

## Recognition and treatment of serotonin syndrome

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**S**erotonin syndrome is an increasingly common adverse drug reaction, which can be life-threatening.<sup>1</sup> Despite the common use of medications with direct or indirect serotonergic effects, many physicians are not aware of the presentation and management of serotonin excess.<sup>2</sup> This is particularly true of less severe presentations of serotonin syndrome, which still contribute to patient morbidity.<sup>3</sup>

Family physicians need to be more aware of serotonin syndrome. This case report explains the syndrome's pathogenesis, diagnosis, and management. Physicians are encouraged to consider the possibility of serotonin syndrome in patients who use serotonergic medications and present with autonomic changes, mental status changes, and neurological hyperexcitability.

### Case description

Mr J.W., an 80-year-old man with a history of depression, was admitted to hospital with pneumonia. His condition deteriorated and he was sent to the intensive care unit (ICU) and placed on mechanical ventilation for several days. During his stay in the ICU, his medications were reviewed. His use of fluoxetine, which he'd taken for depression for almost 10 years, was discontinued. Following discharge from the ICU, his mood was noted to be low by the medical staff. Approximately 1 week after discontinuation of the fluoxetine, he started using 20 mg of paroxetine daily.

Within 24 hours of starting paroxetine, Mr J.W. was found to be confused and agitated with periods of unresponsiveness. Vital signs revealed a temperature of 38.5°C and a pulse of 115 beats per minute. A neurological examination revealed myoclonus in all limbs with any stimulation. Assessment by a family physician with training in care of the elderly identified serotonin syndrome as the probable cause of his presentation.

The paroxetine was discontinued and the patient was given intravenous fluids to decrease the risk of renal failure. Mr J.W. initially received 2 mg of lorazepam intravenously, then received 3, 1-mg doses of lorazepam every 4 hours, resulting in decreased tachycardia, hypertonicity, and clonus. He was discharged from hospital without antidepressants, and

he planned to follow up with his family doctor several weeks after hospitalization in order to have his mood reviewed.

### Discussion

Cochrane Database of Systematic Reviews, MEDLINE, and Google were searched from January 1990 to December 2006 for articles on serotonin syndrome or serotonin toxicity. Although there are research papers related to diagnosis, there are few high-quality data on prospective treatment. No guidelines or consensus statements have been published for either diagnosis or management. Recommendations were drawn from the literature, but there is minimal high-level evidence, especially in the realm of treatment. Most of the suggestions in this paper have level II evidence.

Serotonin (5-HT) was first identified in the 1940s and was initially thought to have its primary effect on vascular tone. Now serotonin is recognized as having an important role in several central nervous system processes and peripheral physiology, particularly in the gastrointestinal tract. The vast majority of serotonin (90%) is synthesized in the periphery, but brain serotonin levels are the main factor in development of serotonin toxicity.<sup>4</sup>

The main sites of serotonin production in the brain are the midline raphe nuclei, found in the brainstem from the midbrain to the medulla. In presynaptic neurons, the amino acid tryptophan is decarboxylated and hydroxylated to produce serotonin. Serotonin is released into the intrasynaptic space after axonal stimulation, and receptors on the presynaptic neuron play a role in regulating release. Following reuptake into the presynaptic neuron, intrasynaptic serotonin is metabolized by the enzyme monoamine oxidase.<sup>4</sup> Knowledge of the regulation and metabolism of serotonin is relevant to understanding the role of different medications in the development of toxicity.

There are 7 serotonin receptor families (5-HT<sub>1</sub> to 5-HT<sub>7</sub>), which are further subdivided into groups based on

### Levels of evidence

**Level I:** At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

**Level II:** Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

**Level III:** Expert opinion or consensus statements

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different activities in neural and peripheral organ systems. A summary of the effects of serotonin receptor subtypes in relation to serotonin toxicity is found in **Table 1**.<sup>4</sup>

### Clinical presentation

The original and revised criteria<sup>5,6</sup> for diagnosis of serotonin syndrome emphasize the mental status changes and clinical findings typically observed in more severe cases. As a result, these criteria have been criticized for not highlighting the wider spectrum of toxic side effects that can be seen with this disorder. For this reason, some authors prefer to use the term *serotonin toxicity* to include findings of earlier or milder cases.<sup>7</sup>

It is important to note that symptoms of serotonin syndrome usually present within 6 to 8 hours of initiating or increasing serotonergic medications.<sup>7,8</sup> The onset

tends to be more acute than in a condition such as neuroleptic malignant syndrome, which shares some other features with serotonin toxicity.

Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. Mild, moderate, and severe signs and symptoms of serotonin syndrome are summarized in **Table 2**.<sup>4</sup> There are no data on the percentage of cases in the mild, moderate, or severe categories, in part because of the low rates of diagnosis of mild cases.

### Medication factor

Various medications are associated with serotonin syndrome.<sup>9-15</sup> Medications that affect any of the steps in serotonin metabolism or regulation can provoke toxicity. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are among the most commonly implicated drugs. Drug interactions can cause severe toxicity and can involve common over-the-counter medications. Drugs with long half-lives can interact several weeks after discontinuation; fluoxetine interactions have been reported up to 5 weeks after discontinuation.<sup>16</sup> Even single doses of SSRIs have been implicated in serotonin syndrome. It is relevant to note that serotonin syndrome is not considered to be an idiosyncratic drug reaction but is a predictable response to elevated levels of serotonin.<sup>11</sup> **Table 3**<sup>9,11-15</sup> provides a list of important drugs and drug interactions and the mechanism of increasing serotonin levels.

Overdosing with single agents such as SSRIs does not often cause severe toxicity. Approximately 15% of SSRI overdoses result in moderate symptoms. Severe cases appear to be more likely after drug interactions, particularly monoamine oxidase inhibitors (MAOIs) interacting with other antidepressants or with serotonin releasers,

**Table 1. Effects of 5-HT receptor subtypes in relation to serotonin toxicity**

5-HT RECEPTOR	MAIN ACTION RELATED TO SEROTONIN TOXICITY
5-HT <sub>1A</sub>	Neuronal inhibition, regulation of sleep, feeding, thermoregulation, hyperactivity associated with anxiety, hypoactivity associated with depression
5-HT <sub>1D</sub>	Locomotion, muscle tone
5-HT <sub>2A</sub>	Neuronal excitation, learning, peripheral vasoconstriction, platelet aggregation
5-HT <sub>2B</sub>	Stomach contraction
5-HT <sub>3</sub>	Nausea and vomiting, anxiety
5-HT <sub>4</sub>	Gastrointestinal motility
5-HT—serotonin.	
Data from Boyer and Shannon. <sup>4</sup>	

**Table 2. Signs and symptoms of serotonin syndrome**

SERIOUSNESS	AUTONOMIC SIGNS	NEUROLOGICAL SIGNS	MENTAL STATUS	OTHER
Mild	<ul style="list-style-type: none"> <li>• Afebrile or low-grade fever</li> <li>• Tachycardia</li> <li>• Mydriasis</li> <li>• Diaphoresis or shivering</li> </ul>	<ul style="list-style-type: none"> <li>• Intermittent tremor</li> <li>• Akathisia</li> <li>• Myoclonus</li> <li>• Mild hyperreflexia</li> </ul>	<ul style="list-style-type: none"> <li>• Restlessness</li> <li>• Anxiety</li> </ul>	
Moderate	<ul style="list-style-type: none"> <li>• Increased tachycardia</li> <li>• Fever (up to 41°C)</li> <li>• Diarrhea with hyperactive bowel sounds</li> <li>• Diaphoresis with normal skin colour</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperreflexia</li> <li>• Inducible clonus</li> <li>• Ocular clonus (slow continuous lateral eye movements)</li> <li>• Myoclonus</li> </ul>	<ul style="list-style-type: none"> <li>• Easily startled</li> <li>• Increased confusion</li> <li>• Agitation and hypervigilance</li> </ul>	<ul style="list-style-type: none"> <li>• Rhabdomyolysis</li> <li>• Metabolic acidosis</li> <li>• Renal failure</li> <li>• Disseminated intravascular coagulopathy (secondary to hyperthermia)</li> </ul>
Severe	<ul style="list-style-type: none"> <li>• Temperature often more than 41°C (Secondary to increased tone)</li> </ul>	<ul style="list-style-type: none"> <li>• Increased muscle tone (lower limb &gt; upper)</li> <li>• Spontaneous clonus</li> <li>• Substantial myoclonus or hyperreflexia</li> </ul>	<ul style="list-style-type: none"> <li>• Delirium</li> <li>• Coma</li> </ul>	<ul style="list-style-type: none"> <li>• As above</li> </ul>

Data from Boyer and Shannon.<sup>4</sup>

such as amphetamines.<sup>11</sup> Patient factors associated with developing toxicity are not clearly identified in the literature but might relate to factors affecting the pharmacokinetics of offending agents (eg, renal and hepatic failure). Patients who are genetically deficient in the cytochrome P450 2D6 enzyme (8% of whites) are more susceptible if they are taking drugs such as venlafaxine, paroxetine, tricyclics, dextromethorphan, and methadone.<sup>17</sup>

### Diagnosis

A thorough history of current and recent medication use is important, as is ruling out the use of illicit drugs and dietary supplements. Clinicians should also consider pupil size and reactivity, skin colour, presence of diaphoresis, dryness of oral mucosa, and presence or absence of bowel sounds. Diagnosis is clinical and investigations are mostly done to identify sequelae of severe toxicity, including renal function, creatine kinase, myoglobin, and clotting parameters.<sup>18</sup>

As previously mentioned, the original criteria for diagnosing serotonin syndrome describe only severe

cases. To help delineate the spectrum of illness, researchers in Australia reviewed more than 2000 cases of self-poisoning with serotonergic drugs and related the clinical findings to a diagnosis of serotonin syndrome made by a clinical toxicologist. From this information, a clinical decision tree was developed. This clinical approach has better sensitivity and specificity than older criteria (sensitivity 84%, specificity 97%).<sup>7</sup> These decision rules are found in **Table 4**.<sup>7</sup>

Several conditions should be considered when evaluating patients with confusion and neurological changes. Neuroleptic malignant syndrome (NMS) bears some resemblance to serotonin syndrome, with similar symptoms of fever, mental status changes, and altered muscle tone. However, patients with NMS are usually akinetic with rigidity, have decreased levels of consciousness, and are more likely to have mutism rather than rambling speech, which is associated with serotonin toxicity. More important, the onset of NMS is slow, developing over days rather than hours.<sup>19</sup>

**Table 3. Medications causing serotonin syndrome**

MECHANISM	DRUGS CAUSING SEROTONIN TOXICITY WITHOUT DRUG INTERACTION	DRUG COMBINATIONS CAUSING MODERATE TO SEVERE TOXICITY
Increased production of serotonin	<ul style="list-style-type: none"> <li>• L-tryptophan</li> </ul>	<ul style="list-style-type: none"> <li>• L-tryptophan with MAOI</li> </ul>
Increased serotonin release from neurons <sup>11</sup>	<ul style="list-style-type: none"> <li>• Amphetamines</li> <li>• NMDA</li> </ul>	<ul style="list-style-type: none"> <li>• Amphetamines and MAOI</li> <li>• NMDA and MAOI</li> <li>• NMDA and SSRI (lower risk)</li> </ul>
5-HT <sub>1A</sub> antagonism <sup>11</sup>	<ul style="list-style-type: none"> <li>• Buspirone</li> <li>• LSD</li> </ul>	<ul style="list-style-type: none"> <li>• Paroxetine and buspirone</li> </ul>
Decreased serotonin reuptake <sup>9,11-13,15</sup>	<ul style="list-style-type: none"> <li>• SSRIs</li> <li>• Venlafaxine</li> <li>• Clomipramine, imipramine</li> <li>• Tramadol, meperidine, methadone, fentanyl</li> <li>• Dextromethorphan</li> <li>• St John's wort</li> </ul>	<ul style="list-style-type: none"> <li>• Analgesics with MAOI or SSRI</li> <li>• Clomipramine with MAOI</li> <li>• SSRIs, venlafaxine with MAOI</li> <li>• SSRIs, venlafaxine, bupropion</li> </ul>
MAO inhibition <sup>11,14</sup>	<ul style="list-style-type: none"> <li>• MAOIs</li> <li>• Selegiline</li> <li>• Linezolid</li> </ul>	<ul style="list-style-type: none"> <li>• Moclobemide and SSRIs or venlafaxine</li> <li>• Irreversible MAOIs with all serotonergic drugs</li> <li>• Linezolid and SSRIs</li> </ul>
Uncertain	<ul style="list-style-type: none"> <li>• Lithium<sup>9</sup></li> </ul>	

5-HT<sub>1A</sub>—serotonin 1A receptor, LSD—lysergic acid diethylamide, MAO—monoamine oxidase, MAOI—monoamine oxidase inhibitor, NMDA—N-methyl-D-aspartate, SSRI—selective serotonin reuptake inhibitor.

**Table 4. Decision rules for diagnosing serotonin syndrome in the presence of serotonergic agents within the past 5 weeks: Hunter serotonin toxicity criteria.**

IN THE PRESENCE OF 1 OR MORE SEROTONERGIC DRUGS (WITHIN THE PAST 5 WEEKS)	YES, THEY HAVE SEROTONIN SYNDROME OR TOXICITY
If patients have spontaneous clonus	Yes
If patients have inducible clonus <i>and</i> either agitation <i>or</i> diaphoresis	Yes
If patients have ocular clonus <i>and</i> agitation <i>or</i> diaphoresis	Yes
If patients have tremor <i>and</i> hyperreflexia	Yes
If patients are hypertonic <i>and</i> have a temperature >38°C <i>and</i> have ocular clonus <i>or</i> inducible clonus	Yes

Adapted from Dunkley et al<sup>7</sup> with permission from Oxford University Press.

One cause of delirium with neurological hyperexcitability is metabolite-mediated opiate toxicity, which can occur with rapid escalation of opioid doses, high opioid doses, or low opioid doses in patients with renal failure. Opiate toxicity is most likely caused by meperidine and morphine but can be seen with all opioid agents.<sup>20</sup>

Anticholinergic toxicity is differentiated by presence of skin colour changes (red as a beet), dry mouth (dry as a bone), and constipation or absence of bowel sounds.<sup>4,19</sup>

## Treatment

Prompt recognition of toxicity and discontinuation of offending medications are most important. Many cases of the syndrome are self-limiting if medications are stopped early. The mortality of severe serotonin syndrome is estimated to range from 2% to 12%. The Toxic Exposure Surveillance System in the United States reported 93 deaths due to serotonin syndrome in 2002.<sup>1</sup>

Treatment is guided by the severity of presentation. There are currently no randomized placebo-controlled trials to guide pharmacologic treatment of serotonin syndrome, although case reports and series suggest several medications that are beneficial in managing the condition.

Supportive care, including intravenous fluids, is indicated in patients with vital sign abnormalities. Neurological symptoms, including serious myoclonus and hyperreflexia, are sometimes treated with benzodiazepines, but there is little evidence for this approach. Hyperthermia should be aggressively managed with external cooling, hydration, and benzodiazepines (eg, diazepam, lorazepam). Patients with a temperature higher than 41°C should be intubated with induced neuromuscular paralysis. There is a limited role for traditional antipyretics, as the mechanism of serotonin syndrome is due to muscle tone rather than central thermoregulation. Patient agitation secondary to delirium should be managed using nonpharmacologic strategies and benzodiazepines, when appropriate. Physical restraints should be avoided, as they can increase hyperthermia, lactic acidosis, and rhabdomyolysis (level II evidence).

The antihistamine cyproheptadine, which is also a 5-HT<sub>2A</sub> inhibitor, should be considered in moderate cases and is recommended in severe cases, despite a lack of randomized controlled trial evidence (level II evidence). It is available only as an oral preparation; the initial dose is 12 mg; the dosage is then adjusted to 2 mg every 2 hours until symptoms improve.<sup>21,22</sup>

Some antipsychotics have 5-HT<sub>2A</sub> antagonist effects and are sometimes used (level II evidence). Sublingual olanzapine and intramuscular chlorpromazine (50 to 100 mg) are options.<sup>23,24</sup> Chlorpromazine can cause serious hypotension and should be avoided in severe cases with shock.

Caution is required in using antipsychotics for treating serotonin syndrome, as NMS can be misdiagnosed as serotonin syndrome. Also, case reports have

implicated antipsychotics as precipitants of serotonin syndrome in individuals receiving concomitant serotonergic medications.<sup>1,25</sup>

Dantrolene, a skeletal muscle relaxant used for treatment of NMS, has been reported to improve symptoms of serotonin syndrome in a case series<sup>26</sup>; however, it has also been implicated in the development of serotonin toxicity and is not generally recommended.<sup>4,11</sup> Propranolol, which has 5-HT<sub>1A</sub> antagonist activity and a long half-life, can potentiate hypotension and make improvement in tachycardia a less effective strategy for monitoring response to treatment.<sup>4,22</sup>

## Mood management

No articles were found that assessed risk in depressed patients needing ongoing mood treatment after resolution of serotonin syndrome. Given that it is a predictable reaction, however, reinitiation after adequate washout should not result in increased risk, especially if an agent with less serotonergic activity is chosen (eg, bupropion, mirtazapine).<sup>10</sup>

All patients newly started on antidepressant medications should be assessed for suicidal thoughts. A recent Canadian study<sup>27</sup> reviewed coroners' reports of suicides and found that patients treated with SSRIs were 5 times more likely to have committed suicide within the first month of treatment than patients treated with other antidepressants. The absolute increase in risk was small (29/100 000 for SSRIs versus 6.2/100 000 for other antidepressants). It is very important to note that patients who were not treated at all were at the highest risk.

This recommendation of increased monitoring of patients newly started on antidepressants is echoed in the guidelines on depression by the Canadian Coalition for Seniors' Mental Health. These guidelines also suggest monitoring for serotonin-related side effects and suicidal thoughts early in treatment. Although a challenge in office practice, the guidelines suggest patients be seen weekly for at least several weeks after initiating treatment.<sup>28,29</sup>

## Conclusion

Serotonin syndrome is increasingly common but not well recognized by physicians. Many medications can cause serotonin toxicity, and drug interactions are an important factor. Family physicians should consider the possibility of serotonin syndrome in patients taking serotonergic drugs who present with autonomic or mental status changes and neurological findings. The findings of clonus, ocular clonus, hyperreflexia, and hypertonicity should prompt evaluation and medication review. Treatment is based on severity and focuses on prompt cessation of offending agents, treatment of hyperthermia, and use of benzodiazepines to decrease hypertonicity and neurological excitability. The use of 5-HT antagonists should be considered in moderate and

severe cases. Increased awareness and monitoring of patients beginning treatment with antidepressants can decrease the risk of worsening anxiety, agitation, and possibly suicide. ❁

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### Competing interests

None declared

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### EDITOR'S KEY POINTS

- Serotonin syndrome is not an idiosyncratic drug reaction, but a predictable response to elevated serotonin levels. Medications that affect any of the steps in serotonin metabolism or regulation can provoke toxicity.
- Antidepressants are frequently implicated in serotonin syndrome. Interactions with other medications, such as common over-the-counter products (eg, dextromethorphan), can cause serious toxicity.
- Symptoms can occur within 6 to 8 hours of initiating or increasing the dosage of serotonergic medications. Drugs with long half-lives can interact several weeks after discontinuation.
- Treatment is based on the severity of the presentation. Many cases will be self-limited if the medications are stopped.

### POINTS DE REPÈRE DU RÉDACTEUR

- Le syndrome sérotoninergique n'est pas une réaction médicamenteuse idiosyncrasique, mais bien une réponse prévisible à des taux élevés de sérotonine. Les médicaments qui influencent l'une ou l'autre des étapes du métabolisme ou de la régulation de la sérotonine peuvent provoquer la toxicité.
- Les antidépresseurs sont souvent en cause dans le syndrome sérotoninergique. Des interactions avec d'autres médicaments aussi courants que des produits en vente libre (p. ex. le dextrométhorphan) peuvent causer une sérieuse toxicité.
- Les symptômes peuvent apparaître de 6 à 8 heures suivant l'amorce ou l'augmentation de la dose des médicaments influant sur la sérotonine. L'interaction des médicaments ayant une longue demi-vie peut se produire plusieurs semaines après leur discontinuation.
- Le traitement dépend de la gravité des symptômes. Dans de nombreux cas, ils disparaissent d'eux-mêmes si on arrête les médicaments.

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