



## Serotonergic Medication and the Risk of Serotonin Syndrome

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### Summary

- Many commonly used medications can influence serotonergic transmission.
- Serotonin syndrome or serotonin toxicity is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity.
- It is seen with therapeutic medication use, inadvertent interactions between medication and intentional self-poisoning.
- The characteristic symptoms of serotonin syndrome fall into three main areas: altered mental state, neuromuscular abnormalities and autonomic dysfunction.
- Clinicians should be aware of medicines that have serotonergic effects and the combination of any two should therefore be used with great caution.

### Introduction

Serotonin syndrome has been highlighted by the widespread use of serotonergic agents, such as those used to treat depression e.g. SSRIs.<sup>1</sup> The incidence of serotonin syndrome is not known but has risen as a result of the increased use of serotonergic medication and the increasing awareness of this syndrome.<sup>1</sup>

Serotonin syndrome can be difficult to differentiate from other medical conditions including, Neuroleptic Malignant Syndrome, anticholinergic toxicity and malignant hyperthermia.<sup>1</sup> Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome in patients receiving medication that affect serotonergic neurotransmission.<sup>4</sup>

## **Serotonin Syndrome**

Serotonin syndrome or serotonin toxicity is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity.<sup>2</sup> Current thinking favours the spectrum concept of 'serotonin toxicity' as a continuum of serotonergic effects.<sup>1</sup> This progresses from side effects through to life-threatening toxicity, with increasing intrasynaptic serotonin levels.<sup>1</sup> Serotonin syndrome results from excessive stimulation of central and peripheral nervous system serotonin receptors, namely 5-hydroxytryptamine (HT)-1A and 5-HT-2A<sup>5,7</sup>, but no single receptor is solely responsible.<sup>7</sup>

The different mechanisms of causing serotonin syndrome are<sup>1,4</sup>

- increase in serotonin synthesis (e.g. tryptophan)
- inhibition of serotonin metabolism (e.g. MAOIs)
- increase in serotonin release (e.g. amphetamines)
- inhibition of serotonin uptake (e.g. SSRIs, SNRIs, TCAs)
- activation of serotonergic receptors (e.g. buspirone)

Serotonin syndrome can occur following:<sup>2</sup>

- The initiation, dose escalation, or overdose of a serotonergic drug
- The addition of an additional serotonergic drug
- The replacement of one serotonergic drug by another without allowing a long enough washout period in-between, particularly when the first drug is an irreversible MAOI or a drug with a long half-life.

## **Symptoms of Serotonin Syndrome**

The characteristic symptoms of serotonin syndrome fall into three main areas: altered mental state, neuromuscular abnormalities and autonomic dysfunction and, although features from each group may not be seen in all patients.<sup>2</sup> Serotonin syndrome comprises a continuum of clinical manifestations ranging from mild to life-threatening.<sup>2,5</sup>

The onset of the serotonin syndrome can range from minutes after initiating therapy with a second serotonergic agent to several weeks after receiving a stable dosage.<sup>4</sup> Preliminary evidence to date suggests that neither the occurrence nor the severity of serotonin syndrome is related to the dose or duration of serotonergic drug therapy.<sup>4</sup>

Around 40% of patients have mental status changes, about 50% of patients have evidence of neuromuscular hyperactivity.<sup>1</sup> Autonomic instability occurs in around 40% of patients.<sup>1</sup>

Severe cases may result in complications, such as seizures, rhabdomyolysis, myoglobinuria, metabolic acidosis, renal failure, acute respiratory distress syndrome, respiratory failure, diffuse intravascular clotting, coma, and death.<sup>1</sup>

**Table 1 Symptoms of Serotonin Syndrome**<sup>1,4,6</sup>

Alteration of mental status	Neuromuscular abnormalities	Autonomic dysfunction
agitation	tremors	hypertension
anxiety	clonus	tachycardia
disorientation	hyperreflexia	tachypnoea
restlessness	muscle rigidity	hyperthermia
excitement	bilateral babinski signs	mydriasis
		diaphoresis
		dry mucous membranes
		flushed skin
		shivering
		vomiting
		diarrhoea
		hyperactive bowel sounds
		arrhythmias

### Serotonergic Medication

Serotonin syndrome can be caused by certain medication alone or combinations of serotonergic medication.<sup>1,3,4</sup> It is seen with therapeutic medication use, inadvertent interactions between medication, and intentional self-poisoning.<sup>7</sup> Clinicians should be aware of medication that have serotonergic effects and the combination of any two should therefore be used with great caution.<sup>1,3,4</sup>

Some of these medicines are in therapeutic groups that would not normally be associated with use in depression, or psychiatry in general, so their serotonergic effects are not immediately apparent.<sup>1</sup>

Life-threatening cases of serotonin syndrome may occur, for example with the use of any MAOI (e.g. phenelzine, tranylcypromine) in combination with SSRIs; washout periods should be observed when switching between these antidepressants.<sup>1</sup>

**Table 2 Examples of medicines with potential to cause serotonin syndrome**<sup>1,2,3,4,6,7,8</sup>

This list includes examples of medicines with serotonergic effects. It is not an exhaustive list.

<b>Therapeutic group</b>	<b>Examples of medicines</b>
SSRI antidepressants	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
SNRI antidepressants	Venlafaxine, duloxetine
MAOI antidepressants	Tranylcypromine, phenelzine, isocarboxazid (irreversible MAOI) Moclobemide (reversible MAO-A inhibitor)
Tricyclic antidepressants	Clomipramine, imipramine, amitriptyline, doxepin, nortriptyline, trimipramine, dosulepin
Miscellaneous	Lithium, trazodone, tryptophan, mirtazapine, dapoxetine, vortioxetine, sibutramine
Opioids (weak serotonin reuptake inhibitors)	Pethidine, tramadol, methadone, fentanyl, dextromethorphan, pentazocine, tapentadol (but not other opioids)
Parkinson's disease treatment	MAO-B inhibitors (selegiline, rasagiline), levodopa, amantadine
Antibacterials	Linezolid (Reversible MAOI activity), isoniazid
Anti-cancer drugs	Procarbazine
Anticonvulsants	Carbamazepine, valproate
Antiemetics	Metoclopramide, ondansetron, granisetron, palonestron
Antihistamines	Chlorphenamine, diphenhydramine, promethazine
Antimigraine drugs	Triptans e.g. frovatriptan, almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, dihydroergotamine.
Anti-smoking aids	Bupropion (SNRI)
Anxiolytics	Buspirone
Diagnostic dye	Methylthioninium chloride (methylene blue) - has MAOI activity
Herbal products	St John's wort

### **Management of Serotonin Syndrome**

Management of serotonin syndrome varies with the severity of illness.<sup>7</sup> Supportive care forms the mainstay of therapy. <sup>7</sup> In mild cases, discontinuation of inciting medications, supportive care, and sedation with benzodiazepines are generally sufficient.<sup>7</sup> However, in more severe instances, emergency care may be needed for more aggressive management. After the resolution of symptoms, careful assessment of the need to resume use of causative serotonergic agents is required.<sup>7</sup>

## References

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