

What is serotonin syndrome and which medicines cause it?

Prepared by UK Medicines Information ([UKMi](#)) pharmacists for NHS healthcare professionals
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Background

Serotonin syndrome (or serotonin toxicity) is a predictable, medication-induced, spectrum of symptoms caused by serotonergic over-activity at synapses of the central and peripheral nervous systems (1-3). The true incidence of serotonin syndrome remains unknown, but the increasing use of serotonergic medication, as well as a greater awareness of the syndrome mean the numbers of cases are rising (3,4).

Serotonin syndrome can be difficult to differentiate from other medical conditions including, Neuroleptic Malignant Syndrome, anticholinergic toxicity, alcohol or antidepressant withdrawal and malignant hyperthermia (3-5). An awareness of the range of symptoms and drugs with serotonergic activity can aid early diagnosis and treatment and reduce patient distress as well as potential morbidity and mortality (3).

For in-depth information on specific interactions and switching between medicines see:

- ◆ [UKMi Q&A Triptans and SSRI or SNRI antidepressants – is there an interaction?](#)
- ◆ [UKMi Q&A How do you switch between tricyclic, SSRI and related antidepressants?](#)
- ◆ [UKMi Q&A How do you switch between monoamine oxidase inhibitors and SSRI, tricyclic or related antidepressants?](#)
- ◆ [UKMi Q&A What is the risk of interaction between opioid analgesics and monoamine oxidase inhibitors \(MAOIs\)?](#)

Answer

The term 'serotonin syndrome' is used to describe significant 'serotonin toxicity' and the two terms tend to be used interchangeably (1,2,5). Current thinking favours the spectrum concept of 'serotonin toxicity' as a continuum of serotonergic effects ranging from mild adverse effects through to a life threatening syndrome (4,5,6). The syndrome is due to high concentrations of serotonin (5-HT) at particular 5-HT receptor subtypes in the CNS. Although no single receptor is solely responsible, 5-HT_{1A} and 5-HT_{2A} receptors have been implicated, with the latter possibly being associated with more severe symptoms (1-3,5,6)

Mechanisms of serotonin syndrome include: increase in serotonin synthesis or release, inhibition of serotonin metabolism or uptake, or activation of serotonergic receptors (3,4).

Serotonin syndrome can occur from:

1. Overdose of serotonergic agents e.g. in a case series approximately 15% of patients taking an acute overdose of SSRIs developed moderate serotonin toxicity (1-4).
2. Drug interactions i.e. when more than one drug affecting the serotonin system or inhibiting the metabolism of serotonergic drugs is taken (4).
 - For example, serotonin toxicity is a potential danger of administering two serotonergic antidepressants together (7). In cases of serotonin syndrome due to drug interactions, the most severe cases are seen when monoamine oxidase inhibitors (MAOIs), are taken in combination with SSRIs, tricyclic antidepressants or venlafaxine. This is because the mechanism of action of MAOIs is to inhibit the breakdown of serotonin (3,4,7,8).
 - Many drugs, in addition to SSRIs, can inhibit the cytochrome P450 2D6 and/or 3A4 isoenzymes, resulting in the accumulation of serotonergic drugs that are being used simultaneously (3,4).

- Taking one serotonergic agent alone at normal therapeutic doses in susceptible individuals (1,5).

A complete and accurate medication history is essential when diagnosing serotonin syndrome (4,5).

Symptoms

Serotonin syndrome or toxicity consists of a triad of features (alteration of mental status, neuromuscular abnormalities and autonomic hyperactivity) that do not necessarily present together and can vary in severity from mild to life threatening (3,4). Around 40% of patients have mental status changes, about 50% of patients have evidence of neuromuscular hyperactivity, while autonomic instability occurs in around 40% of patients (9). Severe cases may result in complications, such as seizures, rhabdomyolysis, myoglobinuria, metabolic acidosis, renal failure, acute respiratory distress syndrome, respiratory failure, disseminated intravascular coagulation, coma, and death (2-5,9).

The onset of symptoms is usually rapid, often within hours of drug or dose changes, with many cases resolving within 24 hours of stopping the serotonergic drug(s) (1,6).

Table 1. Symptoms of Serotonin Syndrome (4,5,9)

Alteration of mental status	Neuromuscular abnormalities	Autonomic hyperactivity
agitation	clonus	hypertension
anxiety	tremors	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

Serotonin syndrome is diagnosed by a detailed history, clinical observation of symptoms and physical and neurological examinations (3-5). Several systems of diagnostic criteria exist, but the Hunter Serotonin Toxicity Criteria (HSTC) are currently recommended as the most accurate and specific criteria and are less likely to miss early, mild or subacute forms of serotonin syndrome.

Hunter Serotonin Toxicity Criteria – in the presence of a serotonergic agent plus one of the following (3-5):

- ◆ Spontaneous clonus
- ◆ Inducible or ocular clonus AND agitation or diaphoresis
- ◆ Tremor AND hyperreflexia
- ◆ Hypertonia AND hyperpyrexia (temperature exceeding 38°C) AND ocular or inducible clonus

Causative medicines

Serotonin syndrome can be caused by certain drugs alone (usually in overdose) or combinations of serotonergic drugs (1,5). Combinations of two or more serotonergic drugs can often be given successfully, but clinicians should be aware of drugs with serotonergic effects and use such combinations sparingly or with great caution (2,4,8). 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 (2). These include drugs such as linezolid or selegiline, both of which have MAOI activity (3,4). See Table 2 below for further examples.

Life-threatening cases of serotonin syndrome may occur, for example with the use of any MAOI (e.g. phenelzine, tranylcypromine) in combination with SSRIs (3,4,8). Washout periods should be strictly observed when switching between these antidepressants. See [UKMi Q&A How do you switch between monoamine oxidase inhibitors and SSRI, tricyclic or related antidepressants?](#) for further details.

Table 2. Examples of medicines with potential to cause serotonin syndrome (1-5,8,10,11)

This list (see limitations below) only includes examples of medicines with serotonergic effects. Examples of medicines which have the potential to cause serotonin syndrome solely via cytochrome P450 interactions have been excluded.

Therapeutic group	Examples of medicines
SSRI antidepressants	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
SNRI antidepressants	Venlafaxine, duloxetine
MAOI antidepressants	Tranylcypromine, phenelzine, moclobemide (reversible MAO-A inhibitor), isocarboxazid
Tricyclic antidepressants	Clomipramine, imipramine, amitriptyline, doxepin, nortriptyline, trimipramine
Miscellaneous	Lithium, trazodone, L-tryptophan, mirtazapine, dapoxetine, vortioxetine
Opioids	Pethidine, tramadol, methadone, fentanyl, dextromethorphan, pentazocine, oxycodone, tapentadol
Parkinson's disease treatment	MAO-B inhibitors: Selegiline, rasagiline, safinamide Amantadine
Antibacterials	Linezolid, tedizolid (reversible MAOI activity)
Anti-cancer drugs	Procarbazine (weak MAO inhibitor)
Antiemetics	Metoclopramide, ondansetron, granisetron, palonosetron
Antihistamines	Chlorphenamine, diphenhydramine
Antimigraine drugs	Triptans e.g. frovatriptan, almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan. Dihydroergotamine.
Anti-smoking aids	Bupropion
Anxiolytics	Buspirone
Diagnostic dye	Methylthioninium chloride (methylene blue) - has MAOI activity
Herbal products	St John's wort (<i>Hypericum perforatum</i>)

Summary

- ◆ The term 'serotonin syndrome' is used to describe significant 'serotonin toxicity' and the two terms tend to be used interchangeably
- ◆ The syndrome is due to high concentrations of serotonin (5-HT) at particular 5-HT receptor subtypes in the CNS. Although no single receptor is solely responsible, 5-HT_{1A} and 5-HT_{2A} receptors have been implicated, with the latter possibly being associated with more severe symptoms
- ◆ Serotonin syndrome can occur from an overdose, drug interaction or even single drug therapy at normal therapeutic doses in susceptible individuals with a serotonergic agent
- ◆ Serotonin syndrome or toxicity consists of a triad of features (alteration of mental status, neuromuscular abnormalities and autonomic hyperactivity) that do not necessarily present together and can vary in severity from mild to life threatening
- ◆ Medicines potentially causing serotonin syndrome all have some form of serotonergic activity
- ◆ The onset of symptoms is usually rapid, often within hours of drug or dose changes, with cases usually resolving within 24 hours of stopping the serotonergic drug(s)

Limitations

Information on the treatment of serotonin syndrome is beyond the scope of this Medicines Q&A. This Medicines Q&A includes key examples only of medicines available in the UK with the potential to cause serotonin syndrome. The list in Table 2 is not exhaustive. This list also only includes examples of medicines with serotonergic effects. Examples of medicines which have the potential to cause serotonin syndrome solely via cytochrome P450 interactions have been excluded. It does not encompass amphetamine and its derivative drugs of misuse, which are also known to cause serotonin syndrome.

This Medicines Q&A is based on key review papers, not single case reports.

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