Serotonin syndrome

Key messages

Serotonin syndrome is a life-threatening adverse drug reaction which is growing in incidence. It can occur with any serotonergic drugs – not just the SSRIs.

The cardinal features are:

- Altered mental state.
- Autonomic hyperactivity.
- Neuromuscular dysfunction.

All suspected cases will require secondary care involvement. Fever indicates severe disease warranting urgent admission.

Most patients will have had a recent serotonergic drug change prior to presentation.

Allow washout periods between serotonergic drugs, and avoid co-prescribing drugs such as SSRIs and tramadol to minimise risk.

The incidence of serotonin syndrome is rising due to increased prescribing of serotonergic medications and increased recreational use of novel psychoactive substances. The true incidence of serotonin syndrome is not known as mild cases are commonly missed. One study showed serotonin syndrome in around 15% of SSRI-related overdoses (BMJ 2014; 348:g1626). In this article, we will cover the signs to look out for in primary care and our role in minimising the risk for our patients, drawing on a DTB review (DTB 2022;60:6).

This article was last reviewed in 2022.

Who is at risk of serotonin syndrome?

Patients presenting with serotonin syndrome will usually be on combinations of serotonergic drugs or have a history of accidental or deliberate overuse. **However, it can also occur with a single serotonergic drug at therapeutic levels.**

A French study found that 84% of patients presenting with serotonin syndrome had had a recent change or initiation of a serotonergic agent (J Clin Psychopharmacol 2015;35:382).

Patients of any age may be at risk of serotonin syndrome. Susceptibility is genetic in part, due to differences in the cytochrome P450 pathway.

Common serotonergic drugs include (DTB 2022;60:6, BNF 2022):

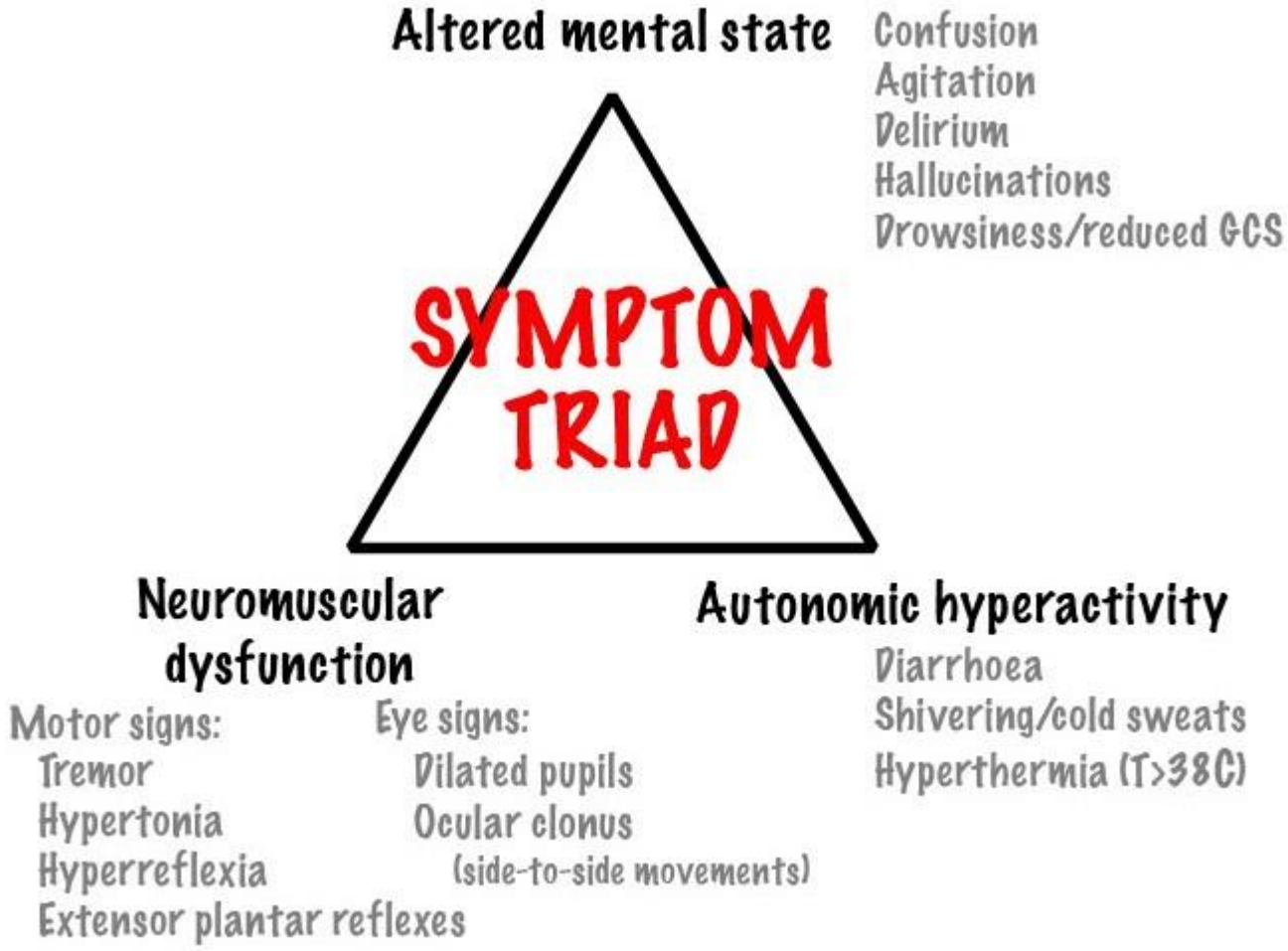
Mental health	SSRIs Mirtazapine Tricyclic antidepressants Venlafaxine Duloxetine Lithium Trazodone Bupropion MAOIs
Pain	Tramadol Opioids
Others	St John's wort Amphetamines Novel psychoactive substances Grapefruit juice

Clinical presentation

Serotonin syndrome is a clinical diagnosis based on the triad of altered mental state, neuromuscular dysfunction and autonomic hyperactivity in a patient on a serotonergic agent with a recent overdose, drug change or second drug addition. **60% of cases will occur within 6 hours of the new drug or dose initiation.**

In primary care, if we suspect the diagnosis, we should always discuss with our secondary care colleagues as progression from mild presentation to more severe life-threatening cases can be rapid.

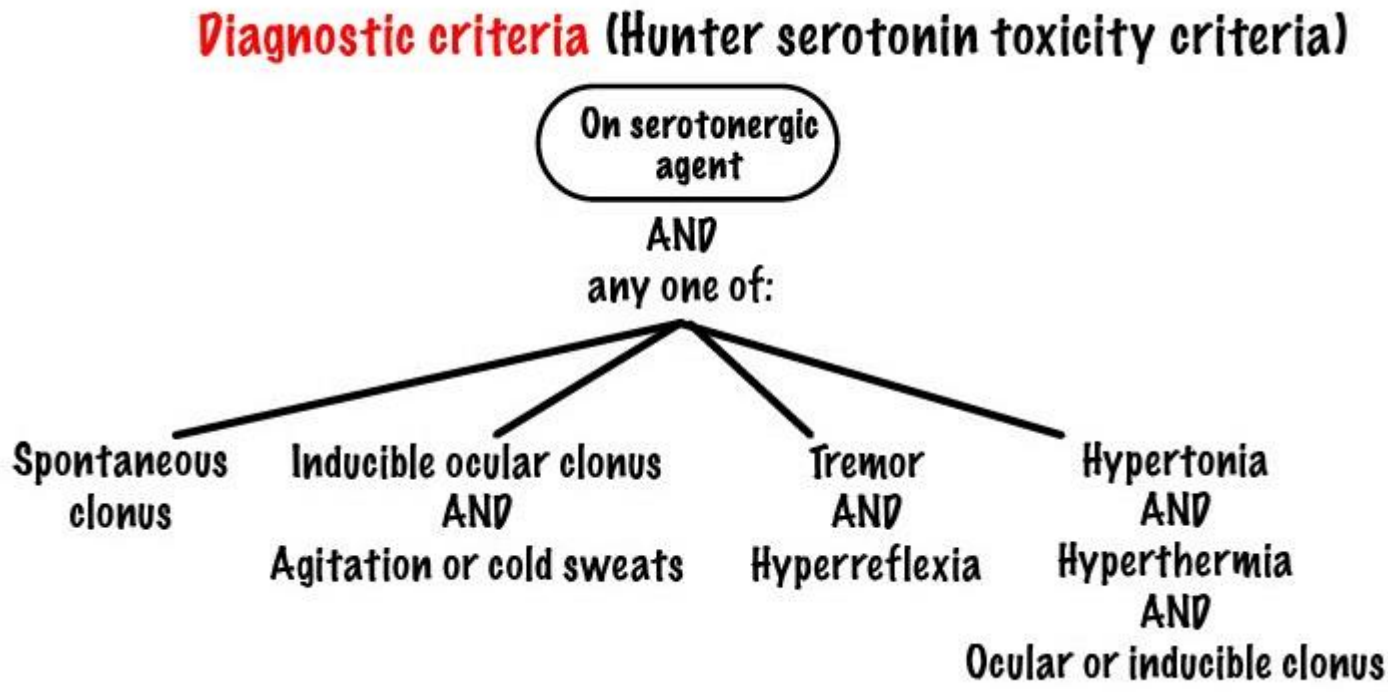
Consider the diagnosis if patients present with any of the following symptoms:



Diagnostic criteria

There are several different diagnostic classification systems which all have varying criteria for diagnosis. The Hunter Serotonin Toxicity Criteria are the most commonly used, and have been shown to be 85% sensitive and 97% specific for diagnosis (DTB 2022;60:6). However, there is concern that these criteria may miss a proportion of less severe cases (which may then progress to being more severe) as they rely heavily on neuromuscular symptoms for diagnosis (BMC Neurol 16, 97 (2016)).

For this reason, we at Red Whale think that if we suspect possible serotonin syndrome, we should discuss with secondary care even if the full Hunter Serotonin Toxicity Criteria are not met.



Differential diagnosis

The differential diagnosis of serotonin syndrome includes neuroleptic malignant syndrome, anticholinergic toxicity, central nervous system infection and metastatic carcinoma (Cleveland Clinic Journal of Medicine 2016,83(11):810). Neuroleptic malignant syndrome is more likely to be triggered by antipsychotics, and serotonin syndrome by antidepressants. However, many of these drugs can have dopamine, serotonin and anticholinergic effects, which can make it difficult to differentiate in practice (BMC Neurol 16, 97 (2016)).

Neuroleptic malignant syndrome – a brief reminder!

In case, like me, you cannot quite recall neuroleptic malignant syndrome from your medical school lectures…

Neuroleptic malignant syndrome is a neurological reaction to a dopamine antagonist (for example aripiprazole, olanzapine, quetiapine, metoclopramide, domperidone) that takes days to weeks to develop. The usual presentation includes agitated delirium, muscle rigidity, cogwheel tremor, followed later by hyperthermia, sweating, tachycardia, tachypnoea and hypertension. Key factors that distinguish it from serotonin syndrome are the slower onset, the absence of clonus and the absence of any nausea and vomiting. Recovery will take an average of 9 days after the triggering drug is stopped (Cleveland Clinic Journal of Medicine 2016,83(11):810).

Management

Patients with serotonin syndrome can deteriorate rapidly and should be referred to secondary care for monitoring over 12–24 hours.

Management involves (Cleveland Clinic Journal of Medicine 2016,83(11):810) stopping the trigger drug and providing supportive care. This may include intravenous fluids, non-serotonergic antiemetics, benzodiazepines and correction of vital signs. Antipyretics will not treat the hyperthermia of serotonin syndrome.

Severe serotonin syndrome causes hyperthermia and muscle rigidity, affecting respiration. These patients need ITU care with cooling and ventilation.

Risks include rhabdomyolysis, renal failure and disseminated intravascular coagulation. ECG may show QT prolongation (DTB 2022;60:6).

Minimising risk

- Be alert to the risk, especially in drug interactions. Electronic prescribing prompts can help with this.
- Consider asking about recreational novel psychoactive substance use if starting a serotonergic drug.
- Avoid co-prescribing serotonergic medications such as SSRIs with tramadol.
- Allow washout periods between changes to serotonergic medications (following the Maudsley prescribing guidelines, for example – outlined in our article on *Antidepressants*).
- Advise patients when starting or adjusting risk medications to report any signs of shakes, shivers or high temperature promptly.

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	• Most patients will have had a recent serotonergic drug change prior to presentation.
	• Allow washout periods between serotonergic drugs and avoid co-prescribing drugs such as SSRIs and tramadol to minimise risk.