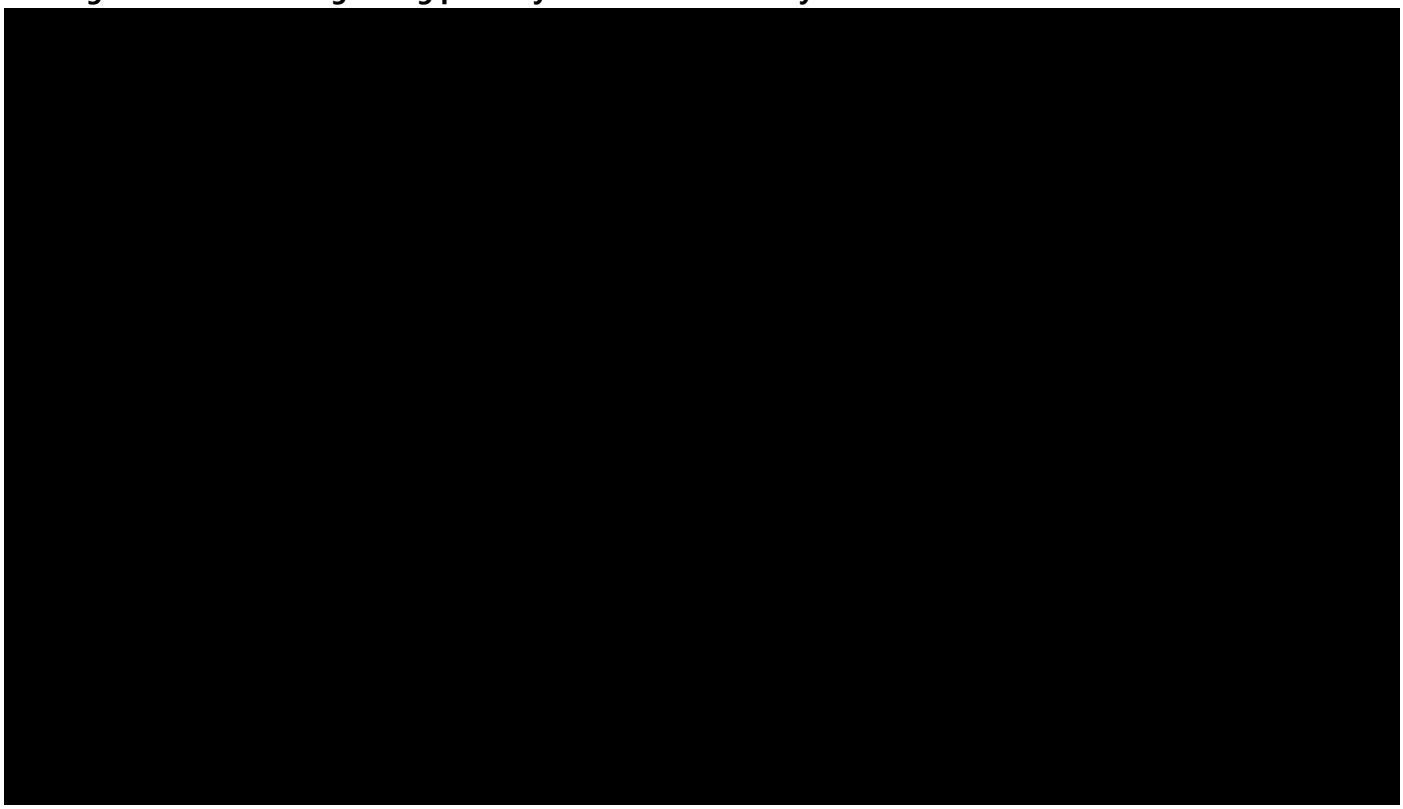
Serotonergic neurons in the CNS are primarily located in the midline raphe nuclei in the brain stem from the midline to the medulla [11].

L-tryptophan is the sole precursor to serotonin. It is ingested from dietary protein and crosses the blood brain barrier. Figure 1 outlines the serotonin signalling pathway in the CNS. Decarboxylation and hydroxylation of L-tryptophan via the enzyme tryptophan hydroxylase 2 (TPH2) forms 5-HT. Once synthesised, 5-HT is stored in the presynaptic vesicles until it is required for neurotransmission [11, 14].

Vesicles inside the presynaptic cleft containing 5-HT undergo exocytosis (fusion to presynaptic wall plasma membrane), resulting in the release 5-HT from the vesicles into the synaptic cleft upon depolarisation of the

presynaptic serotonergic axon. 5-HT then interacts with presynaptic and postsynaptic receptors. Presynaptic receptors function as a feedback loop to inhibit further exocytosis of vesicles. The serotonin reuptake transporter protein (SERT) on the presynaptic neuron transports 5-HT from the intrasynaptic space back into the presynaptic neuron. 5-HT is then broken down by monoamine oxidase subtype A (MAO type A) to hydroxyindoleacetic acid or is transported back into the vesicles to be stored [11, 14].

Figure 1: Serotonin signalling pathway in central nervous system



There are at least 7 families of 5-HT receptors (5-HT1 to 5-HT7) [14]. No single receptor is responsible for SS, however agonism of 5-HT1A and 5-HT2A is thought to be the most influential [11].

2.2.2 Mechanisms of serotonin syndrome

SS is a drug-induced condition, caused by medicines increasing the amount of 5-HT in the CNS [10].

Medicines which increase 5-HT are referred to as 'serotonergic' [13]. SS can develop from excessive doses of a single serotonergic medicine, but more commonly occurs when combinations of serotonergic medicines are used together, particularly when they act via different mechanisms [10].

Figure 2 shows how different medicines can cause serotonin syndrome. Mechanisms include increased levels of 5-HT precursor L-tryptophan, increased 5-HT release from presynaptic neuron, inhibition of 5-HT metabolism, impairment of 5-HT transport into the presynaptic neuron and direct stimulation of post synaptic 5-HT receptors [15].

Figure 2: Mechanisms of Serotonin Syndrome in the central nervous system

Monoamine oxidase inhibitors (MAOIs)

MAOIs block the monoamine oxidase (MAO) enzyme, which slows the breakdown of 5-HT and leads to increased pre-synaptic 5-HT concentrations. MAOIs can be irreversible or reversible and can bind to either MAO A or MAO B, with MAO A being more involved in the breakdown of 5-HT in the CNS [10].

The combination of a MAOI and another serotonergic medicine carries the greatest risk of SS and is generally contraindicated. MAOIs that are irreversible and non-selective are most likely to cause toxicity [10].

Tranylcypromine (irreversible, non-selective MAOI) and moclobemide (reversible, selective MOA A (RIMA)) are approved MAOIs for depression in New Zealand [16].

Linezolid (antibiotic) and methylene blue/methylthioninium chloride (methsemogloinaemia or diagnostic dye) are approved medicines that also have an inhibitory action on MAO, and therefore, decrease 5-HT breakdown. Prescribers may not be aware of their serotonergic activity [10].

Selegiline and rasagiline are selective and irreversible MAOI B inhibitors and are not approved in NZ.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There are five SSRIs currently funded in NZ: citalopram, escitalopram, sertraline, paroxetine and fluoxetine [16].

All SSRIs potently decrease the action of the presynaptic serotonin reuptake pump (SERT), increasing the length of time that serotonin is available in the synapse and increasing postsynaptic serotonin receptor occupancy [17].

SSRIs are the most prescribed antidepressants, and consequently are the most often implicated in SS [18]. Fluoxetine has a long half-life, which is important to take into consideration when starting or stopping other serotonergic medicines [16].

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Venlafaxine is currently the only funded SNRI in NZ [16]. It inhibits the presynaptic 5-HT and norepinephrine (NE) transporter proteins, which increases the levels of these neurotransmitters at the synapse and therefore increases the stimulation of postsynaptic receptors [19].

Tricyclic Antidepressants (TCAs)

There are five TCAs currently funded in NZ: amitriptyline, clomipramine, dosulepin (dothiepin) hydrochloride, imipramine (tertiary amines), and nortriptyline (a secondary amine) [16].

TCAs inhibit reuptake of both 5-HT and NE. Tertiary amines are generally more potent in blocking reuptake of 5-HT compared with NE, whereas secondary amines are more potent in blocking reuptake of NE [20].

There is varied information about the risk of SS with TCAs in the literature. The association between amitriptyline and SS was noted unlikely/disputed by some authors [10, 21]. Others consider TCAs to be associated with SS [12, 14].

Clomipramine and imipramine have a higher affinity with the SERT receptor when compared to the other TCAs, such as amitriptyline and nortriptyline, and therefore are considered to be more serotonergic [22].

Other agents

St John's wort (an SSRI) and L-tryptophan (precursor to 5-HT) are supplementary products that may increase 5-HT due to their mechanism of action [10].

There is disagreement in the serotonergic properties of some medicines thought to be associated with SS, due to lack of mechanism of action to increase 5-HT or stimulate appropriate receptors. This includes medicines such as triptans and 5-HT3 antagonists [10, 21].

Opioids

The role of opioids in serotonin syndrome is becoming more relevant to clinical practice, as more individuals are taking serotonergic medicines [23].

Understanding the mechanism of action of opioids to increase 5-HT levels directly or indirectly has been investigated in *in vitro* studies.

Details from studies and case reports identified from the literature are discussed and summarised in section 5.

2.2.2.2 Drug–drug interaction

The infographic shown in Figure 3 gives guidance on which medicine combinations to avoid or use with caution due to the risk of SS. An MAOI in combination with an SSRI or SNRI is likely to cause toxicity and is usually avoided. Opioids included in figure 3 are tramadol, pethidine (meperidine), methadone, fentanyl, and dextromethorphan [10].

Figure 3: Medicines associated with serotonin syndrome, combinations to avoid, use with caution and monitor

2.2.2.3 Pharmacokinetics and pharmacodynamics

Medicines that inhibit the metabolism of serotonergic medicines could further increase 5-HT levels and the risk of SS. Alternatively, serotonergic medicines may inhibit the metabolism of other serotonergic medicines [12].

Some individuals appear to be more susceptible to mild to moderate SS. It is unclear whether this could have a genetic pharmacokinetic (decreased drug metabolism) or pharmacodynamic (serotonin receptor polymorphism) explanation [24]. In addition, different patients present with SS at varying drug dosages and combinations, suggesting that individual variability probably plays a role [12].

2.2.3 Signs and symptoms of serotonin syndrome

Symptoms of SS are characterised by a triad of neuromuscular excitatory features that include autonomic dysfunction, neuromuscular excitation and altered mental status, however, not all need to present at once [10].

Figure 4 outlines the spectrum of symptoms of SS, ranging from mild to severe symptoms. Individuals with mild symptoms of SS may present with tremor, sweating, anxiety, or diarrhoea [14]. Mild symptoms may be overlooked for other causes, such as a side effect of the medicine or underlying condition [18]. SS resulting in hospitalisation or death is rare [10].

Figure 4: Symptoms of serotonin syndrome

The onset of symptoms of SS are usually rapid. Approximately 30% of patients present within one hour, and 60% within six hours [14]. SS may develop faster in the context of overdoses, surgical or intensive care settings, in which serotonergic agents may be administered quickly. In contrast to medical settings, in which serotonergic medicines are often slowly introduced or cross tapered [11, 13].

2.2.4 Diagnosis and management of serotonin syndrome

Diagnosis of SS is purely clinical and based on the recognition of a combination of symptoms in the presence of serotonergic medicines, and exclusion of other conditions [11].

Serum 5-HT levels are an unreliable indicator and do not correlate well with the clinical presentation [18].

There are three diagnostic classification systems available: the Sternbach, the Radomski and the Hunter Serotonin Toxicity Criteria [12].

Management of SS involves discontinuation of the serotonergic medicine(s) and the provision of supportive care [11]. Most patients improve within 24 hours of stopping the precipitating medicine [18]. Symptoms may persist if the medicine has a long half-life or active metabolites [11].

Cyproheptadine is a potent 5-HT2A antagonist, which has been used in the treatment of SS. However, its efficacy has not been rigorously established [11].

Comment

Serotonin syndrome is a drug induced condition caused by increased levels of 5-HT in the brain leading to symptoms such as sweating, diarrhoea, agitation, hyperthermia, hypertension, clonus, and rigidity.

5-HT is produced in serotonergic neurons in the raphe nuclei. When released, it binds to a range of receptors, with feedback mechanisms inhibiting further release. 5-HT1A and 5-HT2A receptors are suggested to be most involved in SS.

SS can develop from excessive doses of a single serotonergic medicine, but more commonly occurs when combinations of serotonergic medicines are used together, particularly when these medicines act to increase 5-HT via different mechanisms. MAOIs, SSRIs, SRNIs and some TCAs are serotonergic due to their mechanisms of action. Use of an MAOI in combination with other serotonergic medicines is not recommended.

There is increasing use of serotonergic medicines in clinical practice.

The role of opioids in serotonin syndrome is becoming more recognised.

3 DRUG-DRUG INTERACTIONS

Medicines approved in New Zealand were included in the review.

Interactions in relation to St John's wort (or other herbal products) were excluded.

There is disagreement as to the serotonergic nature of certain medicines across the literature. Therefore, there are other medicines that could be involved in this interaction, but they were not reviewed in this report.

3.1 Contraindicated combinations

MAOIs may interact with opioids by two different mechanisms: an excitatory (serotonin syndrome) and a depressive form (increase the risk of opioid toxicity) [25].

These interactions are noted in the codeine New Zealand data sheet [26]:

4.3 Contraindications

Patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment

4.4 Special warnings and precautions for use

The following patients may be more susceptible to the effects of codeine. The lowest effective dose for the shortest period should be prescribed. Signs of toxicity or overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, extreme sleepiness, confusion, shallow breathing and even coma:

Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors – due to the possible risk of excitation or depression, avoid concomitant use and for 14 days after discontinuation of MAOI.

Concomitant use of opioids with MAOIs is usually contraindicated by sponsors due to these safety concerns, these include pethidine, methadone, and morphine [27-29].

For a full list of opioids that are contraindicated with MAOIs, see annex 1 (opioid data sheet information).

3.2 Stockley's/ New Zealand Formulary

The New Zealand Formulary (NZF) interaction information is provided by Stockley's Interaction Alerts [30].

The interaction checker was searched for each opioid and serotonergic medicine combination, with the results shown in Table 2. The interaction and its management were coded as per NZF recommendations. Interactions that did not mention a risk of SS (or had no evidence for an interaction) were coded green.

Codeine, dihydrocodeine, morphine (except with paroxetine), buprenorphine, remifentanil and alfentanil were not considered to interact with any serotonergic medicine included in the search. Whereas tramadol, oxycodone, fentanyl, methadone, pethidine, and dextromethorphan were considered to have an increased risk of SS when used in combination with certain serotonergic medicines, suggesting that these opioids have serotonergic mechanisms.

Concurrent use of tramadol, methadone, fentanyl, dextromethorphan, pethidine, or oxycodone with MAOIs, SSRIs, SNRIs and some TCAs, was either recommended to be avoided or used with caution.

Tramadol was the only opioid where the risk of SS was listed with amitriptyline, nortriptyline and dosulepin (dothiepin).

There was also an increased risk of developing SS when dextromethorphan, fentanyl, methadone, pethidine or tramadol are used in combination [30].

Table 2: Drug-drug interaction for serotonin syndrome, New Zealand Formulary interaction checker, by opioid and particular serotonergic medicine

Key:
Red: avoid combination.
Orange: caution with use, monitor for symptoms.
Yellow: possible SS interaction.
Green: no SS interaction expected/ no evidence for an interaction.

Opioid	Serotonergic medicine: MAOIs				SSRIs					SNRI	TCAs				
	Tranylcypromine[a]	Moclobemide	Linezolid	Methylene Blue[d]	Citalopram	Escitalopram	Sertraline	Paroxetine	Fluoxetine	Venlafaxine	Clomipramine	Imipramine	Amitriptyline	Nortriptyline	Dosulepin (dothiepin)
Codeine															
Dihydrocodeine															
Tramadol		b													
Morphine															
Oxycodone															
Fentanyl															
Methadone					e	e					e				
Pethidine		b	c												
Dextromethorphan		b													
Buprenorphine															
Remifentanil															
Alfentanil															

a. Tranylcypromine data sheet: contraindicated use with pethidine and closely related narcotic analgesics, and dextromethorphan.
b. Aurorix (moclobemide) data sheet: contraindicated with tramadol, pethidine and dextromethorphan. Apo-moclobemide datasheet: concomitant administration of pethidine should be avoided or used with caution. Some cough and cold medicines may contain dextromethorphan, should not be taken without prior consultation with a physician.
c. Linezolid data sheets: contraindicated with pethidine. Data sheets published at: https://www.medsafe.govt.nz/Medicines/infoSearch.asp
d. Proveblue methylene blue data sheet: Co-administration with serotonergic agents is not recommended except where administration of both agents is essential.
e. Use of methadone in combination with citalopram, escitalopram or clomipramine is not recommended due to risk of QT prolongation, in addition to the risk of SS.

Source: New Zealand Formulary (NZF). 2022. NZF *v119: Interaction checker*. URL: https://nzf.org.nz/nzf_1 (accessed 6 May 2022).

Comment

Tramadol, oxycodone, fentanyl, methadone, pethidine and dextromethorphan had increased risk of SS listed as a drug-drug interaction with MAOIs, SSRIs, SNRIs, clomipramine and imipramine. Tramadol also had the interaction with amitriptyline, nortriptyline and dolsulepin (dothiepin).

The risk and management of these interactions differed by the opioid and serotonergic medicine combination.

Risk of developing SS was also noted if serotonergic opioids were used in combination.

3.3 Prescribing information

3.3.1 New Zealand data sheets

A review was conducted on 8 April 2022 to see if New Zealand data sheet for opioids and selected serotonergic medicines contained information on a drug-drug interaction increasing the risk of SS.

The data sheets were retrieved using the Medsafe Data Sheet and Consumer Information Search: https://www.medsafe.govt.nz/Medicines/infoSearch.asp

3.3.1.1 Opioids

Information relating to warnings for SS and/or drug-drug interaction with serotonergic medicines in approved NZ opioid data sheets is summarised in Table 3.

Further details from the relevant sections of opioid data sheets can be reviewed in Annex 1.

Dihydrocodeine and remifentanil data sheets did not list an interaction with serotonergic medicines. However, use of MAOIs with dihydrocodeine was contraindicated.

Interactions with MAOIs only were seen in codeine and codeine combination product data sheets. Most sponsors recommended that the combination is contraindicated or to avoid concomitant use. Except in one codeine combination product data sheet, 'serotonin syndrome' was not specifically mentioned, however, some sponsors noted the combination may increase the risk of CNS excitation.

Tramadol, fentanyl, dextromethorphan, buprenorphine, alfentanil and some morphine, pethidine, and oxycodone data sheets listed an interaction with serotonergic medicines. Information on the interaction varied slightly between each of these opioids, and between different products for the same medicine. Most data sheets had a warning in section 4.4 and interaction information in section 4.5.

The information included in section 4.4 and 4.5 in most fentanyl data sheets is as below:

4.4. Special warnings and precautions for use

Serotonin syndrome

Caution is advised when Fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems. The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, rapid discontinuation of Fentanyl should be considered.

4.5. Interactions with other medicines and forms of interactions

Serotonergic Drugs: Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI), a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition

The information included in section 4.4 and 4.5 in some morphine data sheets is as below:

4.4 Special warnings and precautions for use

Serotonin Syndrome (SS)

The development of serotonin syndrome (SS), which is potentially life-threatening, has been reported with opioid use, including with morphine. These reports generally occurred when morphine was used concomitantly with serotonergic drugs (see section 4.5 Interactions with other medicines and other forms of interaction). Signs of SS may include clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature elevation.

4.5 Interaction with other medicines and other forms of interaction

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, and monoamine oxidase inhibitors (MAOIs)

In the opioid data sheets that listed serotonin syndrome, MAOIs, SSRIs and SNRIs were the most frequently listed interacting medicines. A few data sheets also included other medicines such as TCAs, mirtazapine, triptans and 5-HT_3 antagonists.

Fentanyl combination products (bupivacaine and ropivacaine) were not included in Table 3, however, are listed in Annex 1. These data sheets also list information about SS, in relation to the fentanyl component.

Methadone data sheets only contained information on an interaction with MAOIs in section 4.5, however the term 'serotonin syndrome' is not mentioned.

The data sheets for dextromethorphan included information on concomitant use with CYP2D6 inhibitors, such as fluoxetine and paroxetine, which can increase serum levels of dextromethorphan.

Table 3: New Zealand-approved opioid data sheets: Information on serotonin syndrome and drug-drug interaction with serotonergic medicines in section 4.4 and/or 4.5.

* combination products available.		**Section 4.4** (warning/precaution)	**Section 5.5** (Interaction with other medicines)	**Serotonergic medicines specifically listed in data sheet**									
				MAOIs	SSRIs	SNRIs	TCAs	Mirtazapine	Lithium	CYP2D6 inhibitors	Tramadol	Triptans	5-HT3 receptor antagonists
Opioid	Codeine*	×	×	✔[a]	×	×	×	×	×	×	×	×	×
	Dihydrocodeine	×	×	✔[a]	×	×	×	×	×	×	×	×	×
	Tramadol	✔	✔	✔[a]	✔	✔	✔	✔	×	×	×	×	×
	Morphine	✔/×[b]	✔/×[b]	✔[a]	✔/×[b]	✔/×[b]	✔/×[b]	✔/×[b]	×	×	×	✔/×[b]	✔/×[b]
	Oxycodone	×	✔/×[b]	✔[a]	✔	✔	×	×	×	×	×	×	×
	Fentanyl*	✔	✔	✔[a]	✔	✔	×	×	×	×	×	✔/×[c]	×
	Methadone	×	✔	✔[a]	×	×	×	×	×	×	×	×	×
	Pethidine	✔/×[b]	✔/×[b]	✔[a]	✔/×[b]	✔/×[b]	✔/×[b]	×	×	×	×	✔/×[b]	×
	Dextromethorphan*	✔	✔	✔[a]	✔[d]	✔/×[d]	✔	✔/×[d]	×	✔	×	×	×
	Buprenorphine*	✔/×[e]	✔	✔[f]	✔	✔	✔	✔/×[c]	✔/×[c]	×	✔/×[c]	✔/×[c]	✔/×[c]
	Remifentanil	×	×	×	×	×	×	×	×	×	×	×	×
	Alfentanil	×	✔	✔[a]	✔	✔	×	×	×	×	×	×	×

a. Use with MAOI is contraindicated or recommended to be avoided.
b. Some sponsors list SS (+ serotonergic medicines) in the data sheet and others do not.
c. Some sponsors list additional serotonergic medicines than others for the same opioid.
d. Some dextromethorphan data sheets contraindicate use with serotonergic agents.
e. Some sponsors have a warning in section 4.4, others do not.
f. Some sponsors contraindicate concomitant use with MAOIs, others have concomitant use as a caution.

3.3.1.2 Serotonergic medicines

Serotonergic medicine data sheets were reviewed for the drug-drug interaction with opioids, shown in Table 4.

Further information from the data sheets is available in Annex 2.

Most of the medicines reviewed included information on an interaction with a 'serotonergic agent' (or words of a similar meaning), as opposed to listing specific medicines. However, tramadol was commonly listed as an interacting medicine.

Some serotonergic medicine data sheets listed other opioids in addition to tramadol. Most of the MAOIs listed pethidine and dextromethorphan. Amitriptyline was the only data sheet to list buprenorphine. The sertraline, venlafaxine and nortriptyline data sheets listed fentanyl (and its analogues), tramadol, dextromethorphan, pethidine and methadone.

The information in the sertraline data sheet includes:

4.4. Special warnings and precautions for use

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported with selective serotonin reuptake inhibitors (SSRIs), including treatment with sertraline. The risk of SS or NMS with SSRIs is increased with concomitant use of serotonergic drugs [including amphetamines, triptans, and opioids (e.g., fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone, pentazocine)], with drugs which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. SS symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Some signs of SS, including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes resemble NMS. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome (see section 4.3).

Clomipramine data sheets contain information about SS with SSRIs only, compared to the imipramine data sheet which had a statement about risk with serotonergic agents.

Table 4: Selected New Zealand-approved serotonergic medicine data sheets: Information on drug–drug interaction with an opioid and serotonin syndrome

		General statement		Opioid specifically listed in data sheet											
		Serotonergic medicines	**Opioids**	Codeine	Dihydrocodeine	Tramadol	Morphine	Oxycodone	Fentanyl	Methadone	Pethidine	Dextromethorphan	Buprenorphine (+/- naltrexone)	Remifentanil	Alfentanil
Serotonergic medicine	Tranylcypromine	×	✔[a]	×	×	×	×	×	×	×	✔	✔	×	×	×
	Moclobemide	✔	×	×	×	✔[b]	×	×	×	×	✔[b]	✔[b]	×	×	×
	Linezolid	✔	✔[c]	×	×	×	×	×	×	×	✔	×	×	×	×
	Methylene blue	✔	×	×	×	×	×	×	×	×	×	×	×	×	×
	Citalopram	✔	×	×	×	✔	×	×	×	×	×	×	×	×	×
	Escitalopram	✔	×	×	×	✔	×	×	×	×	×	×	×	×	×
	Sertraline	✔	✔[d]	×	×	✔	×	×	✔	✔	✔	✔	×	✔	✔
	Paroxetine	✔	×	×	×	✔	×	×	✔	×	×	×	×	×	×
	Fluoxetine	✔	×	×	×	✔	×	×	×	×	×	×	×	×	×
	Venlafaxine	✔	✔	×	×	✔	×	×	✔	✔	✔	✔	×	✔	✔
	Imipramine	✔	×	×	×	×	×	×	×	×	×	×	×	×	×
	Clomipramine	×	×	×	×	×	×	×	×	×	×	×	×	×	×
	Amitriptyline	✔	×	×	×	✔	×	×	×	×	×	×	✔	×	×
	Nortriptyline	✔	×	×	×	✔	×	×	✔	✔	✔	✔	×	✔	✔
	Dosulepin (dothiepin)	×	×	×	×	×	×	×	×	×	×	×	×	×	×

a. Tranylcypromine: CI with opioids.
b. Moclobemide (Aurorix brand product only): CI with pethidine, tramadol, dextromethorphan.
c. Zyvox data sheet.
d. Setona and Zoloft data sheets include 'opioids'.

Comment

The serotonergic medicine data sheets had less information about the drug-drug interaction compared to the opioid data sheets.

Most serotonergic data sheets list 'serotonergic medicines' and risk of SS, but do not list specific opioids, except tramadol. An awareness and understanding of serotonergic activity of individual opioids, when reviewing this information would be needed.

Where opioids were listed in a serotonergic medicine data sheet, methadone was included. However, SS is not listed in the methadone data sheet.

Oxycodone and morphine were listed in some sponsors' opioid data sheets; however, these medicines were not listed in the serotonergic datasheets that listed serotonergic opioids.

SS is noted in some buprenorphine data sheets. However, amitriptyline was the only serotonergic data sheet that listed buprenorphine.

Fentanyl, alfentanil, pethidine, tramadol and dextromethorphan had the SS interaction in their data sheets and were listed as serotonergic medicines in certain serotonergic medicine data sheets.

Fentanyl, pethidine, tramadol, methadone, oxycodone, and fentanyl were shown to have serotonergic interactions in NZF interaction checker. However, oxycodone was not listed in serotonergic medicine data sheets.

Addition of serotonergic opioids to section 4.4 and/or section 4.5 of serotonergic medicine data sheets could be considered, as most opioid data sheets that list SS include these serotonergic medicines as part of the interaction.

3.3.2 International product information

The Australian Product Information (PI) and UK Summary of Product Characteristics (SmPC) for the same medicines was reviewed for the opioid-serotonergic medicine interaction.

The Australian Product Information was retrieved from the Therapeutic Goods Administration (TGA) website: https://www.tga.gov.au/product-information-0.

The UK SmPC was retrieved from the Electronic Medicines Compendium (emc) website: https://www.medicines.org.uk/emc#gref.

3.3.2.1 Opioids

UK (as of 15 April)

The codeine, dihydrocodeine, morphine and remifentanil SmPC did not contain any information about an interaction between serotonergic medicines and risk of SS. Sponsors of these medicines (except remifentanil) contraindicated or advised caution with MAOIs.

The tramadol, oxycodone, fentanyl, pethidine, dextromethorphan, buprenorphine and alfentanil SmPC included information about risk of serotonin syndrome with interacting medicines in section 4.4 and/or section 4.5.

Some methadone SmPC also included the interaction in section 4.5:

Serotonergic drugs:

Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms

In the opioid SmPC that listed serotonin syndrome, the most frequently listed serotonergic medicines were MAOIs, SSRIs, SNRIs and TCAs.

Australia (as of 15 April)

The codeine, dihydrocodeine, methadone and remifentanil PI did not contain any information about an interaction between serotonergic medicines and risk of SS. However, use with MAOIs was contraindicated or not recommended (except remifentanil).

The tramadol, oxycodone, fentanyl, pethidine, dextromethorphan, buprenorphine, alfentanil and some morphine PI listed the interaction with serotonergic medicines.

In the opioid PI that listed serotonin syndrome, the most frequently listed serotonergic medicines were MAOIs, SSRIs, SNRIs and TCAs.

Comment

On review of international opioid prescribing information, tramadol, oxycodone, fentanyl, pethidine, dextromethorphan, buprenorphine and alfentanil listed the interaction, which is similar to the NZ data sheets. Some morphine PI also had information on SS.

SS was noted in the some UK methadone SmPC; however, it was not in the NZ data sheet nor the Australian PI.

In the opioid prescribing information, the most frequently listed interacting medicines were MAOIs, SSRIs and SNRIs, followed by TCAs.

3.3.2.2 Serotonergic medicines

UK (as of 18 April)

The moclobemide and linezolid SmPC recommend avoiding use with specific opioids, including pethidine, tramadol and dextromethorphan. Use of serotonergic agents with linezolid was not recommended, unless essential. Tranylcypromine was contraindicated with opioid analgesics.

The venlafaxine SmPC included specific opioids, such as tramadol, fentanyl (and its analogues), methadone, pethidine and dextromethorphan. Some venlafaxine products also listed buprenorphine.

'Opioids' was included in section 4.4 of some SSRIs, SNRIs and TCAs SmPC, with buprenorphine and tramadol given as examples:

Section 4.4 Special warnings and precautions for use

Citalopram (Rivopharm UK Ltd)

Serotonergic medicines

Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, opioids such as buprenorphine and tramadol, oxitriptan and tryptophan.

Escitalopram (Glenmark Pharmaceuticals Europe Ltd)

Serotonin syndrome

Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol, buprenorphine and tryptophan. If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

In rare cases, serotonin syndrome, a potentially life-threatening condition (see section 4.5), has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

Imipramine (Accord-UK Ltd)

Serotonin syndrome

Concomitant administration of Imipramine and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Some serotonergic medicines did not include 'opioids', but instead specified tramadol as an interacting medicine. Other SmPC also specified fentanyl and/or buprenorphine.

Comment:

Buprenorphine is frequently listed as an example of a serotonergic opioid in the UK information. The EU PRAC recommended updates to the EU SmPC for serotonergic medicines to include the interaction with buprenorphine leading to serotonin syndrome (see section 6.4). This is potentially why the SmPC for serotonergic medicines in the UK list the buprenorphine interaction, as these sponsors likely also distribute their products in the EU.

Australia (as of 4 May 2022)

The moclobemide PI contraindicates concomitant use with pethidine, tramadol and dextromethorphan. Cases of SS have been reported with opioids and linezolid, as noted in some linezolid PI. The tranylcypromine PI also contraindicates concomitant use with opioids.

Some citalopram and escitalopram PI have recently been updated to include a drug-drug interaction with opioids:

Section 4.5 Interactions with other medicines and other forms of interactions

Citalopram (Lundbeck Australia)

Serotonergic drugs

Co-administration with serotonergic drugs e.g. opioids (including tramadol) triptans (including sumatriptan and oxitriptan) may lead to an enhancement of serotonergic effects. Similarly, Hypericum perforatum (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

The sertraline PI listed specific opioids, which included fentanyl (and its analogues), tramadol, methadone, pethidine and dextromethorphan. These opioids were also listed in the venlafaxine PI.

In relation to SS, the TCA PI did not list specific opioids or opioids as a class.

Comment

Where specific opioids were listed in the Australian and UK prescribing information, these included tramadol, fentanyl (and its analogues), methadone, pethidine, and dextromethorphan.

Using 'buprenorphine/opioids', which is noted in many UK SmPC for serotonergic medicines, may be potentially confusing and associates all opioids with the interaction. In addition, the interaction is not replicated in corresponding opioid information. For example, the dihydrocodeine SmPC do not list the interaction with serotonergic medicines.

The venlafaxine prescribing information included the interaction with 'opioids' and then listed specific examples. This management of the interaction may be more informative for prescribers, as these opioids have a higher risk of SS.

3.3.3 Summary of drug-drug interaction

Dihydrocodeine and remifentanil did not have an interaction with serotonergic medicines and risk of SS in the interaction checker in NZF, and SS was not listed in their data sheets. Dihydrocodeine was not listed in serotonergic medicine data sheets as an interacting medicine, however fentanyl analogues (which includes remifentanil) was listed in some serotoninergic medicine data sheets.

Codeine product data sheets (including combination products) listed an interaction with MAOIs, some sponsors included the possible risk of excitation or depression reactions. Warnings about SS and/or interactions with other serotonergic medicines were not listed in the data sheets. Codeine was not an interacting medicine in NZF nor was included as an interacting medicine in serotonergic medicine data sheets.

The remaining opioids (tramadol, morphine, oxycodone, fentanyl, methadone, pethidine, dextromethorphan, buprenorphine and alfentanil) had either an interaction in NZF, and/or information about the interaction in their data sheet that increased the risk of SS in combination with serotonergic medicines. From these opioids, morphine and oxycodone were not included in the serotonergic medicine data sheets that listed interacting opioids.

4 USAGE

Data extracted from the Pharmaceutical data web tool is summarised below.

This tool provides data from the Pharmaceutical Collection about funded medicines that were dispensed in the community only.

It is not possible to review how many individuals are dispensed both an opioid with a serotonergic medicine(s) in the same prescription.

4.1 Opioids

Remifentanil and alfentanil are only funded in hospital. Dextromethorphan is available as pharmacist only and is not funded in community. The usage data for these opioids was not included.

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. Therefore, the data below will not capture individuals taking codeine who purchased it in a pharmacy also.

Table 5 shows the total number of people who received a dispensing of an approved community-dispensed opioid (all formulations) as a named person from a pharmacy at least once during the year, from 2017 to 2020.

A higher number of people were dispensed codeine, tramadol, morphine, and oxycodone during 2017 to 2020, compared to the other opioids. The number of people who were dispensed buprenorphine with naloxone, morphine and oxycodone has increased over this time, whereas the number of people using tramadol has slightly reduced. The largest increase was seen with morphine and oxycodone.

Table 5: Number of people dispensed an approved community opioid, 2017 to 2020

Opioid	2017	2018	2019	2020
Buprenorphine with naloxone	1,143	1,242	1,329	1,378
Codeine phosphate	309,985	311,084	313,148	299,244
Dihydrocodeine tartrate	12,998	12,114	12,028	11,235
Fentanyl	8,621	8,032	7,918	8,030
Methadone hydrochloride	7,365	7,243	7,240	7,241
Morphine hydrochloride, morphine sulphate, morphine tartrate[a]	63,528	62,846	64,197	66,610
Oxycodone hydrochloride	26,556	26,509	26,637	29,027
Pethidine hydrochloride	694	574	518	473
Tramadol hydrochloride	244,869	242,463	240,672	241,368

a. Morphine tartrate is no longer an approved medicine since January 2020.

Source: Ministry of Health's Pharmaceutical Collection, extracted on 26 November 2021. URL: Pharmaceutical Data web tool (shinyapps.io) (accessed 2 May 2022)

Comment

A limitation of the using pharmaceutical dispensing information is that it is not known how the opioid was taken by the individual. Opioids are most commonly prescribed for pain. Some of these dispensing's may have been for a short duration and prescribed as needed, versus long term prescribing for ongoing pain relief.

Methadone is likely to be most used for management of opioid use disorder, and for chronic pain in a small number of individuals. Specialists are most likely involved in these prescribing decisions.

As per the NZF, opioids with interactions with serotonergic medicines include tramadol, fentanyl, methadone, pethidine, oxycodone, and dextromethorphan (see Table 2). Tramadol appears to be frequently prescribed. Use of oxycodone increased slightly in 2020 and this should be monitored. Interactions between fentanyl and serotonergic medicines are likely to be more prevalent in hospital and palliative care.

It is not known how many people are using dextromethorphan, as this is restricted medicine.

4.2 Serotonergic medicines

Table 6 shows the total number of people dispensed a particular approved serotonergic medicine, by class, from 2017 to 2020.

The number of people who have been dispensed an SSRI, TCA and SNRI had increased from 2017 to 2020. More people were dispensed an SSRI compared to other classes of serotonergic medicines, as shown in Table 6.

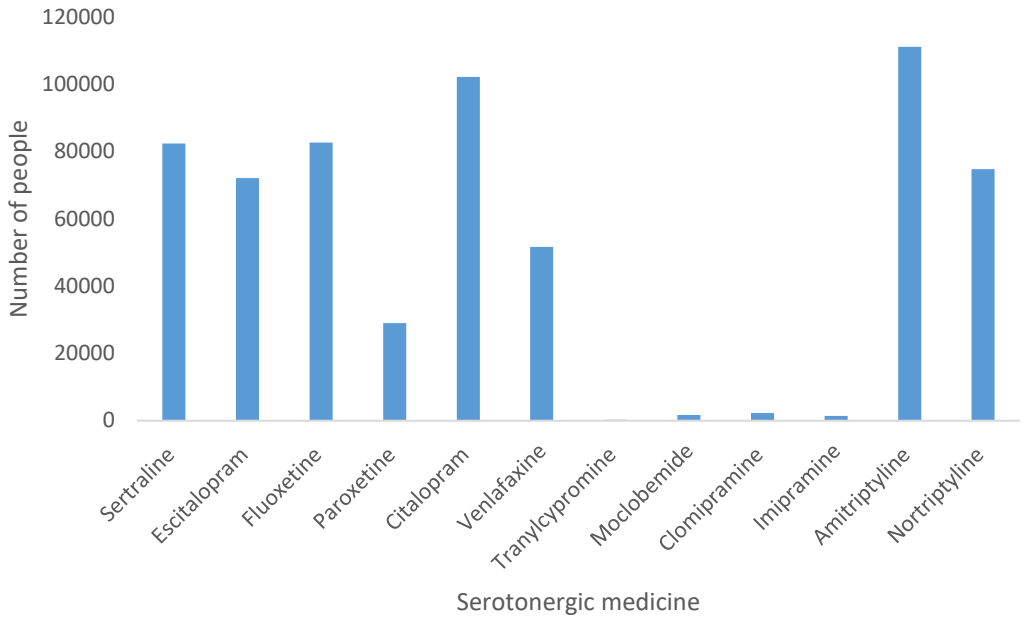
Table 6: Number of people dispensed a particular approved serotonergic medicine, by class, 2017 - 2020

Serotonergic medicine class	Total number of people				Trend
	2017	2018	2019	2020	
SSRIs (sertraline, escitalopram, fluoxetine, paroxetine, citalopram)	332,185	339,083	352,132	368,230	↑
SNRIs (venlafaxine)	51,307	50,986	50,181	51,650	↑
MAOIs (Tranylcypromine, moclobemide)	2,113	2,037	2,016	2,046	↓
TCAs (Clomipramine, imipramine, nortriptyline, amitriptyline)	174,748	176,705	183,221	189,579	↑

Source: Ministry of Health's Pharmaceutical Collection, extracted on 26 November 2021. URL: Pharmaceutical Data web tool (shinyapps.io) (accessed 2 May 2022).

Figure 5 is a breakdown of the number of people dispensed a particular serotonergic medicine in 2020. Amitriptyline, citalopram, escitalopram, sertraline, and nortriptyline were dispensed most often. Very few people were dispensed tranylcypromine (306), moclobemide (1741), imipramine (1422) and clomipramine (2269).

Figure 5: Number of people dispensed a particular approved serotonergic medicine, 2020



Source: Ministry of Health's Pharmaceutical Collection, extracted on 26 November 2021. URL: Pharmaceutical Data web tool (shinyapps.io) (accessed 2 May 2022).

Comment

SSRIs were the dispensed to the greatest number of people, compared to other classes of antidepressant medicines in 2017 to 2020.

SSRIs are first line for treatment in depression. The number of people dispensed SSRIs has increased each year from 2017 to 2020, in line with the increasing population size.

SSRIs are medicines with known serotonergic properties. Given the increase, there may be more instances whereby a drug-drug interaction with opioids may occur.

Amitriptyline and nortriptyline also had high use. Off-label use of these medicines for neuropathic pain, rather than depression, may be why these medicines have similar dispensing rates to that of SSRIs. Lower doses used for off label indications may reduce the risk of SS with other serotonergic medicines.

There were fewer individuals taking tranylcypromine and moclobemide, however these medicines are more likely to be associated with severe SS reactions.

5 SCIENTIFIC INFORMATION

Review of the literature was undertaken for opioids and serotonin syndrome to further understand the proposed mechanisms of different opioids in the interaction, and published case reports.

Comment

Articles and case reports focusing on solely tramadol were excluded. Tramadol is well known to cause SS alone and due to interactions with other medicines.

5.1 Opioids and serotonin syndrome

5.1.1 Opioids and antidepressants: which combinations to avoid - Perananthan & Buckley, 2021 [23]

The authors discuss the risk of SS with different opioids and antidepressant medicines, and recommendations on management of this interaction.

Opioid dispensing increased fourfold in Australia from 1990 to 2014 and prescribing of antidepressants doubled from 2000 to 2016. Some combinations of opioids and antidepressants increase the risk of serotonergic effects, even at therapeutic doses.

Figure 6 highlights the risk of serotonergic effects with combinations of different opioids and serotonergic medicines, and management of the interaction. The highest risk opioids are tramadol, pethidine, and dextromethorphan. Monoamine oxidase inhibitors, such as tranylcypromine and phenelzine, are the highest risk serotonergic medicines.

Figure 6: The risk of serotonergic toxicity with combinations of antidepressants and opioids

The authors conclude that the risk of serotonin toxicity should be evaluated routinely, as these combinations of medications is common. The simplest preventative strategy is to generally avoid prescribing opioids associated with higher risks of interaction.

5.1.2 Case Scenario: Opioid Association with Serotonin Syndrome implications to the practitioners - Rastogi et al, 2011 [31]

This paper presents two case scenarios to illustrate the concern of potential adverse interactions of serotonergic medicines with commonly prescribed opioids in chronic pain patients.

- Case 1: 45-year-old male taking methadone, duloxetine and desipramine who was subsequently diagnosed with SS.

- Case 2: 58-year-old male taking fentanyl (patch), oxycodone/paracetamol, celecoxib and mirtazapine who presented with SS.

The authors discuss how both cases expose the consequences of polypharmacy and limited knowledge of the medicine interactions. In both cases increasing does of the opioid, on the background of other serotonergic medicines, precipitated the reaction.

The mechanism of increased 5-HT levels caused by opioids is still being investigated. The authors state that anaesthesiologists and practitioners in chronic pain management need to be aware of the increased risk of SS.

5.1.3 Serotonin Toxicity Associated Agents and Clinical Characteristics – Moss & Hendrickson, 2019 [32]

This study evaluated cases of SS in the Toxicology Investigators Consortium (ToxIC) registry. This is an international database of prospectively collected cases seen by medical toxicologists.

The ToxIC database was searched for the term 'serotonin syndrome' in the 'Toxidrome' section for the 7-year period from 1 January 2010 to 31 December 2016. Cases were excluded if multiple toxidromes were listed or if the case was marked 'unlikely tox related'. Cases were only required to have entered 'serotonin syndrome', and were still included if other information, symptoms, or outcomes were not recorded. If clinical signs and symptoms were not recorded, these were assumed to be absent.

A total of 1010 cases were included. Medicines listed as primary agents of toxicity are shown in Table 7. These are grouped by overall total number of times mentioned in the database. Antidepressant medicines were the most common agents.

Table 7: Medicines associated with serotonin syndrome from cases in Toxicology Investigators Consortium registry

Dextromethorphan was one of the most common medicines noted, and was reported in cases of intentional overdose, drug abuse and adverse drug reactions. Dextromethorphan inhibits the reuptake of serotonin and has been described as cause of SS previously. Fentanyl and tramadol were also found to be associated with SS.

5.1.4 Opioid-induced inhibition of the human 5-HT and noradrenaline transporters *in vitro*: link to clinical reports of serotonin syndrome – Rickli et al, 2018 [33]

The aim of this study was to investigate the potencies of different opioids to inhibit human 5-HT transporter (SERT), noradrenaline transporter (NET) and dopamine transporter (DAT) *in vitro*. The study also tested whether opioids that interact with one of these monoamine transporters induce transporter-mediated monoamine release. Additionally, the affinities of opioids binding directly to the 5-HT1A, 5-HT2A and 5-HT2C receptors was tested.

The investigation was carried out using HEK293 cells (cell line isolated from kidney of a human embryo) transfected with human SERT for the inhibition study. HEK293 cells were transfected with 5-HT1A, 5-HT2A and 5-HT2C for the receptor binding studies.

IC_{50} values for SERT inhibition of different opioids and certain SSRIs and SNRIs for reference, are shown in Table 8. The lower the IC_{50} value the more potent the medicine at inhibiting the transporter. Estimated human drug concentrations in the brain of the opioids are shown in Table 9, to further explore the potential for these medicines to contribute to increasing 5-HT in the CNS leading to SS.

Table 8: Monoamine transporter inhibition and 5-HT receptor binding by different opioids and known SERT/NET inhibitors

Table 9: Estimates of human plasma and brain concentrations of different opioids when used clinically

Dextromethorphan, 1(R)-methadone and racemic methadone potently inhibited the SERT, with concentrations that are likely to be reached in the human brain when these drugs are used in patients, shown in Tables 8 and 9. Dextromethorphan was as potent as fluoxetine. Pethidine, tramadol, tapentadol and d(S)-methadone also inhibited the SERT at low micromolar concentrations, and at concentrations like or close to those reached in human brain at therapeutic doses. Buprenorphine, codeine, dihydrocodeine, morphine and oxycodone, did not inhibit the SERT.

The opioids that inhibited 5-HT uptake were also tested with regard to transporter-mediated monoamine release. None of the opioids acted as a releaser of 5-HT at a high concentration of 100 uM.

Only fentanyl exhibited relevant affinity for the 5-HT1A receptor, in contrast to other opioids. Methadone, pethidine and fentanyl showed affinity for the 5-HT2A receptor at low molecular concentrations that were in range of those concentrations observed in plasma or estimated to be present in the brain in humans. Methadone but not of the other opioids showed very low affinity for 5-HT2C receptor.

The authors collected data on the frequency of reports of SS associated with opioids and sought to establish links between the *in vitro* data and clinical data. A search of PubMed up to 31 August 2016 yielded 99 patient cases that involved 114 administrations of opioids, as seen in Table 10. Fentanyl and tramadol (> 10 cases), followed by oxycodone and dextromethorphan, were the most frequently reported opioids that were associated with SS. However, five of these cases involved both fentanyl and oxycodone. All cases, except for a tramadol overdose and therapeutic doses of dextromethorphan, involved other medicines. In most cases, SSRIs were also involved, and are commonly reported as potentially causes of SS. SSRIs inhibited the SERT more potently than the opioids shown in Table 8.

Table 10: Cases of serotonin syndrome reported, classified by opioid associated with report

The WHO database search performed on 18 April 2016, yielded a total of 1641 reports with at least one of the opioids noted as the suspected drug or an interacting drug, and 147 reports with the opioid as the only suspected cause. The opioids that were most frequently reported in association with SS either alone or in combination with other drugs were tramadol, fentanyl, tapentadol, oxycodone, methadone, and dextromethorphan (Table 10). The single suspected opioids that were most frequently linked to SS were tramadol, tapentadol, fentanyl, dextromethorphan, and pethidine. In most cases, SS occurred within the usual dosage range with overdose reported in less than 10% of the cases. Serotonergic medicines used in the treatment of depression, were the most suspected or interacting medicines these case reports involving opioids.

The *in vitro* study showed that the synthetic atypical opioids dextromethorphan, methadone, pethidine, tramadol and tapentadol acted as SERT inhibitors at or close to clinically observed free drug plasma and estimated free human brain concentrations. This is consistent with findings from previous studies in dextromethorphan, methadone, pethidine, tramadol and tapentadol have previously been shown to block the rat SERT and NET in rat brain synaptosome in vitro assays. The opioids that were SERT inhibitors in vitro were also among those that were most frequently reported to be associated with SS.

Fentanyl and oxycodone were reported in SS cases, however, did not have any SERT activity *in vitro*. This suggesting SERT-independent effects on the 5-HT system *in vivo*.

Some opioids may also directly interact with 5-HT receptors such as 5-HT1A and 5-HT2A or indirectly activate 5-HT release via opioid receptor stimulation. This present study showed that fentanyl directly bound to 5-HT1A, and 5-HT2A, although at concentrations higher than those observed in human plasma. Methadone and pethidine also showed relevant affinity for the 5-HT1A receptor at or near human plasma concentrations during therapeutic use of these opioids.

Analysis of present and previous data suggest a higher risk of SS when opioids are used with serotonergic substances.

This study concludes that SS may result from SERT inhibition by tramadol, tapentadol, methadone, dextromethorphan and pethidine, especially combined with other serotonergic medicines. However, there may also be SERT-independent effects with other opioids, such as fentanyl and oxycodone. These mechanisms and the risk of SS need to be further investigated.

5.1.5 Effects of opioids on human serotonin transporters – Barann et all, 2016 [34]

This study investigated the effects of different opioids on the 5-HT transporter and whether this leads to an increase in free plasma 5-HT concentrations.

Human embryonic kidney cells (HEK293) were stably transfected with the human 5-HT transported cDNA and human platelets ex vivo were used. The end point of this trial was inhibition of the 5-HT transporter by different analgesics either in HERK293 cells or in human platelets ex vivo. Citalopram, a well-known inhibitor of 5-HT uptake, was used as a reference. The opioids tramadol, alfentanil, fentanyl, hydromorphone, morphine, and pethidine were investigated. The study also looked at ketamine.

5-HT was applied to the HEK293 cells expressing the human 5-HT transported resulting in 5-HT accumulation. Figure 7 shows the result from citalopram and the opioids on 5-HT uptake to the HEK293 cells on application of each. Tramadol and pethidine showed a concentration-dependent inhibition of 5-HT uptake. In contrast, morphine, hydromorphone, fentanyl and alfentanil no inhibition of 5-HT uptake was observed.

Figure 7: Effect of citalopram 1 µM, opioids and ketamine on 5-HT uptake via the human 5-HT transporter in HEK293 cells

Results of 5-HT uptake from human platelets are shown in Figure 8. Tramadol and pethidine showed a concentration-dependent elevated free plasma 5-HT. Alfentanil, fentanyl, morphine and hydromorphone had no increase of free 5-HT concentration.

Figure 8: Effect of citalopram 1 µM, opioids and ketamine on free plasma 5-HT levels

Overall, from the results of the two experiments, the medicines tested exerted similar effects on 5-HT uptake *in vitro* and 5-HT uptake in platelets. The study confirms that the human 5-HT transporter is a target for not only tramadol but also for pethidine. These results were obtained both for the 5-HT transported expressed in HEK293 cells in vitro as well as for native 5-HT transporter in platelets *ex vivo*. The potencies of tramadol and pethidine were low compared to SSRIs used in clinical practice. Tramadol and pethidine have been reported in previous studies to possess weak serotonin reuptake inhibitory properties. The study showed that high concentrations of pethidine in this setting were needed to inhibit 5-HT reuptake. It has to be determined whether these effects contribute to SS when administered in patients on other serotonergic medicines.

While morphine has been ruled out as a serotonin reuptake inhibitor before, there has been uncertainty whether fentanyl may be involved in serotonin toxicity. Although older publications suggested fentanyl to be safe, some case reports highlighted SS and fatalities after co-medication with MAOIs and SSRIS. However, the present study could not confirm any relevant effect on 5-HT uptake in HEK293 cells and 5-HT uptake in platelets for fentanyl and alfentanil. These findings suggest that not only serotonin reuptake inhibition alone, but also other serotonergic effects may contribute to SS. Future studies are needed to evaluate whether a clinically useful value for 5-HT concentrations associated with toxic symptoms can be identified.

Comment

Serum 5-HT levels do not correlate with the diagnosis of SS. This is a limitation of this study.

5.1.6 Effects of opioids at monoamine transporters: a potential for interactions of pain medications with antidepressants – Rickli & Liechti, 2016 [35]

This was an *in vitro* study to assess how dextromethorphan, methadone, pethidine, tramadol, and fentanyl, inhibit the reuptake transporters for 5-HT and NET.

5-HT and NET reuptake inhibition in human embryonic kidney (HEK) 293 cells expressing the respective human monoamine transporter was assessed (Table 11). The lower the IC_{50} value the more potent the medicine at inhibiting the transporter.

Table 11: Inhibition potencies for serotonin transporter (SERT) for different opioids, by mean IC_{50} values and 95% confidence intervals

[redacted]

In relation to 5-HT inhibition only, dextromethorphan was the most potent SERT-inhibitor and inhibited SERT with a similar IC_{50} value as fluoxetine. Methadone was the next potent opioid, followed by pethidine and tramadol. Fentanyl was a weak SERT inhibitor. Tramadol and pethidine showed dual SERT and NET inhibition, whereas dextromethorphan and methadone were SERT selective inhibitors.

The monoaminergic effect of some opioids may have additional beneficial analgesic effects but may also trigger serotonergic toxicity when combined with other serotonergic medicines. Awareness of this interaction is crucial since co-administration of synthetic opioids and antidepressant medications is frequent.

5.1.7 The anaesthetist, opioid analgesic drugs, and serotonin toxicity: a mechanistic and clinical review – Baldo & Rose, 2020 [36]

The authors review the proposed mechanisms for opioid-induced SS and provide a clinical perspective for risk assessment.

Investigations using rat synaptic nerve terminals or human tissue have shown certain opioids interact directly with serotonin transporter (SERT). Results from Codd et al, shown in Figure 9, found that tramadol, methadone and dextromethorphan inhibit the rat synaptosomal uptake of 5-HT, however morphine, codeine and oxycodone did not. Other *in vitro* studies addressed by Baldo & Rose, are discussed in detail in sections 5.1.4 and 5.1.5 of this report.

Figure 9: Inhibition of 5-HT uptake in rat synaptosomes, results from study by Codd et al

[redacted]

The authors present a summary of important medicines and considerations of management of interactions, highlighted in Figure 10. Individuals who are potentially at a higher risk are those with a history of SS or taking MAOIs. Tramadol and pethidine should be avoided in these individuals, and the possibility of SS should be considered when given with methadone, fentanyl or oxycodone are given. A rare reaction could occur with MAOI and low risk opioids such as fentanyl congeners (remifentanil and sufentanil), morphine, codeine, dihydrocodeine and buprenorphine. For patients taking SSRIs, SNRIs and certain TCAs (clomipramine and

impramine), pethidine and tramadol should be used in caution, while low risk opioids are considered to have no restrictions.

Figure 10: Stratification of risk of serotonin syndrome by patient and opioid analgesic drug risk

The authors conclude that results from *in vitro* studies suggest that dextromethorphan, tramadol, methadone, pethidine and tapentadol are SERT inhibitors. These opioids are also more likely to be associated with SS in case reports. Fentanyl and oxycodone have been ranked at the top of databases in relation to SS interactions, however, do not interact with SERT. This suggests the possibility of SERT-independent effects on the serotonergic system *in vivo*. There is not much information about oxycodone *in vitro*, however fentanyl has been shown to bind to 5-HT1A and 5-HT2A. This direct activation of receptors may be part of the mechanism for fentanyl role in SS.

An explanation into the mechanisms for morphine, codeine and buprenorphine has not yet been identified. These medicines are generally considered to be non-serotonergic, however there have been rare reports of SS. Morphine may stimulate the release of 5-HT by a disinhibitory mechanism. It is proposed that in the rat DRN, u-opioid receptor bind opioids reduce gamma-aminobutyric-acid (GABA) mediated post synaptic currents in 5-HT neurones and this inhibition of GABAergic afferents leads to an increase in 5-HT efflux.

5.1.8 Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity – Gillman, 2005 [37]

This review paper aims to review recent data in relation to drug interactions involving MAOIs and opioid analgesics, and serotonin toxicity. Most frequently encountered MAOIs are phenelzine, and newer reversible MAOIs, including moclobemide and linezolid.

Table 12 provides an estimate of each drug's potency as a serotonin reuptake inhibitor (SRI). The data in the table cannot be compared drug-drug as it comes from different sources and species. Binding affinities (Ki) at the serotonin transporter of less than 1nM are associated with the ability to precipitate toxicity with MAOIs, and potencies in the 1–10 nM range are borderline. Tramadol, methadone, dextromethorphan, and pethidine show weak SRI properties. The author states that tramadol and pethidine have a higher Ki value than expected. Evidence that tramadol also acts as a serotonin releaser may account for this discrepancy. This could also be the case for pethidine, however there is no direct evidence for this. There are also potential

uncertainties over fentanyl involvement in SS reaction. Fentanyl congeners (eg, remifentanil) have short half-lives and would be expected to be safer than fentanyl.

Table 12: Serotonin transporter affinity of opioid analgesics and comparator drugs, compiled from different sources

Morphine, codeine, oxycodone, and buprenorphine are known not to be SRIs and they do not precipitate SS with MAOIs. Pethidine, tramadol, dextromethorphan and methadone are weak SRIs and may infrequently precipitate dose-dependent SS. The reaction may be more likely in larger doses or susceptible individual. Lack of pharmacological data concerning their SRI potency or 5-HT releasers, limits the ability to estimate the risk with particular drugs.

5.1.9 Phenelzine and morphine drug-drug interaction? A literature review – Beenchinor et al, 2021[38]

The authors presented a patient case where discontinuation of phenelzine due to concern for a drug-drug interaction with morphine let to a negative patient outcome. The authors also reviewed the literature in relation to MAOIs and morphine drug-drug interaction. They searched Medline/PubMed for articles containing the terms 'morphine' or 'opioid' and 'monoamine oxidase inhibitor'. Articles were included if they described *in vitro* data from human cell lines, case reports, human studies, or review articles. A total of 14 publications were found.

Three studies of human cell lines demonstrated that morphine may interact with specific subtypes of serotonin receptors. However, two more recent studies concluded that morphine did not inhibit the serotonin transporter. *In vitro* evidence for a potential drug-drug interaction between morphine and other serotonergic medicines is limited.

One case report suggesting the potential for a morphine–MAOI interaction was identified. Three additional articles were identified, with patients stable on MAOI therapy and treated with morphine. No adverse effects were seen.

Six review articles were found. PK Gillman concluded that morphine did not inhibit serotonin reuptake and did not induce serotonin syndrome when combined with MAOIs. In 2014, Juhn et al conducted a MEDLINE literature search and found that specific opioid analgesics reportedly associated with SS included tramadol, meperidine (pethidine), fentanyl, methadone, oxycodone, buprenorphine, naloxone and hydromorphone. Although several of these drugs would not be expected to have serotonergic effects, the case reports identified were found to have significant confounding variables which could explain these findings. No case reports of SS associated with morphine, codeine, or hydrocodone. The UK NICE published a medicine questions and answers document, 'What is the risk of interaction between opioids and monoamine oxidase inhibitors (MAOIs)?' The report concluded that meperidine should be avoided in combination with MAOIs, however morphine could be considered as an alternative or even the opioid of choice. Two review articles published by Baldo et al and Brown concluded that morphine does not have any serotonergic properties and should generally be considered the drug of choice for patients on MAOIs.

The authors concluded that concomitant use of both phenelzine and morphine, with close monitoring for signs and symptoms of SS, is reasonable for patients who have appropriate indications for both agents.

5.1.10 Interaction of serotonergic antidepressants and opioid analgesics: Is serotonin syndrome going undetected? - Gnanadesigan et al, 2005 [39]

This paper described four cases of probable SS among elderly residents in a long-term care facility (LTC) taking serotonergic antidepressants and opioid analgesics.

The prevalence of depression in older people living in nursing homes is high. One study found that 79% of nursing home residents with depression were treated with antidepressants, of which 59% were on an SSRI. Another study found that 65% of patients with depression also suffer from pain, suggesting that these two conditions commonly co-exist. Neural pathways integrating pain and depression have been described.

- Case 1: 86-year-old female taking sertraline and an increased dose of oxycodone who developed probable SS.
- Case 2: 88-year-old female became hypertensive while taking escitalopram and extended-release oxycodone.
- Case 3: 90-year-old female changed from citalopram to escitalopram and was also taking hydrocodone. She developed visual hallucinations.
- Case 4: 85-year-old female taking an increased dose of mirtazapine while on tramadol. She had recurrent episodes of lethargy, confusion, hypotension, bronchospasm and hypoxia.

The authors noted that in all four cases, symptoms resolved after the medicines were stopped. This constitutes strong evidence for a drug-induced illness. In two cases, the patients were on a stable dose of SSRI and the syndrome was precipitated when the oxycodone dose was increased. The combination of both the SSRI and oxycodone, rather the one alone, is likely to have precipitated the syndrome.

In case 4 where SS developed soon after the addition of mirtazapine to tramadol, it is thought that combination of tramadol with another alpha-2 adrenergic receptor blocker like mirtazapine could cause excess serotonin.

The authors noted that none of the patients met all the diagnostic criteria for SS, however it is not unusual for symptoms from one or two categories to predominate.

SS is usually described as a sudden onset, presenting with 24 hours of medication initiation or change in dose. In the cases reported here, the time between medication change and the diagnosis of probable SS ranged from a few days to weeks. This could be due to delay in reporting of mild symptoms and unawareness of the spectrum of SS clinical presentation.

The authors highlight that patients in LTC are at particular risk of the interaction, because of the high prevalence of pain and depression. There is concern whether cases of SS are going undetected. Heightened clinical awareness of the possibly of SS among patients receiving SSRI or mirtazapine in combination with opioids may lead to earlier detection and avoidance of severe reactions.

5.1.11 Opioid analgesic drugs and serotonin toxicity (syndrome): mechanisms, animal models and links to clinical effects – Baldo, 2018 [40]

The author reviews the increasingly recognised role of opioid analgesic medicines in SS, which is largely a consequence of the many different combinations of serotonergic medicines in use. The author refers to the FDA's safety announcement in 2016 concerning the association of opioids with SS. Prior to this, pethidine, tramadol and tapentadol were already subject to FDA warnings.

Case reports of SS have been called into question with several criticisms. These include inconsistent reporting, failure to report important positive and negative findings, failure to adequately review and quote the relevant literature, and the presentation of incomplete or erroneous information on medicines involved, symptoms and treatments. Cases involving polypharmacy also make cases of SS difficult to diagnose.

There is a lack of research on the pathophysiology of SS in humans, however there is extensive animal literature on the effects of 5-HT in the CNS. The relevance and value of this research to human studies are questionable. Studies in humans in relation to responses to serotonergic medicines and assessment of the risk potential of individual medication and combination are few, as the outcome of certain interactions could be life-threatening.

The FDA's warning acknowledges the increasingly recognised possibility of the induction of SS in some patients that take opioids. There is increasing use of opioids in hospital and to treat different types of pain.

Serotonergic medications used in psychiatry may increase the possibility of SS in the perioperative setting, where fentanyl is commonly used. The authors conclude that patients and physicians need to be aware of the potential for SS, especially in polypharmacy. Some physicians may not be fully aware of the presentation of SS, especially milder symptoms. Heightened clinical awareness of the possibility of SS with opioids and serotonergic antidepressants has been suggested.

5.1.12 Serotonin syndrome in the perioperative period – Bartakke et al, 2020 [41]

The author summarises 29 case reports (31 patients) of perioperative SS that have been reported in the literature from 1994 – 2018.

Cardiac surgery was found to have the highest number of reported cases of SS, followed by orthopaedic and general surgery.

Fentanyl was reported in 5 cases as the potential trigger of SS identified by the authors from the case reports and was reported as the second most common trigger behind methylene blue (15 reports). Remifentanil and dextromethorphan were also reported as potential triggers.

Multiple mechanisms have been postulated to explain the serotonergic effects of opioids. These include weak serotonin uptake inhibition, increased release of serotonin through stimulation of 5-HT1A receptor (fentanyl) and increase of intrasynaptic concentrations of serotonin (morphine, oxycodone, and tramadol).

SSRIs mediated inhibition of cytochrome P450 enzymes may lead to the accumulation of opioids such as tramadol, oxycodone and dextromethorphan. If these medicines are used in combination, there is potential for the pro-serotoninergic effect to be potentiated.

Cases of severe SS due to opioids alone have not been recorded in the literature. However, cases have been reported in combination with other serotonergic drugs such as SSRIs.

5.1.13 Incidence of serotonin syndrome in patients treated with fentanyl on serotonergic agents – Koury et al, 2015 [42]

This study was a retrospective analysis, for all patients admitted to hospital who had received a serotonergic medicine, using the Research Patient Database Registry for a 2-year period from January 2012 to December 2013.

The authors note a surge in the literature case reports highlighting the association of fentanyl as a pro-serotonergic agent. The purpose of the study was to understand the incidence of SS in patients who receive fentanyl while on serotonergic agents.

Fentanyl is a commonly given opioid in hospital, especially in the perioperative setting. Fentanyl patches are also used for chronic pain management along with other serotonergic medicines.

112,045 patients were taking serotonergic agents, approximately 4% (4538 patients) also received fentanyl. 23 of patients taking both a serotonergic agent and fentanyl had been documented with some of the symptoms of SS, however only 4 met Hunter's Criteria for diagnosis. Three of these patients were on fentanyl patch, and one had intravenous fentanyl.

The incidence of SS was found to be 0.09% in patients that received both fentanyl and a serotonergic agent, in comparison to 0.005% in patients that did not receive fentanyl while on a serotonergic agent ($p < 0.01$).

The authors were not able to ascertain a relationship to the number of serotonergic agents used, dose of drugs given, or duration of use that could be attributed risk factors. They also highlight limitations of the study including only being undertaken in one hospital and under diagnosis of SS.

Overall, the results suggested that the incidence of SS is significantly higher in patients receiving fentanyl and a serotonergic agent. However, the low incidence of SS in patients receiving both fentanyl and serotonergic agents raises the need for additional research.

5.1.14 Serotonin syndrome analysis of cases registered in the French pharmacovigilance database – Abadie et al, 2015 [43]

This study was a retrospective analysis of SS spontaneous reports registered in the French pharmacovigilance database between 1 January 1985 to 27 May 2013.

203 cases of SS were found during the study period, 125 fulfilled diagnostic criteria. Among these cases, the patients had been exposed to a total of 578 drugs, among which 209 with potential serotonergic properties. The most frequently involved serotonergic medicines were SSRIs, and to a lesser extent, opioids and MOAIs.

From the 209 medicines with potential serotonergic activity, 31 were opioids (tramadol (20), dextropropoxyphene (5), methadone (3), fentanyl (2), remifentanil (1)).

A pharmacodynamic (PD) interaction related to the association of 2 or more serotonergic medicines was identified in 74 cases. The two most encountered serotonergic associations were SRIs + opioids (mainly paroxetine and tramadol), and SSRI + MOAIs.

Opioids (mainly tramadol) were the second most often encountered drug. Even if a lack of information concerning the serotonergic potency of opioid analgesics remains, the available literature data suggest that some of them (such as tramadol or phenylpiperidine series opioids) are weak SRIs. In the study, opioids were mostly associated with other serotonergic medicines, generally SSRIs. It would be preferable to use the opioids known not to be SRI when using with other serotonergic medicines.

Comment

Opioids have been recognised as serotonergic agents, and interactions with serotonergic medicines has been reported. However, the mechanism in which this occurs is still being investigated and further pharmacological data is needed.

Table 13 outlines a summary of proposed mechanisms of opioids in SS, currently in the literature.

Dextromethorphan, methadone, pethidine, and tramadol have been shown to inhibit serotonin reuptake in *in vitro* studies. Concentrations of these medicines to inhibit serotonin reuptake, may be higher than doses used in clinical practice. Fentanyl has weak inhibitor properties, however unlike other opioids has affinity to 5-HT2A and 5-HT1A receptors. These receptors are thought to be involved in SS. Codeine, morphine, buprenorphine and oxycodone did not show serotonin reuptake inhibition or affinity for 5-HT receptors.

Table 13: Summary of proposed mechanisms of opioids and serotonin syndrome from literature studies and review articles.

		Proposed mechanism(s) from *in vitro* studies				
		Serotonin reuptake inhibitor	5-HT1A	5-HT2A	5-HT2C	Other mechanisms/information:
Opioid	Codeine	×	×	×	×	Prodrug of morphine
	Morphine	×	×	×	×	Thought to stimulate serotonin release via activation of opioid receptors on gamma-amino butyric acid (GABA)-ergic and glutamatergic afferent neurons in the dorsal raphe nucleus.
	Buprenorphine	×	×	×	×	Mechanism not known
	Tramadol	✓	×	×	×	Forth potent SRI opioid. SS like behaviour seen in mice studies.
	Oxycodone	×	×	×	×	Mechanism not known. May increase 5-HT release. Possible SERT independent effects *in vivo*. Limited information on affinity for 5-HT receptors.
	Fentanyl	✓ (weak)	✓	✓		Potential SERT independent effects *in vivo*
	Methadone	✓	×	✓	✓	Second potent SRI opioid. Variable hepatic clearance. Metabolism interactions with other medicines.
	Pethidine	✓	×	✓	×	Third potent SRI opioid. SS like behaviour seen in mice studies.
	Dextromethorphan	✓	×	×	×	Most potent SRI opioid. IC50 SERT inhibition similar to fluoxetine. Reduced metabolism if used with CYP2D6 inhibitor.

Two articles proposed risk stratification of the serotonergic effects of different opioids that could be used to manage the interaction in practice (there was disagreement between the two articles as to the risk associated with oxycodone):

- Low risk: morphine, codeine, dihydrocodeine, buprenorphine, alfentanil, remifentanil, +/- oxycodone
- Medium risk: fentanyl, methadone, +/- oxycodone
- High risk: tramadol, pethidine, dextromethorphan

Those opioids that were shown to have serotonin reuptake inhibition properties *in vitro* are listed as medium and high-risk opioids. Whereas the opioids that did not show SRI are listed as low risk.

High risk opioids were recommended to be avoided in combination with MAOIs or patients with a history of SS. Individuals taking SSRIs, SNRs, and certain TCAs, pethidine and tramadol should be used in caution, whereas low risk opioids had no restrictions.

A rare reaction could occur with MAOI and a low-risk opioid, which was highlighted in a literature case report of a SS with morphine and phenelzine. However, other articles which reviewed this case thought it reasonable to use morphine with MAOI, with close monitoring.

One article reviewed reports of SS with opioids in WHO database and literature case reports. Opioids most reported included tramadol, fentanyl, oxycodone, methadone, and dextromethorphan. Pethidine was reported amongst reports with single suspected opioids, along with tramadol, fentanyl, and dextromethorphan. Fentanyl and oxycodone were not found to inhibit SRI, however, were among suspected medicines in SS reports. The possibility of SRI independent effects *in vivo* has been proposed for their role in SS. There were also reports from low-risk opioids, such as morphine and buprenorphine.

Some articles acknowledged that case reports of SS may be influenced by confounding factors, and that polypharmacy makes SS hard to diagnose. This could potentially be influential in case reports involving low risk opioids. It is not fully understood or unknown the mechanisms in SS these opioids have.

The risk of SS should be evaluated in individuals taking serotonergic medicines and opioids. Certain individuals maybe more vulnerable to the interaction. Antidepressants were the most commonly co-reported medicines in the interaction on review of case reports.

5.2 Literature case reports

There are many case reports in the literature where opioids and serotonergic medicines are implicated the development of serotonin syndrome. Table 14 is a high-level summary of some of these case reports.

Table 14: Literature case reports of drug-drug interaction between opioid(s) and serotonergic medicine(s) leading to serotonin syndrome

Author/year	Opioid	Age	Gender	Clinical presentation	Suspected medicines	Potential triggering event	Outcome
Codeine							
Milano et al, 2017 [44]	Codeine	70	F	Nervousness, irritability, agitation, mania, confusion, tremor, diaphoresis, nausea	Venlafaxine, rizatriptan, codeine	Administration of codeine dose	Venlafaxine and codeine stopped. Symptoms resolved Authors suggested elevated CYP2D6 activity in this individual may have increased levels of morphine (pro-drug of codeine), triggering an increase in 5-HT
Morphine							
Beenchinor et al, 2021 [38]	Morphine	57	F	n/a	Morphine, phenelzine	Addition of morphine	Symptoms resolved on stopping morphine
Pethidine							
Tissot, 2003 [45]	Pethidine	43	M	Agitated, restless, confused, hypertensive, tachycardic, diaphoretic, dilated pupils	Pethidine, fluoxetine (2 weeks prior)	Administration of pethidine dose	Symptoms resolved
Guo et al, 2009 [46]	Pethidine	41	M	Dizziness, nausea, numbness of limbs, palpitations, mild tremor, clonic jerks in feet, hypertensive, tachycardic, febrile	Pethidine	Administration of pethidine dose	Symptoms resolved Authors noted the individuals had a history of SS with clomipramine
Methadone							
Martinez & Martinez, 2008 [47]	Methadone	n/a	n/a	Hallucinations, elevated blood pressure, pulse and respiration.	Methadone (overdose), sertraline, venlafaxine	Overdose of methadone	Did not recover
Rastogi et al, 2011 [31]	Methadone	45	M	Tremulousness, fatigue, weakness in bilateral upper and lower extremities, worsening insomnia, anxiety, hypertensive, diaphoretic, stiff extremities	Methadone, duloxetine, desipramine	Increased methadone dose	Reduced methadone stopped duloxetine. Symptoms resolved
Martin-Lazaro et al, 2017 [48]	Methadone	41	M	Hypertensive, tachycardic, confusion, akathisia, diaphoresis, hyperthermic, generalised spontaneous myoclonus, ocular clonus, ataxia, muscular spasm alternating with hyperreflexia.	Methadone, sertraline, mirtazapine	Addition of sertraline and mirtazapine	Sertraline and mirtazapine stopped. Symptoms resolved. Authors noted that methadone was possibly not the triggering medicine as the individual had been taking it long term, however mirtazapine and

							sertraline had been prescribed in the past two months. Metabolism interactions with methadone may have occurred.
Fentanyl							
Altman & Jahangiri, 2010 [49]	Fentanyl	44	F	Rigid upper and lower extremities, horizontal nystagmus, spontaneous bilateral upper extremity clonus, febrile	Fentanyl (intraoperative), clonazepam, duloxetine, lamotrigine, topiramate, lithium, quetiapine.	Intraoperative fentanyl	Symptoms resolved
Rang et al, 2008 [50]	Fentanyl	60	F	Bilateral hypertonia and hyperreflexia, bilateral ankle clonus, agitated, hypertensive	Fentanyl (perioperative), paroxetine	Perioperative fentanyl	Fentanyl stopped. Symptoms resolved.
Choudhury et al, 2011 [51]	Fentanyl	57	F	Agitated, hypertensive, diaphoretic, myoclonus, headache, nausea, vomiting	Fentanyl (intraoperative), fluoxetine	Intraoperative fentanyl	Symptoms resolved.
Warner et al, 2017 [52]	Fentanyl	72	M	Unresponsive, seizure like activity	Fentanyl (pre-procedure), fluoxetine, turmeric	Pre-procedure fentanyl dose	Symptoms resolved
Warner et al, 2017 [52]	Fentanyl	19	M	Anxious, agitated, shaking, unresponsive, generalised muscle jerking, eye fluttering, nystagmus, head turning, irregular eye movements, myoclonic activity	Fentanyl (pre-procedure), fluoxetine, trazodone	Pre – procedure fentanyl dose	Symptoms resolved
Marino et al, 2021 [53]	Fentanyl	54	F	Diffuse rigidity, back arching, jaw clenching, hyperreflexia, bilateral clonus, increased agitation, decrease responsiveness	Fentanyl, fluoxetine and buspirone (stopped on admission to hospital)	Addition of fentanyl (sedation)	Fentanyl stopped. Symptoms resolved. Authors note fluoxetine's long half-life.
Kirschner & Donovan, 2010 [54]	Fentanyl	46	F	Tachycardia, restless, shivering, agitated, diaphoretic, hypertensive, febrile, patella reflexes hyperactive, bilateral ankle clonus	Fentanyl (pre-procedure), sertraline,	Pre-procedure fentanyl dose	Symptoms resolved.
Oxycodone							
Karunatilake & Buckley, 2006 [55]	Oxycodone	70	F	Confusion, nausea, fevers, agitation, tachycardia, sustained clonus, increased tone, brisk reflexes more prominent in lower limbs	Oxycodone, fluvoxamine, doxepin	Addition and increased dose of oxycodone	Fluvoxamine, doxepin, oxycodone stopped. Symptoms resolved.
Walter et al, 2012 [56]	Oxycodone	77	F	Tremor, weakness, inability to coordinate movements, confusion	Oxycodone, citalopram, (esomeprazole)	Addition of citalopram	Oxycodone changed to morphine; dose of esomeprazole reduced. Symptoms resolved.
Gnanadesigan et al, 2005 [39]	Oxycodone	86	F	Agitated, increased muscle tone in lower extremities, trucal ataxia, coarse tremors, myoclonic jerks	Oxycodone, sertraline	Increased dose of oxycodone	Sertraline stopped; oxycodone reduced. Symptoms improved.

Gnanadesigan et al, 2005 [39]	Oxycodone	88	F	Hypertensive, myoclonic jerks of lower extremities	Oxycodone, escitalopram	Increased dose of oxycodone	Stopped escitalopram and oxycodone. Symptoms resolved.
Hundal et al, 2021 [57]	Oxycodone	22	F	Body shaking, jerky movements of bilateral lower extremities, hypertension, tachycardia, hyperreflexia of upper and lower extremities, mild ocular clonus	Oxycodone, fluoxetine	Addition of oxycodone	Medications stopped. Symptoms resolved.
Song, 2013 [58]	Oxycodone	75	F	Extremities limited passive range of motion with rigidity and spontaneous clonus, confused, agitation	Oxycodone, pregabalin	Addition of pregabalin	Symptoms resolved.
Rosebraugh et al, 2001 [59]	Oxycodone	34	M	Visual hallucinations, severe tremor	Oxycodone, sertraline	Increased dose of oxycodone	Sertraline withheld. Symptoms resolved.
Dextromethorphan							
Dy et al, 2017 [60]	Dextromethorphan	63	F	Altered mental status, upper extremity twitching, bilateral lower extremity clonus	Dextromethorphan, escitalopram	Addition of dextromethorphan (and promethazine) cough syrup	Escitalopram and cough syrup stopped. Symptoms resolved.
Schwartz et al, 2008 [61]	Dextromethorphan	20	M	Confused, febrile, tremulous, tachycardic, hypertensive, diaphoresis, lower extremities rigid and hyperreflexia, clonus in both ankles	Dextromethorphan (overdose), aripiprazole, benztropine, escitalopram	Overdose of dextromethorphan cough syrup	Symptoms resolved
Schwartz et al, 2008 [61]	Dextromethorphan	6	M	Lethargic, confused, febrile, tachycardic, hypertensive, rigidity, clonus in lower extremities, diaphoretic	Dextromethorphan (overdose), sertraline	Overdose of dextromethorphan cough syrup	Symptoms resolved
Remifentanil							
Davis et al, 2013 [62]	Remifentanil	n/a	n/a	Lower extremity clonus, nystagmus, diaphoresis	Remifentanil, fluoxetine	Remifentanil intraoperatively (?)	All opioids stopped. Symptoms resolved.
Buprenorphine							
Isenberg et al, 2008 [63]	Buprenorphine	54	M	Clonus, agitation, altered mental statis	Buprenorphine + naloxone, doxepin, amitriptyline	Unprescribed dose of buprenorphine + naloxone	Symptoms resolved.
>1 opioid							
Gollapudy et al, 2012 [64]	Fentanyl Oxycodone	68	F	Confused, hypertensive, hyperreflexia of lower extremities, increased temperature	Fentanyl (perioperatively) oxycodone, paroxetine, bupropion, duloxetine	Addition of fentanyl (perioperatively)	Anti-anxiety and anti-depressant medicines withheld. Fentanyl stopped. Symptoms resolved.

Kirschner & Donovan, 2010 [54]	Fentanyl Oxycodone Morphine	59	F	Tachycardic, agitated, diaphoretic, patellar hyperreflexia, bilateral ankle clonus	Fentanyl (perioperatively), escitalopram	Addition of fentanyl perioperatively	Symptoms resolved
Takata et al, 2019 [65]	Fentanyl Remifentanil	31	F	Muscle rigidity, myoclonus, stiff neck, hyperreflexia, diaphoresis, tachypnoea, tachycardia, mydriasis, myoclonus seizure, increased blood pressure and heart rate, febrile	Fentanyl (postoperative) duloxetine, remifentanil (intraoperative)	Addition of usual duloxetine post operation with use of fentanyl (and remifentanil) perioperatively	Symptoms resolved
Gurrera & Falls, 2014 [66]	Oxycodone Tramadol	62	M	Disorientated, fluctuating level of consciousness, visual hallucinations, anxious, restless, febrile, tachycardia, hypertensive, myoclonic jerks, tremulousness, rigidity in all four limbs, diaphoretic, dilated pupils,	Oxycodone, tramadol, trazadone, bupropion	Addition of tramadol and oxycodone	Serotonergic medicines withheld. Symptoms improved.
Hardy & Panikkar, 2020 [67]	Dextromethorphan Tramadol	68	F	Weakness, difficulty walking, nausea, vomiting, diarrhoea, tachycardia, diaphoresis, dry mucous membranes, abdominal tenderness, tremor, inducible ankle clonus, lower extremity hypertonia, diffuse hyperreflexia	Dextromethorphan + guaifenesin, duloxetine, mirtazapine, trazodone, lamotrigine, tramadol	Addition of dextromethorphan + guaifenesin cough syrup	Serotonergic medicines withheld. Symptoms resolved.
Smischney et al, 2018 [68]	Fentanyl Pethidine	70	M	Myoclonic jerks in bilateral upper and lower extremities, hypertonia	Fentanyl, pethidine, venlafaxine	Intraoperative fentanyl Post-operative administration of pethidine (worsened symptoms)	Symptoms resolved
Reich & Lefebrve-Kuntz, 2010 [69]	Fentanyl Oxycodone	n/a	n/a	Diaphoresis, night sweating, tremor, diarrhoea, visual disorders, weight loss	Fentanyl, oxycodone, escitalopram	Addition of escitalopram	Stopped escitalopram. Symptoms resolved.
Rastogi et al,2011 [31]	Fentanyl Oxycodone	58	M	Anxiety, tremulousness, fever, sweating.	Fentanyl, oxycodone, citalopram, mirtazapine	Increased frequency of fentanyl patch	Stopped fentanyl, oxycodone/paracetamol, citalopram, mirtazapine. Symptoms resolved
Cameron, 2006 [70]	Dextromethorphan Methadone	46	M	Headache, vomiting, confusion, fevers, sweating, hypertension, fluctuating pulse, dilated reactive pupils, increased tone in both legs, brisk reflexes, clonus at both ankles	Dextromethorphan (night + day capsules), methadone, citalopram.	Addition of dextromethorphan (night + day capsules),	Dextromethorphan stopped; citalopram withheld. Symptoms resolved.

Kumai et al, 2020 [71]	Methadone Oxycodone	47	F	Chills, tremor, excessive perspiration	Methadone, oxycodone, duloxetine, celecoxib, prochlorperazine, esomeprazole	Addition of methadone	Methadone stopped. Symptoms resolved.
Lee et al, 2009 [72]	Methadone Hydromorphone Oxycodone	61	M	Whole body tremors, ataxic, diaphoretic, diarrhoea, involuntary myoclonic jerks, hyperreflexia without clonus, ataxic, falls	Methadone, hydromorphone, oxycodone, venlafaxine, ciprofloxacin, metoclopramide	Increased venlafaxine dose	Venlafaxine, methadone, metoclopramide, ciprofloxacin stopped. Symptoms resolved. Authors note that ciprofloxacin is a CYP3A4 inhibitor of methadone
Altman & Manos, 2007 [73]	Pethidine Fentanyl patch	44	F	Acute agitation, paranoia, disorientation, nausea, hypertensive, tachycardic, febrile	Pethidine, fentanyl patch, citalopram	Administration of pethidine patient-controlled analgesia	Stopped pethidine. Symptoms resolved.
Allawadhi et al, 2007 [74]	Fentanyl Hydrocodone	65	F	Confusion, agitation, combativeness, upper extremity tremors, hyperreflexia, myoclonic jerks, unsteady gait, tachycardic	Fentanyl, citalopram	Addition of fentanyl patch	Fentanyl stopped. Symptoms resolved.

Comment

Limited reports of SS with codeine or morphine were found in the literature, in comparison to a higher number of reports involving fentanyl or oxycodone, or more than one opioid.

Case reports involving pethidine or fentanyl, were most commonly in the perioperative setting in patients taking serotonergic medicine (s). Higher doses of fentanyl are used in anaesthesia, which should be considered on review of potential drug-drug interactions. However, in some of the case reports, individuals experienced symptoms with only one dose.

Authors suggest avoidance or caution is needed with use of serotonergic opioids in patients at risk of SS perioperatively. An accurate medication history is important to prevent any potential interactions, as well as clinician awareness of possible interactions.

A common theme of the case reports from the literature noted was that the SS reaction was triggered by addition of an opioid on the background of a stable combination of known serotonergic medicines. It is possible that these patients who are tolerating usual therapy, received additional opioids and began to show symptoms of SS. For example, some case reports described when patients required pain relief, such as fentanyl or oxycodone, addition of these medicines to usual therapy resulted in SS.

The case reports that included oxycodone mostly involved elderly patients. Polypharmacy in this population is common, and therefore use of multiple serotonergic medicines, in addition to opioid(s) therapy is possible. Potentially oxycodone is more prevalent in this population, as morphine accumulates in renal impairment. Lower doses of oxycodone would be expected as elderly patients are more sensitive to opioids.

In all the case reports, discontinuation of serotonergic medicines led to symptom resolution, strengthening the potential for SS in these cases.

Pharmacokinetic (PK) interactions between medicines were discussed in some case reports, especially with methadone. Methadone has complicated PK interactions and a long half-life. Two case reports also highlighted the long half-life of fluoxetine being implicated in the reaction. In addition, dextromethorphan is metabolised by CYP2D6. Fluoxetine, paroxetine, and citalopram are CYP2D6 inhibitors and may increase levels of dextromethorphan, and may increase the risk of SS.

Several case reports included more than one opioid. It would be important to consider the serotonergic properties of all opioids being administered.

6 REGULATORY COMMUNICATIONS

6.1 Medsafe (New Zealand)

Medsafe has not previously specifically looked at opioids and serotonin syndrome. However, there have been several publications in *Prescriber Update* and a safety communication related to SS.

The opioids pethidine, tramadol, fentanyl, methadone, and dextromethorphan were included in a list of serotonergic medicines in the December 2010 issue of *Prescriber Update,* in the article 'Serotonin syndrome/toxicity' [75]. A reminder article was published in September 2015 [76].

In 2015, Medsafe published an alert communication about SS. In this communication, medicines and drugs linked to SS (list not exhaustive) were included, see figure 11 [77].

Medsafe has also published a consumer information leaflet about serotonin syndrome, highlighting similar medications as shown in Figure 11 [78].

Figure 11: Serotonergic medicines, as described in Medsafe alert communication in 2015

Medicine/Drug Group	Examples
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Dapoxetine*
Tricyclic Antidepressants (TCAs)	Clomipramine, Imipramine, Amitriptyline, Nortriptyline
Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)	Venlafaxine, Duloxetine
Atypical Antidepressants	Mirtazapine
Monoamine Oxidase Inhibitors (MAOIs)	Moclobemide, Phenelzine, Tranylcypromine
Opioid Analgesics	Pethidine, Fentanyl, Tramadol
Antimigraine Agents	Sumatriptan, Rizatriptan, Zolmitriptan
Antinausea Agents	Ondansetron, Granisetron
Herbal Products	St John's wort
Miscellaneous	Methylene Blue, Linezolid (antibiotic), Dextromethorphan (cough suppressant)

*Not indicated for depression

Source: Medsafe. 2015. *Trans-Tasman Early Warning System – Alert Communication: Advice about serotonin syndrome* 31 July 2015. https://www.medsafe.govt.nz/safety/ews/2015/SerotoninSyndrome.asp (accessed 15 April 2022)

6.2 US Food and Drug Administration (FDA)

In 2016, the FDA investigated several safety issues with the entire class of opioid pain medicines, one of which being risk of serotonin syndrome. Prior to 2016, the opioids pethidine, tramadol and tapentadol were already subject to FDA warnings [79].

A search of the FDA Adverse Event Reporting System (FAERS) database for the period of 1 January 1969 to 12 June 2013, identified 43 cases of serotonin syndrome in which opioids were concomitantly used with other serotonergic drugs. Tramadol, tapentadol and meperidine (pethidine) were excluded from the search as these medicines were already labelled for the risk of serotonin syndrome at the time of the review [79].

The most reported opioids associated with serotonin syndrome were fentanyl (28), oxycodone (7) and methadone (5). Other reported opioids included morphine, hydromorphone, alfentanil/remifentanil/sufentanil, hydrocone, naltrexone and pentazocine [79].

There were no reports of SS when an opioid was used alone. Five cases reported that SS occurred with the use of two or more opioids. All of these cases included fentanyl along with at least one other opioid (oxycodone (4), morphine (1), hydromorphone (1), and hydrocodone (1)) [79].

The labels (prescribing information) of opioid medicines (including codeine and morphine) were updated to include information about risk of serotonin syndrome with opioids and serotonergic medicines.

The following information is included in the FDA label for morphine sulphate capsule, extended release (Actavis Pharma Inc.) [80]:

Section 6.2 Post-marketing experience

Serotonin syndrome: cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic medicines.

Section 7 Drug interactions

Serotonergic Drugs

Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue morphine sulfate extended-release capsules if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e.,

cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

6.3 Australia

6.3.1 Australian Prescriber

The April 2021 publication of *Australian Prescriber* contained an article by Perananthan and Buckley 'Opioids and antidepressants: which combinations to avoid' [23].

This article provided information on opioids which have serotonergic activity, and how to manage interactions with antidepressant medication. Information from the article is further discussed in section 5.1.1 of this report.

In summary, tramadol, pethidine, and dextromethorphan were considered high risk opioids for serotonergic properties; fentanyl, tapentadol and methadone were considered medium risk, and morphine, codeine, buprenorphine, oxymorphone, hydromorphone and oxycodone were low risk.

Suggested management of a drug-drug interaction with different serotonergic medicines was discussed. Use of a high-risk opioid, in combination with a high-risk serotonergic medicine such as MAOI was not recommended.

6.3.2 Therapeutic Goods Administration (TGA)

The TGA were asked if they had reviewed the drug-drug interaction between opioids and serotonergic medicines.

Updates to opioid product information (PI) had occurred on review of this interaction, and more recently to serotonergic medicines.

The Cipramil (citalopram) and Loxalate (escitalopram) PI have been updated to include drug–drug interaction with opioids [81, 82]. These updates have not been included in the current NZ data sheets for these products.

6.4 European Medicines Agency (EMA)

The Pharmacovigilance Risk Assessment Committee (PRAC) have previously recommended updates to SmPC for some opioids and SS.

<u>Buprenorphine</u>

At the 2020 PRAC meeting, the signal of buprenorphine and SS was reviewed. The PRAC recommended adding information (see below) to the SmPC of buprenorphine-containing products, and that the interaction is also reflected in SmPC of serotonergic medicines [1]:

4.4 Special warnings and precautions for use Serotonin syndrome Concomitant administration of [product name] and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. **4.5. Interaction with other medicinal products and other forms of interaction** [Product name] should be used cautiously when co-administered with: • Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Oxycodone

The PRAC Assessment Report on the PSUR(s) for oxycodone recommended updates to the oxycodone SmPC with information on SS. This recommendation was adopted at the December 2018 meeting [83].

The following information was suggested to be added into section 4.5 of SmPC:

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Methadone

In 2020, PRAC Assessment report on the methadone PSUR suggested to include interaction with serotonergic medicines. The recommendation was adopted at the January 2020 meeting [84].

An increased body of published literature describing SS in methadone users has also been noted and the role of methadone in these cases cannot be ruled out. Synthetic piperidine opioids such as methadone are weak serotonin reuptake inhibitions which could lead to an increase in serotonin level. Based on this data the following updates to the section 4.5 of the SmPC were suggested:

4.5. Interaction with other medicinal products and other forms of interaction

Serotonergic drugs: Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

7 SPONTANEOUS REPORTING OF CASES

7.1 CARM data

The CARM data base was searched for New Zealand case reports related to serotonin syndrome up to 31 December 2021.

From a total of 59 serotonin syndrome cases, 14 cases involved a suspect opioid. These cases are summarised in Table 15. See Annex 3 for the data received from CARM.

Table 15: Summary of cases reported to CARM where an opioid is reported as suspected or concomitant medicine, up to 31 December 2021

Report	Date	Age M/F	Medicine (s)	Reaction (s)
043680	Feb 00	28, F	Tramadol*, paroxetine*, thioridazine, zopiclone, danazol	Serotonin syndrome, agitation, drug interaction, tremor, sweating increased.
063621	Jan 05	19, F	Citalopram*, tramadol*, ciprofloxacin*, codeine, oral contraceptive	Nausea, myoclonus, sweating increased, drug interaction, serotonin syndrome
077067	Nov 07	33, F	Pethidine*, fluoxetine*, omeprazole, azathioprine, calcium carbonate	Serotonin syndrome
077178	Dec 07	34, F	Methylene blue*, tramadol*, fentanyl*, paroxetine*, omeprazole	Serotonin syndrome
078309	Apr 08	51, F	Fluoxetine*, tramadol*, cyclizine, ondansetron, morphine	Serotonin syndrome, drug interaction
083854	Apr 09	56, F	Ondansetron*, tramadol*, oxycodone*, fentanyl*, haloperidol	Serotonin syndrome
089873	May 10	39, F	Tramadol*, oxycodone*, paracetamol, sibutramine	Serotonin syndrome
109912	Feb 14	26, F	Tramadol*, sertraline*, diclofenac	Serotonin syndrome, drug interaction
113320	Aug 14	84, F	Tramadol*, venlafaxine*	Serotonin syndrome
115985	Apr 15	57, F	Fluoxetine*, tramadol*, ondansetron*	Serotonin syndrome
116267	May 15	31, F	Fluoxetine*, tramadol*	Serotonin syndrome
121427	Jul 16	25, M	Tramadol*, quetiapine, codeine	Serotonin syndrome, convulsions
129817	Sep 18	64, F	Venlafaxine*, tramadol*	Serotonin syndrome, drug interaction
134414	Sep 19	28, F	Tramadol*, sertraline*	Serotonin syndrome, drug interaction

*=reported as suspect medicine

Comment

Tramadol was the most frequently reported opioid and was reported in 13 cases as a suspect medicine. Fentanyl, oxycodone, and pethidine were the only other opioids that were in the cases.

Two reports listed fentanyl as a suspected medicine. Tramadol was also listed as a suspected medicine in these cases.

Oxycodone was listed in two cases. In one case, fentanyl and tramadol were also listed as suspected medicines and, in another case, tramadol was also listed.

One report listed pethidine in combination with the SSRI fluoxetine.

All cases involved additional serotonergic medicines, except one case which was attributed to tramadol alone.

Tramadol was more likely to list only one additional medicine. In the cases involving fentanyl, three other serotonergic medicines were listed as suspected medicines in the interaction.

Other medicines involved were an SSRI or SNRI, however some cases involved more than one opioid.

7.2 International Reports

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

8 DISCUSSION AND CONCLUSIONS

Serotonin syndrome is a rare, but potentially life-threatening, condition.

An understanding of the serotonergic properties of different opioids is becoming increasingly important. The number of people dispensed SSRIs and TCAs in NZ increased from 2017 to 2020, potentially suggesting more individuals are using serotonergic medicines.

Opioids are used both in hospital and in the community. There is a range of different clinical scenarios whereby an individual may be exposed to an opioid(s)–serotonergic medicine(s) drug-drug interaction.

Individuals who are prescribed opioids may be on antidepressant therapy or other medicines with serotonergic effects. The trigger for SS in several literature case reports was the addition or a dose increase of a particular opioid, on the background of regular serotonergic medicines. Often these medicines were antidepressants, however some antidepressants may be used off-label for other indications. In addition, some individuals may be more vulnerable to the interaction, or have other medicines influencing the metabolism of the opioid and/or serotonergic medicine. Understanding the risk of SS with different opioids in combination with different serotonergic agents for an individual patient is needed, to best manage the interaction and prevent any unwanted adverse events.

From the available information reviewed in this report, it is suggested dextromethorphan, tramadol, and pethidine are high risk opioids. These opioids were found to be amongst the most potent serotonin reuptake inhibitors (SRIs) *in vitro*.

More people were dispensed tramadol in the community in comparison to other high-risk opioids. Tramadol was also the most frequently reported opioid in case reports of SS, either alone or in combination with serotonergic medicines. Information about this interaction is noted in both the tramadol and serotonergic medicine data sheets.

Pethidine is potentially less used in clinical practice due to its adverse effect profile compared to other opioids. Its use in the community from NZ dispensing data was low. Case reports of SS when pethidine was used in combination with other medicines have been reported, most commonly in the perioperative setting.

Several case reports of SS with dextromethorphan were noted in the literature. Dextromethorphan is a cough suppressant. Addition of dextromethorphan to an individual's normal therapy of serotonergic medicines may be a trigger for SS. Individuals may also be taking SSRIs that reduce the metabolism of dextromethorphan, increasing the risk of the interaction. Dextromethorphan is available as a restricted medicine, and usage data could not be obtained.

Fentanyl, methadone and possibly oxycodone were considered medium-risk opioids in the literature highlighted above and were recommended to be used with caution in combination with serotonergic medicines. Methadone had shown SRI properties *in vitro*. It is used for opioid substitution therapy, where it may be used in high doses. Medicines that reduce the metabolism of methadone may lead to toxicity and increase the risk of SS interaction.

Fentanyl is potentially a weak SRI and has affinity for 5-HT1A and 5-HT2A receptors. Other unknown mechanisms or SRI independent effects have been suggested for fentanyl mechanisms in SS, and there have been several cases of SS with fentanyl and other serotonergic medicines reported in the literature. Most of these cases were noted perioperatively. Higher doses of fentanyl are used in anaesthesia, which may explain the SS cases that occurred perioperatively. Fentanyl was the second most frequently reported opioid in international spontaneous reports of SS cases, after tramadol.

There have been reports of SS with oxycodone in the literature, and in international spontaneous reporting. Oxycodone does not have SRI properties nor 5-HT receptor affinity, and further research is needed to understand whether it can cause SS and what the mechanisms might be.

The involvement of codeine, dihydrocodeine, morphine and buprenorphine in causing SS are less certain. These opioids are considered low risk, and an interaction with serotonergic medicines was noted to be rare.

No reports of these medicines causing SS on their own were noted. Out of all the opioids, these medicines had the lowest number of cases reported in the literature and international spontaneous case reports. There were more reports with morphine than codeine and buprenorphine, however these cases also included tramadol and/or fentanyl, and this may simply reflect higher use. Morphine, codeine, and buprenorphine have no SRI properties *in vitro*. In the UK SmPC for serotonergic medicines, buprenorphine is commonly listed in the interactions section. The PRAC recommended addition of the interaction after a review found an increased risk of SS with use of buprenorphine and a serotonergic medicine. Further information from the review was unavailable. The FDA required a warning for all opioid agonists for risk of SS.

The New Zealand data sheets for tramadol, oxycodone, fentanyl, pethidine, dextromethorphan, morphine, buprenorphine and alfentanil all list an interaction with serotonergic medicines that can cause SS. Variation was seen across different products, for example, some morphine data sheets included SS and others did not. Information for the same medicine should be made consistent if clinically appropriate. SS was not listed in the remifentanil data sheet; this is consistent across international prescribing information. There was also a low number of spontaneous reports for remifentanil. Additional information about the interaction could be added to methadone data sheets.

In some serotonergic data sheets, there was limited information about the drug-drug interaction with opioids. There is potential for SS with certain opioids in combination with MAOIs, SSRI, SNRI and TCAs (potentially certain TCAs over others). Alignment of information on the interaction between medicines of the same class should be considered.

Most serotonergic medicine data sheets listed an interaction with a 'serotonergic agent'. Prescribers may not be aware of the serotonergic potential of some opioids. However, the NZ sertraline and venlafaxine data sheets listed opioids in section 4.5. These opioids were the same as those suggested to be high and medium risk in the literature, and included fentanyl, methadone, pethidine, dextromethorphan, and tramadol. The oxycodone, buprenorphine and some morphine data sheets had information on SS. Except for the amitriptyline data sheet which included buprenorphine, these opioids were not included in serotonergic medicine data sheets.

9 ADVICE SOUGHT

The Committee is asked to advise:

- If the information in the opioid data sheets about the risk of a drug-drug interaction with serotonergic medicines increasing the risk of serotonin syndrome is sufficient or are data sheet updates required for codeine, dihydrocodeine, oxycodone, buprenorphine, dextromethorphan, morphine, methadone, tramadol, pethidine, fentanyl, alfentanil and remifentanil?
- If the information in the serotonergic medicine data sheets about the risk of a drug-drug interaction with opioid medicines increasing the risk of serotonin syndrome is sufficient or are data sheet updates required for SSRIs (sertraline, citalopram, escitalopram, paroxetine, fluoxetine), SNRIs (venlafaxine), MAOIs (tranylcypromine, moclobemide, linezolid, methylene blue) and TCAs (imipramine, clomipramine, amitriptyline, nortriptyline, dosulepin) or other serotonergic medicines?
- Does the topic require further communication, other than MARC's Remarks in *Prescriber Update*?

10 ANNEXES

Annex 1: New Zealand opioid data sheet information on serotonin syndrome

Annex 2: New Zealand serotonergic medicine data sheet information on drug-drug interaction with opioids

Annex 3: CARM cases

11 REFERENCES

1. PRAC. 2020. *PRAC recommendations on signals adopted at the 11-14 May 2020 PRAC meeting* 22 June 2020. URL: https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-11-14-may-2020-prac-meeting_en.pdf (accessed 4 April 2022).
2. 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 6 May 2022).
3. Williams J. 2008. Basic Opioid Pharmacology. *Rev Pain* 1(2): 2-5. URL: https://pubmed.ncbi.nlm.nih.gov/26524987/ (accessed 2 May 2022).
4. New Zealand Formulary (NZF). 2022 *NZF v119: Pain management of common specific conditions* 1 May 2022 URL: https://nzf.org.nz/nzf_2556 (accessed 2 May 2022).
5. Best Practice Advocacy Centre New Zealand (BPAC). 2018 *The principles of managing acute pain in primary care* URL: https://bpac.org.nz/2018/docs/acute-pain.pdf (accessed 20 April 2022).
6. New Zealand Formulary (NZF). 2022 *NZF v119: Analgesics* 1 May 2022. URL: https://nzf.org.nz/nzf_2415 (accessed 2 May 2022).
7. Best Practice Advocacy Centre (BPAC). 2018 *Understanding the role of opioids in chronic non-malignant pain* URL: https://bpac.org.nz/2018/docs/opioids-chronic.pdf (accessed 20 March 2022).
8. Best Practice Advocacy Centre (BPAC). 2018 *When to consider strong opioids for patients with acute pain* URL: https://bpac.org.nz/2018/docs/opioids.pdf (accessed 20 April 2022).
9. New Zealand Formulary (NZF). 2022 *NZF v119: Local anaesthesia* 1 May 2022 URL: https://nzf.org.nz/nzf_7022 (accessed 6 May 2022).
10. Foong AL, Grindrod KA, Patel T, et al. 2018. Demystifying serotonin syndrome (or serotonin toxicity). *Can Fam Physician* 64(10): 720-727. URL: https://pubmed.ncbi.nlm.nih.gov/30315014/ (accessed 4 April 2022).
11. Boyer EW and Shannon M. 2005. The serotonin syndrome. *N Engl J Med* 352(11): 1112-20. DOI: 10.1056/NEJMra041867 (accessed 4 April 2022).
12. Scotton WJ, Hill LJ, Williams AC, et al. 2019. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. *Int J Tryptophan Res* 12: 1178646919873925. DOI: 10.1177/1178646919873925 (accessed 5 April 2022).
13. Werneke U, Truedson P, Wikström H, et al. 2020. Serotonin syndrome: a clinical review of current controversies. *Journal of Integrative Neuroscience* 19(4): 719-727. URL: https://pubmed.ncbi.nlm.nih.gov/33378846 (accessed 5 April 2022).
14. Francescangeli J, Karamchandani K, Powell M, et al. 2019. The Serotonin Syndrome: From Molecular Mechanisms to Clinical Practice. *Int J Mol Sci* 20(9): DOI: 10.3390/ijms20092288 (accessed 5 April 2022).
15. Birmes P, Coppin D, Schmitt L, et al. 2003. Serotonin syndrome: a brief review. *Cmaj* 168(11): 1439-42. URL: https://pubmed.ncbi.nlm.nih.gov/12771076/ (accessed 5 April 2022).
16. New Zealand Formulary (NZF). 2022. *NZF v118: Antidepressants drugs* 1 April 2022 URL: https://nzf.org.nz/nzf_2225 (accessed 22 March 2022).
17. Hirsch M, Birnbaum, R 2022. Selective serotonin reuptake inhibitors: Pharmacology, administration and side effects. In: *UpToDate* 11 April 2022. URL: https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects (accessed 21 March 2022).
18. Wang RZ, Vashistha V, Kaur S, et al. 2016. Serotonin syndrome: preventing, recognizing, and treating it. *Cleve Clin J Med* 83(11): 810-817. URL: https://pubmed.ncbi.nlm.nih.gov/27824534/ (accessed 5 April 2022).
19. Singh D and Saadabadi A. 2022. *Venlafaxine* URL: https://www.ncbi.nlm.nih.gov/books/NBK535363/ (accessed 20 May 2022).
20. Hirsch M and Birnbaum R. 2022. Tricyclic and tetracyclic drugs: Pharmacology, administration and side effects. In: *UpToDate* 3 December 2021. URL: https://www.uptodate.com/contents/tricyclic-and-tetracyclic-drugs-pharmacology-administration-and-side-effects (accessed 22 March 2022).

21. Talton CW. 2020. Serotonin Syndrome/Serotonin Toxicity. *Fed Pract* 37(10): 452-459. DOI: 10.12788/fp.0042 (accessed 5 April 2022).
22. Gillman PK. 2007. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 151(6): 737-48. DOI: 10.1038/sj.bjp.0707253 (accessed 6 April 2022).
23. Perananthan V, Buckley, NA, . 2021. Opioids and antidepressants: which combinations to avoid *Australian Prescriber* 44(2): 41-44. URL: https://www.nps.org.au/australian-prescriber/articles/opioids-and-antidepressants-which-combinations-to-avoid (accessed 19 April 2022).
24. Isbister GK, Buckley NA and Whyte IM. 2007. Serotonin toxicity: a practical approach to diagnosis and treatment. *Med J Aust* 187(6): 361-5. DOI: 10.5694/j.1326-5377.2007.tb01282.x (accessed 19 April 2022).
25. Browne B and Linter S. 1987. Monoamine oxidase inhibitors and narcotic analgesics: A critical review for the implications for treatment *British Journal of Psychiatry* 151(2): 210-212. URL: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/C6C60BDFA1759A62BF524F4FCED12996/S0007125000216103a.pdf (accessed 9 May 2022).
26. PSM Healthcare Limited t/a API Consumer Brands. 2021. *Codeine Phosphate tablets (PSM) New Zealand data sheet* 18 August 2021 URL: https://www.medsafe.govt.nz/profs/Datasheet/c/CodeinePhosphatePSMtab.pdf (accessed 24 May 2022).
27. Pharmaco New Zealand Limted. 2021. *Severdol 10mg and 20mg tablets New Zealand Data Sheet* September 2021 URL: https://www.medsafe.govt.nz/profs/Datasheet/s/Sevredoltab.pdf (accessed 20 May 2022).
28. Pfizer New Zealand Limited. 2020. *DBL Pethidine Hydrochloride Injection BP 50mg/mL New Zealand Data Sheet* 14 August 2020 URL: https://www.medsafe.govt.nz/profs/Datasheet/d/dblPethidineinj.pdf (accessed 20 May 2022).
29. Biomed Limited. 2022 *Biodone 2mg/mL, Biodone Forte 5mg/mL, Biodone Extra Forte 10mg/mL oral solution New Zealand Data Sheet* 9 May 2022 URL: https://www.medsafe.govt.nz/profs/Datasheet/b/Biodoneoralsoln.pdf (accessed 20 May 2022).
30. New Zealand Formulary (NZF). 2022 *NZF v119: Interaction checker* 1 May 2022 URL: https://nzf.org.nz/nzf_2472 (accessed 6 May 2022).
31. Rastogi R, Swarm Robert A, Patel Trusharth A, et al. 2011. Case Scenario: Opioid Association with Serotonin Syndrome: Implications to the Practitioners. *The Journal of the American Society of Anesthesiologists* 115(6): 1291-1298. DOI: 10.1097/ALN.0b013e31823940c0 (accessed 21 March 2022).
32. Moss MJ, Hendrickson RG and Consortium TI. 2019. Serotonin toxicity: associated agents and clinical characteristics. *Journal of clinical psychopharmacology* 39(6): 628-633. URL: https://pubmed.ncbi.nlm.nih.gov/31688388/ (accessed 12 April 2022).
33. Rickli A, Liakoni E, Hoener MC, et al. 2018. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome. *Br J Pharmacol* 175(3): 532-543. DOI: 10.1111/bph.14105 (accessed 12 April 2022).
34. Barann M, Stamer UM, Lyutenska M, et al. 2015. Effects of opioids on human serotonin transporters. *Naunyn Schmiedebergs Arch Pharmacol* 388(1): 43-9. DOI: 10.1007/s00210-014-1056-3 (accessed 13 April 2022).
35. Rickli A, Liecht, M 2016. Effects of opioids at monoamine transporters: a potential for interactons of pain medications with antidepressants. . *European Neuropsychopharmacology* 26: 258 - 259 URL: https://www.ecnp.eu/presentationpdfs/70/P.1.g.077.pdf (accessed 22 April 2022).
36. Baldo BA and Rose MA. 2020. The anaesthetist, opioid analgesic drugs, and serotonin toxicity: a mechanistic and clinical review. *Br J Anaesth* 124(1): 44-62. DOI: 10.1016/j.bja.2019.08.010 (accessed 18 April 2022).
37. Gillman PK. 2005. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth* 95(4): 434-41. DOI: 10.1093/bja/aei210 (accessed 28 March 2022).

38. Beechinor RJ, Tyson R and Roth ME. 2021. Phenelzine and Morphine Drug-Drug Interaction? A Literature Review. *J Pharm Pract* 34(5): 818-823. DOI: 10.1177/0897190020970752 (accessed 18 April 2022).
39. Gnanadesigan N, Espinoza RT, Smith R, et al. 2005. Interaction of serotonergic antidepressants and opioid analgesics: is serotonin syndrome going undetected? *Journal of the American Medical Directors Association* 6(4): 265-269. URL: https://pubmed.ncbi.nlm.nih.gov/16005413/ (accessed 13 April 2022).
40. Baldo B. 2018. Opioid analgesic drugs and serotonin toxicity (syndrome): mechanisms, animal models, and links to clinical effects. *Archives of toxicology* 92(8): 2457-2473. URL: https://pubmed.ncbi.nlm.nih.gov/29916050/ (accessed 18 April 2022).
41. Bartakke A, Corredor C and van Rensburg A. 2020. Serotonin syndrome in the perioperative period. *BJA Educ* 20(1): 10-17. DOI: 10.1016/j.bjae.2019.10.003 (accessed 18 April 2022).
42. Koury KM, Tsui B and Gulur P. 2015. Incidence of serotonin syndrome in patients treated with fentanyl on serotonergic agents. *Pain Physician* 18(1): E27-30. URL: https://pubmed.ncbi.nlm.nih.gov/25675067/ (accessed 18 April 2022).
43. Abadie D, Rousseau V, Logerot S, et al. 2015. Serotonin Syndrome: Analysis of Cases Registered in the French Pharmacovigilance Database. *J Clin Psychopharmacol* 35(4): 382-8. DOI: 10.1097/jcp.0000000000000344 (accessed 5 April 2022).
44. Milano G, Werner M, Bello A, et al. 2017. Codeine precipitating serotonin syndrome in a patients in therapy with antidepressant and triptan *Clin Psycopharmacol Neurosci.* 15(3): 292 - 295 URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5565085/ (accessed 21 April 2022).
45. Tissot TA. 2003. Probable meperidine-induced serotonin syndrome in a patient with a history of fluoxetine use. *Anesthesiology* 98(6): 1511-2. DOI: 10.1097/00000542-200306000-00033 (accessed 15 April 2022).
46. Guo S, Wu T, Liu C, et al. 2009. Meperidine - induced serotonin syndrome in a susceptible patient. *British Journal of Anaesthsia* 103 (3): 369-70. URL: https://www.bjanaesthesia.org/article/S0007-0912(17)33973-9/pdf (accessed 21 April 2022).
47. Martinez T and Martinez D. 2008. A case of serotonin syndrome associated with methadone overdose. *Proceedings of the Western Pharmacology Society* 51: 42-44. URL: https://pubmed.ncbi.nlm.nih.gov/19544673/ (accessed 15 April 2022).
48. Martin-Lazaro J, Hayde-West J, Chatzimicheal S, et al. 2017 A dangerous triad: sertaline, mirtazepine and methadone *Clin Med Rev Case Rep* 4(1): 154. URL: https://clinmedjournals.org/articles/cmrcr/clinical-medical-reviews-and-case-reports-cmrcr-4-154.pdf (accessed 22 April 2022).
49. Altman CS and Jahangiri MF. 2010. Serotonin syndrome in the perioperative period. *Anesthesia & Analgesia* 110(2): 526-528. URL: https://pubmed.ncbi.nlm.nih.gov/19955502/ (accessed 12 April 2022).
50. Rang ST, Field J and Irving C. 2008. Serotonin toxicity caused by an interaction between fentanyl and paroxetine. *Canadian journal of anaesthesia* 55(8): 521-525. URL: https://pubmed.ncbi.nlm.nih.gov/18676387 (accessed 15 April 2022).
51. Choudhury M, Hote MP and Verma Y. 2011. Serotonin syndrome in a postoperative patient. *Journal of anaesthesiology, clinical pharmacology* 27(2): 233. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3127305 (accessed 19 April 2022).
52. Warner ME, Naranjo J, Pollard EM, et al. 2017. Serotonergic medications, herbal supplements, and perioperative serotonin syndrome. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie* 64(9): 940-946. URL: https://pubmed.ncbi.nlm.nih.gov/28667541/ (accessed 15 April 2022).
53. Marino N, Bellamy N, Subramaniyarn R, et al. 2021 Fentanyl-assoicated serotonin syndrome five days after discontinuation of fluoxetine: a case report *Critical Care Medicine* 49(1): 402 URL: https://journals.lww.com/ccmjournal/Citation/2021/01001/811__Fentanyl_Associated_Serotonin_Syndrome_Five.779.aspx (accessed 20 April 2022).
54. Kirschner R and Donovan JW. 2010. Serotonin syndrome precipitated by fentanyl during procedural sedation. *The Journal of emergency medicine* 38(4): 477-480. URL: https://pubmed.ncbi.nlm.nih.gov/18757161/ (accessed 28 March 2022).

55. Karunatilake H and Buckley NA. 2006. Serotonin syndrome induced by fluvoxamine and oxycodone. *Ann Pharmacother* 40(1): 155-7. DOI: 10.1345/aph.1E671 (accessed 8 April 2022).
56. Walter C, Ball D, Duffy M, et al. 2012. An unusual case of serotonin syndrome with oxycodone and citalopram. *Case Rep Oncol Med* 2012: 261787. DOI: 10.1155/2012/261787 (accessed 8 April 2022).
57. Hundal J, Ahmed O, Hyder S, et al. 2021. Postoperative serotonin syndrome *Critical Care Medicine* 49(1): 403 DOI: 10.1097/01.ccm.0000729140.32083.85 (accessed 22 April 2022).
58. Song HK. 2013. Serotonin syndrome with perioperative oxycodone and pregabalin. *Pain Physician* 16(5): E632-3. URL: https://www.painphysicianjournal.com/current/pdf (accessed 8 April 2022).
59. Rosebraugh CJ, Flockhart DA, Yasuda SU, et al. 2001. Visual hallucination and tremor induced by sertraline and oxycodone in a bone marrow transplant patient. *J Clin Pharmacol* 41(2): 224-7. DOI: 10.1177/00912700122009926 (accessed 5 April 2022).
60. Dy P, Arcega V, Ghali W, et al. 2017. Serotonin syndrome caused by drug to drug interaction between escitalopram and dextromethorphan. *Case Reports* 2017: bcr-2017-221486. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5747823 (accessed 28 March 2022).
61. Schwartz AR, Pizon AF and Brooks DE. 2008. Dextromethorphan-induced serotonin syndrome. *Clinical Toxicology* 46(8): 771-773. URL: https://pubmed.ncbi.nlm.nih.gov/19238739/ (accessed 7 April 2022).
62. Davis JJ, Buck NS, Swenson JD, et al. 2013. Serotonin syndrome manifesting as patient movement during total intravenous anesthesia with propofol and remifentanil. *J Clin Anesth* 25(1): 52-4. DOI: 10.1016/j.jclinane.2012.05.002 (accessed 22 March 2022).
63. Isenberg D, Wong SC and Curtis JA. 2008. Serotonin syndrome triggered by a single dose of suboxone. *The American Journal of Emergency Medicine* 26(7): 840. e3-840. e5. URL: https://pubmed.ncbi.nlm.nih.gov/18774063/ (accessed 7 April 2022).
64. Gollapudy S, Kumar V and Dhamee MS. 2012. A case of serotonin syndrome precipitated by fentanyl and ondansetron in a patient receiving paroxetine, duloxetine, and bupropion. *J Clin Anesth* 24(3): 251-2. DOI: 10.1016/j.jclinane.2011.04.017 (accessed 22 March 2022).
65. Takata J, Arashi T, Abe A, et al. 2019. Serotonin syndrome triggered by postoperative administration of serotonin noradrenaline reuptake inhibitor (SNRI). *JA Clinical Reports* 5(1): 1-4. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6967275/ (accessed 12 April 2022).
66. Falls BA and Gurrera RJ. 2014. Serotonin syndrome in a patient on tramadol, bupropion, trazodone, and oxycodone. *Psychosomatics* 55(3): 305-9. DOI: 10.1016/j.psym.2013.05.013 (accessed 8 April 2022).
67. Hardy M and Panikkar G. 2020. A Case of Serotonin Syndrome in the Setting of Dextromethorphan-Based Cough Medicine, Tramadol, and Multiple Antidepressants. *Prim Care Companion CNS Disord* 22(2): DOI: 10.4088/PCC.19l02518 (accessed 8 April 2022).
68. Smischney NJ, Pollard EM, Nookala AU, et al. 2018. Serotonin Syndrome in the Perioperative Setting. *Am J Case Rep* 19: 833-835. DOI: 10.12659/ajcr.909497 (accessed 15 April 2022).
69. Reich M and Lefebvre-Kuntz D. 2010. [Serotoninergic antidepressants and opiate analgesics: a sometimes-painful association. A case report]. *Encephale* 36 Suppl 2: D119-23. DOI: 10.1016/j.encep.2009.03.010 (accessed 28 March 2022

).
70. Cameron C. 2006. Serotonin syndrome precipitated by an over-the-counter cold remedy *Australian Prescriber* 29(3): 71. URL: https://www.nps.org.au/australian-prescriber/articles/serotonin-syndrome-precipitated-by-an-over-the-counter-cold-remedy (accessed 22 April 2022).
71. Kumai M, Maeda Y, Miura M, et al. 2020. Serotonin syndrome developing immediately after the initiation of low-dose methadone therapy: a case report. *Case Rep Oncol* 13(1): 281-284. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7154242/ (accessed 22 April 2022).
72. Lee J, Franz L and Goforth HW. 2009. Serotonin syndrome in a chronic-pain patient receiving concurrent methadone, ciprofloxacin, and venlafaxine. *Psychosomatics* 50(6): 638-9. DOI: 10.1176/appi.psy.50.6.638 (accessed 18 April 2022).
73. Altman EM and Manos GH. 2007. Serotonin syndrome associated with citalopram and meperidine. *Psychosomatics* 48(4): 361-3. DOI: 10.1176/appi.psy.48.4.361-a (accessed 18 April 2022).

74. Ailawadhi S, Sung KW, Carlson L, et al. 2007. Serotonin syndrome caused by interaction between citalopram and fentanyl. *Journal of clinical pharmacy and therapeutics* 32(2): 199-202. URL: https://pubmed.ncbi.nlm.nih.gov/17381671/ (accessed 22 March 2022).
75. Medsafe. 2010. *Serotonin syndrome/toxicity - reminder. Prescriber Update 31(4):30-31.* URL: https://www.medsafe.govt.nz/profs/PUArticles/SerotoninSyndromeToxicityReminder.htm (accessed 15 April 2022).
76. Medsafe. 2015. *Reminder: Interactions resulting in serotonin syndrome. Prescriber Update 36(3): 35* URL: https://www.medsafe.govt.nz/profs/PUArticles/Sep2015/InteractionsSerotoninSyndrome.htm (accessed 15 April 2022).
77. Medsafe. 2015. *Trans-tasman early warning system - alert communication* 31 July 2015 URL: https://www.medsafe.govt.nz/safety/ews/2015/SerotoninSyndrome.asp (accessed 15 April 2022).
78. Medsafe. 2015. *Serotonin syndrome* 2015. URL: https://www.medsafe.govt.nz/consumers/educational-material/Serotonin%20Syndrome%20December%202015.pdf (accessed 15 April 2022).
79. Food and Drug Administration (FDA). 2016. *FDA drug safety communication: FDA warns about severeal safety issues with opioid pain medicines; requires label changes* 22 March 2016. URL: https://www.fda.gov/media/96472/download (accessed 15 April 2022).
80. Activis Pharma Inc. 2021 *Morphine Sulfate extended-release capsules FDA Label* March 2021. URL: https://www.accessdata.fda.gov/spl/data/8dd61ce7-69ff-44a1-8efa-3f7f2169d316/8dd61ce7-69ff-44a1-8efa-3f7f2169d316.xml (accessed 15 April 2022).
81. Lundbeck Australia Pty Ltd. 2021. *Cipramil (citalopram hydrobromide) film-coated tablets Australian Product Information* 24 December 2021 URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05612-3 (accessed 6 May 2022).
82. Viatris. 2022. *Loxalate escitalopram oxalate tablets Australian Product Information* 27 April 2022 URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-07057-3&d=20220516172310101 (accessed 6 May 2022).
83. Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh). 2018 *Annex I Scientific conclusions and greouns for the variation to the terms of the marketing authorisation(s)* December 2018 URL: https://www.ema.europa.eu/en/documents/psusa/oxycodone-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00002254/201804_en.pdf (accessed 27 April 2022).
84. Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh). 2020 *Annex I scientific conclusions and grounds for the variation to the terms of the marketing authorisation* January 2020 URL: https://www.ema.europa.eu/en/documents/psusa/methadone-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00002004/201905_en.pdf (accessed 6 May 2022).