Serotonin toxicity

When co-prescribing serotonergic medications, it is important to be able to assess the risk of clinically significant interactions – to prevent serotonin toxicity but also to avoid unnecessary restriction of therapeutic options. In this article, **Pauline McQuoid** looks at the likelihood of serotonin toxicity when the computerised drug interaction alert says 'no'

Computerised drug interaction alerts are an everyday part of clinical practice for prescribers. These same alerts also flash onto the pharmacist's computer screen when they are dispensing medications, and this may trigger a phone call to check if the prescriber was aware of the interaction. Computerised alerts seldom provide useful information on how to manage the interaction, leaving the prescriber to weigh up the risks versus benefits.

One of the common drug interaction alerts is for possible serotonin syndrome, more accurately known as serotonin toxicity since the cause is known and there is a clear association between the magnitude of serotonin elevation and the resulting signs and symptoms.[1] These terms are used interchangeably, but serotonin toxicity is referred to in this article.

Serotonin toxicity is a clinical diagnosis based on signs and symptoms of neuromuscular excitation, autonomic dysfunction and/or changes in mental state, occurring in the presence of one or more substances that elevate levels of the neurotransmitter serotonin. It manifests as a spectrum from mild to severe (Table 1, next page). At the mild end of the spectrum, signs and symptoms can be vague and non-specific and are easy to overlook – nausea, diarrhoea, insomnia, restlessness. At the severe end of the spectrum, serotonin toxicity can be fatal.[2,3]

Diagnostic criteria were proposed by psychiatrist Harvey Sternbach in 1991 based on a small case series,[4] but these have been superseded by the Hunter Serotonin Toxicity Criteria, which were derived from a large database of selective serotonin reuptake inhibitor (SSRI) overdoses managed by the Hunter Area Toxicology Service in Australia.[5] Clonus is a cardinal sign and features in four out of the five Hunter diagnostic categories (see panel above).[6]

Hunter is widely recognised as the gold standard for diagnosing serotonin toxicity, but it has limitations.[7,8] In severe

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Hunter Serotonin Toxicity Criteria

Presence of serotonergic agent (recent addition, increased dose/overdose, interaction) plus *one* of the following conditions:[6]

- Spontaneous clonus
- Inducible clonus + agitation *or* diaphoresis
- Ocular clonus + agitation *or* diaphoresis
- Ocular clonus *or* inducible clonus + hypertonia + temperature >38°C*
- Tremor + hyperreflexia

**The presence of temperature ≥38.5°C and/or marked hypertonia or rigidity (especially truncal) indicates severe serotonin toxicity with a risk of progression with respiratory compromise*

Do you need to read this article?

Try this quiz

1. **Serotonin toxicity can be fatal. True/False**
2. **Hyporeflexia and decreased bowel sounds are useful diagnostic features of serotonin toxicity. True/False**
3. **Serotonin reuptake inhibitors attenuate the effect of serotonin releasers (eg, ecstasy). True/False**
4. **Serotonin toxicity is likely when a selective serotonin reuptake inhibitor is co-prescribed with a triptan. True/False**

Answers on page 32

Variable toxicity risk with different drug combinations

Although case reports describing what we would now recognise as serotonin toxicity were published in the 1950s and 1960s,[6,9] it was not widely known until 1984 when it caused the death of an 18-year-old woman, Libby Zion, in New York Hospital.[10]

The doctors involved were tried in both criminal and civil courts, and although the grand jury indicted the doctors for medical negligence, this charge was later cleared. However, the civil court found deficiencies in the care provided and ordered the defendants to pay Ms Zion's family US$375,000.[10]

A key finding was the contribution of long working hours to the decisions made by junior doctors, and lack of supervision by more senior medical staff. This ultimately resulted in the introduction of the "Libby Zion Law", which restricts the number of hours residents are allowed to work and requires a senior medical practitioner to be on site at all times.

Ms Zion had been taking phenelzine, a monoamine oxidase inhibitor (MAOI), for depression when she developed symptoms of upper respiratory tract and ear infection and was prescribed erythromycin and chlorphenamine. She became febrile and flushed with dilated pupils and "roving eye movements", so was taken to hospital and prescribed pethidine for agitation and shivering. She subsequently developed a temperature of 41.7°C and had a fatal cardiac arrest.

Pethidine is an opioid with serotonin reuptake inhibitor (SRI) properties and was thought to have caused the fatal serotonin toxicity in combination with the MAOI; however, Ms Zion was already showing signs and symptoms of serotonin toxicity before receiving the pethidine.

Traces of cocaine were found in her system postmortem, and even though valid doubts were raised over the reliability of the reports, the jury seized on this as an important contributor to Ms Zion's death.

Despite the intense amount of scrutiny and analysis of the case over more than a decade of litigation, the potential contributory role of chlorphenamine was not recognised until years later by psychiatrist and clinical neuropharmacologist Ken Gillman.[11]

The serotonin toxicity triangle

Serotonin toxicity is a drug-induced condition caused by serotonergic agents. It can develop from excessive doses of a single serotonergic medication but most commonly occurs when combinations are used together, particularly if they act to increase serotonin via different mechanisms.

Mechanisms include increased levels of the serotonin precursor L-tryptophan, increased serotonin release from the presynaptic neurone, inhibition of serotonin reuptake into the presynaptic neurone, inhibition of serotonin metabolism, stimulation of postsynaptic serotonin (5-HT) receptors, and inhibition of metabolism of serotonergic medications.

Dr Gillman is recognised as an international expert on serotonin toxicity, has published extensively on the subject, and has developed a serotonin toxicity triangle to illustrate the varying degrees of risk and severity with combinations of medications that increase serotonin (see figure).[12]

The combination of an MAOI with another serotonergic medication carries the greatest risk of toxicity and is generally contraindicated. By blocking the monoamine oxidase enzyme, MAOIs reduce the breakdown of serotonin in the presynaptic neurone. Irreversible and non-selective MAOIs are most likely to cause serotonin toxicity.

Also note the attenuation relationship – methylenedioxymethamphetamine (MDMA) is a serotonin releaser but requires reuptake into the presynaptic neurone to exert this effect. SRIs block this and hence reduce MDMA's effect on serotonin.

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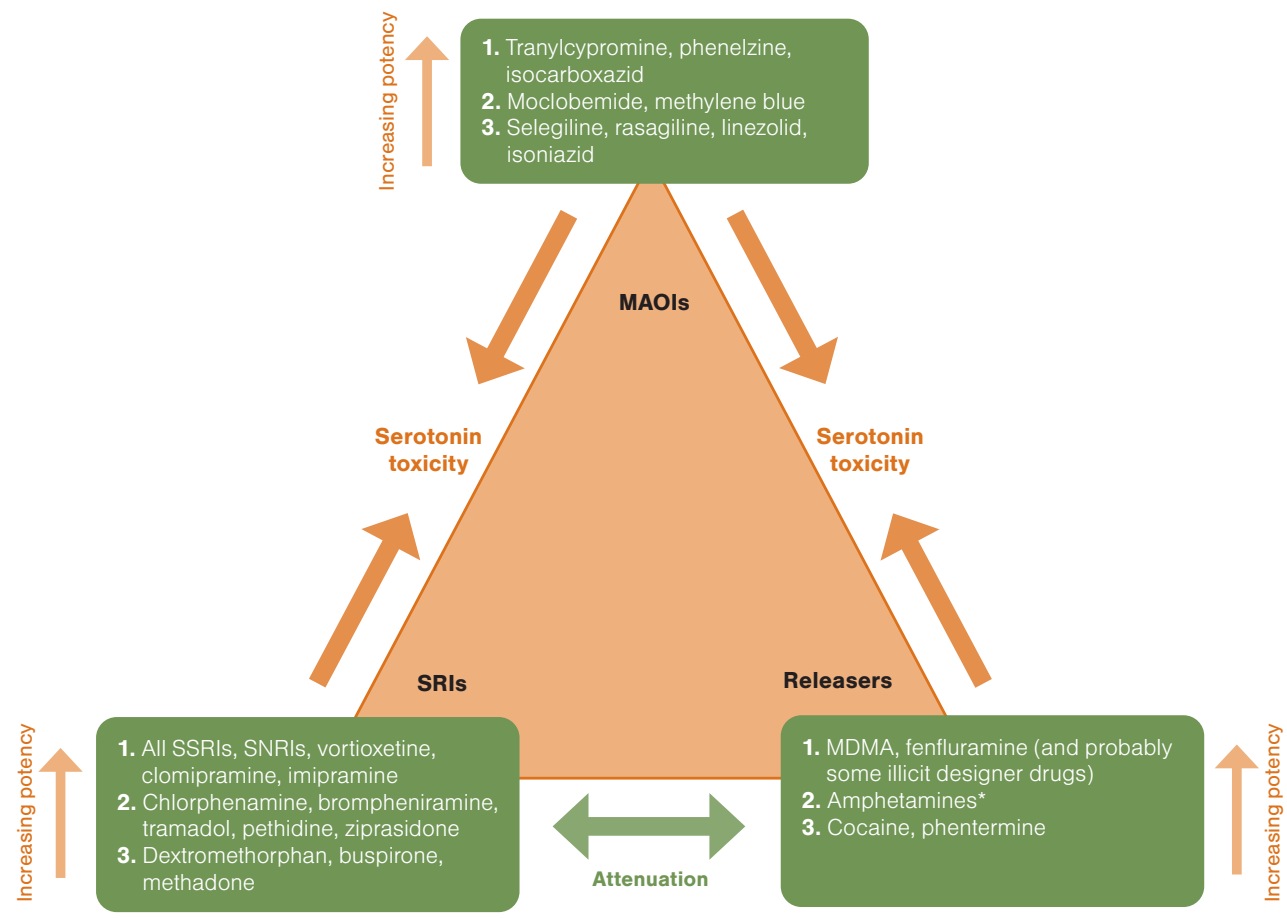
cases, muscle rigidity may mask hyperreflexia and clonus;[1] hyperreflexia may also be attenuated by polyneuropathy.[7]

Hyperreflexia and increased bowel sounds are useful diagnostic features to differentiate serotonin toxicity from other presentations, such as neuroleptic malignant syndrome, anticholinergic toxicity, malignant hyperthermia and sympathomimetic toxidrome (Table 2).[6]



The serotonin toxicity triangle represents the potentiating and attenuating relationships between three classes of drugs at typical clinical doses. Serotonin reuptake inhibitors attenuate the effect of releasers. Increasing potency indicates serious interactions are more probable

*Serious reactions and deaths have (rarely) been reported from hypertension, but probably not from serotonin toxicity, because amphetamines are considerably more potent dopamine (compared with serotonin) releasers

Adapted from Gillman et al, 2023[12]

> "Despite... analysis of the case over more than a decade of litigation, the potential contributory role of chlorphenamine was not recognised until years later"

Table 1. **The spectrum of clinical features in serotonin toxicity**

Serotonin toxicity	Neuromuscular	Autonomic	Mental state
Severe	Respiratory failure Rigidity	Severe hyperthermia	Low Glasgow Coma Scale Confusion
Moderate	Sustained clonus Ocular clonus Myoclonus Tremor	Hyperthermia (>38.5°C) Mydriasis Diaphoresis Flushing	Agitation
Mild	Hyperreflexia Inducible clonus	Tachycardia Hypertension	Anxiety
Common drug side effects	Brisk reflexes	Diarrhoea Nausea	Insomnia

Adapted from Scotton et al, 2019[6]

Table 2. **Differentiating serotonin syndrome from other presentations**

Presentation	Reflexes	Muscle tone	Bowel sounds	Pupils
Serotonin toxicity	Hyperreflexia	Hypertonia (lower limbs > upper limbs)	Hyperactive	Dilated
Sympathomimetic toxidrome	Normal/brisk	Normal	Normal	Dilated
Anticholinergic toxicity	Normal	Normal	Hypoactive or absent	Dilated
Neuroleptic malignant syndrome	Hyporeflexia	"Lead-pipe" rigidity	Normal or hypoactive	Normal
Malignant hyperthermia	Hyporeflexia	Rigor-mortis-like rigidity	Hypoactive	Normal

Quiz answers

1. True **2.** False **3.** True **4.** False

Avoiding unnecessary restrictions on therapeutic options

SSRIs are the most prescribed antidepressants, and consequently the most often implicated in serotonin toxicity. SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs; ie, venlafaxine) impair transport of serotonin back into the presynaptic neurone, increasing neurotransmitter levels at the synapse.

In weighing up the potential risks of adding new medications to an SSRI or SNRI, conventional drug interaction checkers (eg, Stockley's Interaction Alerts, which is used by the New Zealand Formulary [NZF]) and literature review can be misleading. Understanding how to assess the risk of a clinically significant interaction can avoid unnecessary restriction on therapeutic options.

For people taking SSRIs or SNRIs, let's look at the risk of serotonin toxicity when co-prescribing the following medications.

Table 3. **The risk of serotonin toxicity with combinations of antidepressants and opioids**

		Antidepressants	
		Low to intermediate risk: SSRIs, SNRIs, TCAs, St John's wort, lithium	**High risk:** MAOIs (or previous history of serotonin toxicity)
Opioids	**Low risk:** Morphine, codeine, buprenorphine, oxycodone	Should be safe	Possible rare interaction; use with caution
	Medium risk: Fentanyl, methadone	Possible rare interaction; use with caution	Increased risk of serotonin toxicity
	High risk: Tramadol, pethidine, dextromethorphan	Increased risk of serotonin toxicity	Contraindicated

Adapted from Perananthan and Buckley, 2021[18]

Triptans

NZF interactions checker: "Dosage adjustment or close monitoring is needed. Rarely, the use of a triptan with an SSRI/SNRI results in serotonin syndrome. Monitor for signs of serotonin syndrome (eg, weakness, hyperreflexia and incoordination)."

Evidence: alerts for serotonin toxicity with triptans and SSRIs/SNRIs originate from a US Food and Drug Administration warning in 2006 based on 29 cases of "serotonin syndrome" in people taking an SSRI and a triptan. Subsequent analysis of these cases found that none of them met the Hunter diagnostic criteria, and some were clear misdiagnoses.

Several studies looking at people taking a triptan and either an SSRI or SNRI found extremely low rates of serotonin toxicity (triptan plus SSRI: two cases out of 19,017; triptan plus SNRI: zero cases out of approximately 2000),[13] similar to the risk seen with SSRI/SNRI monotherapy.[14]

Serotonin toxicity is pharmacologically unlikely as triptans are 5-HT_{1B} and 5-HT_{1D} receptor agonists, and serotonin toxicity is thought to be mediated via 5-HT_{2A} and 5-HT_{1A} receptors.[13,14] The severe and life-threatening manifestations of serotonin toxicity (eg, hyperthermia) are mediated by the 5-HT_{2A} receptor, and the 5-HT_{1A} receptor is responsible for symptoms such as anxiety.[15]

Bottom line: serotonin toxicity is unlikely.

Tramadol

NZF interactions checker: "Dosage adjustment or close monitoring is needed. There have been reports of seizures and serotonin syndrome in patients taking SSRIs/SNRIs and tramadol. Consider an alternative analgesic if possible. Bear the possibility of an interaction in mind should a patient develop signs of serotonin syndrome (agitation, fever, diarrhoea or tremor). Concurrent treatment should be stopped if serotonin syndrome occurs."

Evidence: as tramadol is an SNRI, when prescribed with an SSRI or SNRI, it triggers a warning based on additive serotonin effects.

Paroxetine and fluoxetine are expected to have a higher risk than other SSRIs or venlafaxine because they also increase tramadol exposure by inhibiting the metabolism of tramadol to its active metabolite O-desmethyltramadol via cytochrome P450 2D6. Tramadol has more SNRI activity and O-desmethyltramadol has more mu receptor agonist activity, so blocking its activation enhances the serotonin effect and diminishes the opioid effect.

This interaction is reflected in the NZF warning for paroxetine or fluoxetine with tramadol. In addition to the warning for other SSRIs (above), it says: "Paroxetine/fluoxetine is predicted to increase the exposure to tramadol, but to reduce the exposure to its active metabolite; tramadol adverse effects are therefore increased but not the analgesic effect. If both drugs are given, be aware of reduced tramadol efficacy, and adjust the tramadol dose as necessary."

Bottom line: can be used together with caution. Serotonin toxicity is possible but dose related – risk is higher in someone on a high dose of SSRI/SNRI plus high dose of tramadol. Risk is also increased with genetic polymorphisms (CYP2D6 intermediate or poor metabolisers) and with fluoxetine and paroxetine (which inhibit CYP2D6).

Tricyclic antidepressants (TCAs)

NZF interactions checker: warnings vary between individual TCAs and SSRIs/venlafaxine.

Evidence: depression and chronic pain are highly comorbid, so it would not be an uncommon clinical scenario to consider a TCA for chronic neuropathic pain in someone taking an SSRI/SNRI.

> "Even in SSRI overdose, only one in seven cases results in serotonin toxicity that fulfils the Hunter diagnostic criteria"

There are considerable differences between individual TCAs in the potency of their serotonin and noradrenaline reuptake inhibition. Clomipramine has the highest SRI activity, followed by imipramine (moderate), then amitriptyline (weak)[12] and nortriptyline (lowest).

In addition, there are potential pharmacokinetic differences between individual SSRIs and their ability to inhibit the metabolism of TCAs.

Bottom line: serotonin toxicity is possible, but the likelihood depends on which TCA is used. Avoid using clomipramine or imipramine with an SSRI/SNRI. For other TCAs, the risk is low but depends on the doses of SSRI/SNRI and TCA. The lowest risk is with nortriptyline. If adding amitriptyline or nortriptyline to an SSRI/SNRI, start low (5–10mg at night) and increase gradually. Counsel the patient to monitor for symptoms.

Mirtazapine

NZF interactions checker: "Dosage adjustment or close monitoring is needed. The combination of SSRIs/venlafaxine with mirtazapine has led to the development of serotonin syndrome. Monitor patients for symptoms of serotonin syndrome (eg, fever, tremors, diarrhoea, agitation). Concurrent treatment should be stopped if serotonin syndrome occurs."

Evidence: although mirtazapine is classed as a noradrenergic and specific serotonergic antidepressant, its effect on serotonin is questionable.[16] It is a 5-HT_{2A} receptor antagonist, and this can be protective against serotonin toxicity. In an animal model, mirtazapine reduced serotonin toxicity when given before an MAOI and SSRI.[17]

Bottom line: serotonin toxicity is unlikely but not impossible.

Opioids (except tramadol; see above)

NZF interactions checker: warnings vary between individual opioids and SSRIs/venlafaxine.

Evidence: some opioids have SRI activity, and some can stimulate the 5-HT_{2A} receptor.

Bottom line: serotonin toxicity is well recognised, but risk depends on which opioid (Table 3),[18] the dose of opioid and dose of SSRI/SNRI.

Atypical antipsychotics

NZF interactions checker: warnings are for interactions with ziprasidone only (weak SRI).

Evidence: apart from ziprasidone, atypical antipsychotics are protective against serotonin toxicity as they block the receptor responsible for the life-threatening effects (5-HT_{2A}). A study analysing the effects of concomitant medication in SSRI overdose found that olanzapine and risperidone reduced the risk of developing serotonin toxicity by two to six times.[19]

Bottom line: except for ziprasidone, serotonin toxicity is unlikely but not impossible.

5-HT_3 receptor antagonists (ondansetron)

NZF interactions checker: "Dosage adjustment or close monitoring is needed. There is a possible increased risk of serotonin syndrome when ondansetron is used with SSRIs/SNRIs. Monitor patients for symptoms of serotonin syndrome (eg, fever, tremors, diarrhoea and agitation). Concurrent treatment should be stopped if serotonin syndrome occurs."

Note that the combination of ondansetron and citalopram or escitalopram should be avoided due to the possibility of QT prolongation.

Evidence: 5-HT_3 receptor antagonists *should not* cause serotonin toxicity because they do not release, or inhibit the reuptake of, serotonin. The authors of an early case report speculated that by blocking a serotonin receptor, there is more serotonin available to interact with other receptors,[20] which is biologically implausible.[21] Therapeutic doses of SSRIs elevate serotonin three to 10 times physiological levels,[12] and even in SSRI overdose, only one in seven cases results in serotonin toxicity that fulfils the Hunter diagnostic criteria.[19]

Bottom line: serotonin toxicity is unlikely.

Notable mentions

Medications with potentially clinically significant effects on serotonin include chlorphenamine, dextromethorphan (both available in cough and cold products), methylene blue and linezolid (both specialist hospital medicines).

Other explanations

Despite the pharmacological implausibility of some of these drug interactions, there may be other explanations for reported cases of serotonin toxicity:

- The accuracy, veracity and reliability of some case reports have been challenged.
- Genetic polymorphisms can influence and determine variability in individual responses.
- There may be mechanisms that we don't yet understand.
- The patient may have been taking other substances with known or unknown effects on serotonin (illicit substances, complementary medicines).

Healthcare professionals are still encouraged to report potential serotonin toxicity reactions to the Centre for Adverse Reactions Monitoring and to include as much information as possible (pophealth.my.site.com/carmreportnz/s/). Management involves stopping the serotonergic agent and providing supportive care. ■

Advice to give patients when prescribing another serotonergic medicine

These two medicines have some overlapping effects on serotonin, which is one of your body's chemical messengers. They can sometimes amplify each other's actions, and there is a very small chance they might disagree with each other. If this happens, it is likely to happen in the first day or two after starting your new medicine. These are some of the signs and symptoms to watch out for:

- nausea, diarrhoea
- tremors, muscle twitches, restlessness
- agitation – feeling a bit "wound up" or anxious
- noticeable and unexplained increase in sweating
- new and unexplained insomnia.

The references for this article are available with the online version on nzdoctor.co.nz