

# Differentiating serotonin syndrome and neuroleptic malignant syndrome



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Symptoms can overlap, but accurate diagnosis is critical because treatments are distinct

**S**erotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are each rare psychiatric emergencies that can lead to fatal outcomes. Their clinical presentations can overlap, which can make it difficult to differentiate between the 2 syndromes; however, their treatments are distinct, and it is imperative to know how to identify symptoms and accurately diagnose each of them to provide appropriate intervention. This article summarizes the 2 syndromes and their treatments, with a focus on how clinicians can distinguish them, provide prompt intervention, and prevent occurrence.

## Serotonin syndrome

**Mechanism.** The decarboxylation and hydroxylation of tryptophan forms serotonin, also known as 5-hydroxytryptamine (5-HT), which can then be metabolized by monoamine oxidase-A (MAO-A) into 5-hydroxyindoleacetic acid (5-HIAA).<sup>1</sup> Medications can disrupt this pathway of serotonin production or its metabolism, and result in excessive levels of serotonin, which subsequently leads to an overactivation of central and peripheral serotonin receptors.<sup>1</sup> Increased receptor activation leads to further upregulation, and ultimately more serotonin transmission. This can be caused by monotherapy or use of multiple serotonergic agents, polypharmacy with a combination of medication classes, drug interactions, or overdose. The wide variety of medications often prescribed by different clinicians can make identification of excessive serotonergic activity difficult, especially because mood stabilizers such as lithium,<sup>2</sup> and non-psychiatric medications such as ciprofloxacin and

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Table 1

## Medications that can cause serotonin syndrome

Action	Medications
Increases serotonin formation	Tryptophan
Increases release of serotonin	Amphetamines and amphetamine derivatives Cocaine MDMA
Impairs serotonin reuptake	Cocaine, MDMA, meperidine, tramadol, pentazocine SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) SNRIs (desvenlafaxine, duloxetine, milnacipran, venlafaxine, levomilnacipran) Dopamine-norepinephrine reuptake inhibitors (bupropion) Serotonin modulators (nefazodone, trazodone, vilazodone, vortioxetine) TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin) St. John's wort 5-HT <sub>3</sub> antagonists (dolasetron, granisetron, ondansetron, palonosetron) Metoclopramide, valproate, carbamazepine, sibutramine, dextromethorphan, cyclobenzaprine
Inhibits serotonin metabolism	MAOIs (phenelzine, tranylcypromine, isocarboxazid, moclobemide, safinamide, selegiline, rasagiline, linezolid, tedizolid, methylene blue, procarbazine)
Direct serotonin agonist	Bupirone, triptans, ergot derivatives, fentanyl, LSD
Increases sensitivity of postsynaptic receptor	Lithium

LSD: lysergic acid diethylamide; MAOIs: monoamine oxidase inhibitors; MDMA: 3,4-methylenedioxyamphetamine; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Source: Reference 3

### Clinical Point

Serotonergic agents can cause SS, whereas dopamine blockers cause NMS

fluconazole, can also contribute. *Table 1*<sup>3</sup> lists medications that can cause SS. The pathways that increase serotonin transmission, potentially causing SS, include:

- inhibition of serotonin uptake (seen with selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and tricyclic antidepressants [TCAs])
- inhibition of serotonin metabolism (seen with monoamine oxidase inhibitors [MAOIs])
- increased serotonin synthesis (seen with stimulants)
- increased serotonin release (seen with stimulants and opiates)
- activation of serotonin receptors (seen with lithium)
- inhibition of certain cytochrome P450 (CYP450) enzymes (seen with ciprofloxacin, fluconazole, etc.).

Table 2

## Sternbach's diagnostic criteria for serotonin syndrome

A. Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least 3 of the following clinical features are present:

- mental status changes (confusion, hypomania)
- agitation
- myoclonus
- hyperreflexia
- diaphoresis
- shivering
- tremor
- diarrhea
- incoordination
- fever

B. Other etiologies (eg, infectious, metabolic, substance abuse, or withdrawal)

C. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above

Source: Reference 5



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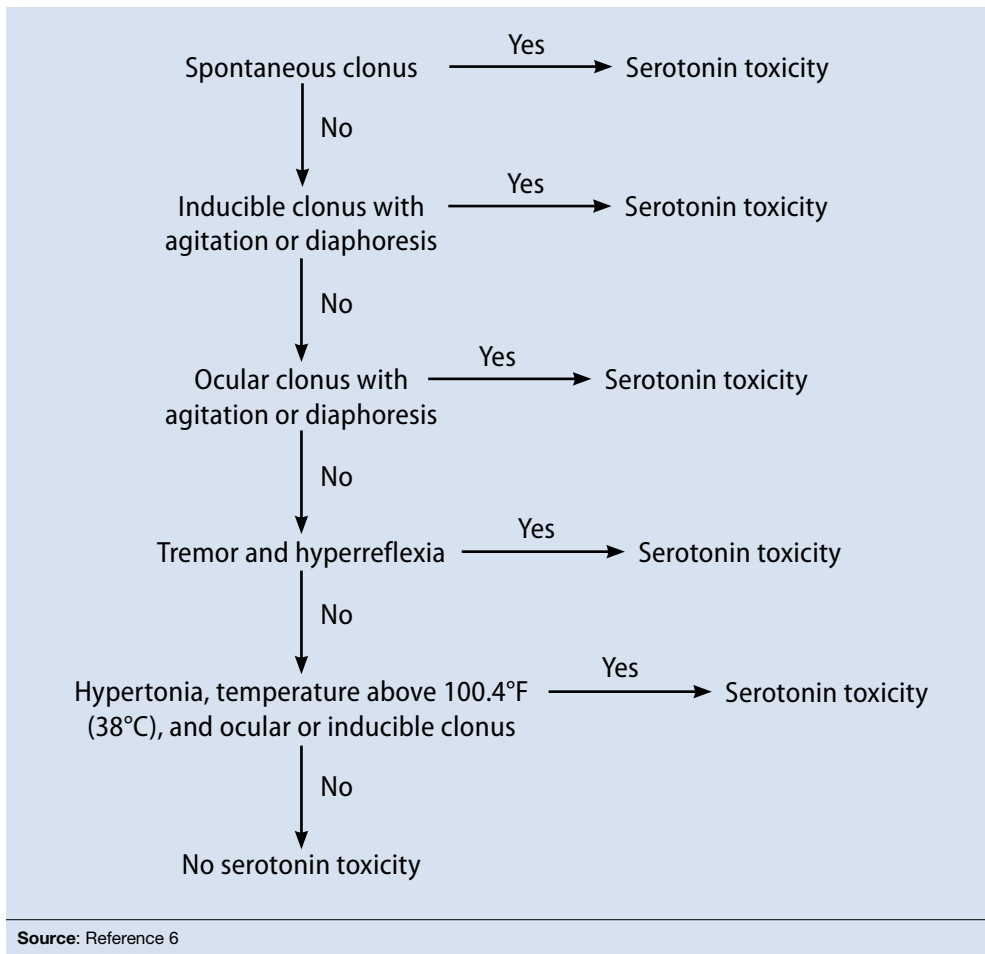
## Serotonin syndrome or NMS?

### Clinical Point

Symptoms of SS present within 24 hours of starting or changing therapy

Figure

## Hunter serotonin toxicity criteria



It is important to recognize that various serotonergic agents are involved in the CYP450 system. Inhibition of the CYP450 pathway by common antibiotics such as ciprofloxacin, or antifungals such as fluconazole, may result in an accumulation of serotonergic agents and place patients at increased risk for developing SS.

**Clinical presentation.** The clinical presentation of SS can range from mild to fatal. There is no specific laboratory test for diagnosis, although an elevation of the total creatine kinase (CK) and leukocyte count, as well as increased transaminase levels or lower bicarbonate levels, have been reported in the literature.<sup>4</sup>

Symptoms of SS generally present within 24 hours of starting/changing therapy and include a triad of mental status changes

(altered mental status [AMS]), autonomic instability, and abnormalities of neuromuscular tone. Examples of AMS include agitation, anxiety, disorientation, and restlessness. Symptoms of autonomic instability include hypertension, tachycardia, tachypnea, hyperthermia, diaphoresis, flushed skin, vomiting, diarrhea, and arrhythmias. Symptoms stemming from changes in neuromuscular tone include tremors, clonus, hyperreflexia, and muscle rigidity.<sup>1</sup> The multiple possible clinical presentations, as well as symptoms that overlap with those of other syndromes, can make SS difficult to recognize quickly in a clinical setting.

**Diagnostic criteria.** Sternbach's diagnostic criteria for SS are defined as the presence of 3 or more of the 10 most common clinical features (Table 2,<sup>5</sup> page 31). Due to concerns

Table 3

### Medications that can cause neuroleptic malignant syndrome

Class	Medications
Neuroleptic agents	Aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, risperidone, thioridazine, ziprasidone, amisulpride, zotepine
Antiemetic agents	Domperidone, droperidol, metoclopramide, prochlorperazine, promethazine

Source: Reference 1

Table 4

### Differentiating neuroleptic malignant syndrome and serotonin syndrome

Factor	Serotonin syndrome	Neuroleptic malignant syndrome
Causative medications	Serotonergic agents	Dopamine antagonists
Physical exam findings	Hyperreflexia, myoclonus, ocular clonus	Severe rigidity (lead pipe), hyporeflexia
Laboratory findings	More commonly no lab findings	More commonly increased creatine kinase, leukocytosis, low serum iron
Course of illness	Symptoms seen within 24 hours of starting/changing therapy and resolves within a few days of treatment	Slower in onset (1 to 2 weeks after starting/changing therapy) and resolves within 9 to 14 days of treatment

Source: Reference 17

### Clinical Point

SS treatment ranges from supportive care to use of a serotonergic antagonist, neuromuscular sedation, and intubation

that Sternbach's diagnostic criteria overemphasized an abnormal mental state (leading to possible confusion of SS with other AMS syndromes), the Hunter serotonin toxicity criteria<sup>6</sup> (*Figure, page 32*) were developed in 2003, and were found to be more sensitive and specific than Sternbach's criteria. Both tools are often used in clinical practice.

**Treatment.** Treatment of SS begins with prompt discontinuation of all serotonergic agents. The intensity of treatment depends on the severity of the symptoms. Mild symptoms can be managed with supportive care,<sup>3</sup> and in such cases, the syndrome generally resolves within 24 hours.<sup>7</sup> Clinicians may use supportive care to normalize vital signs (oxygenation to maintain SpO<sub>2</sub> >94%, IV fluids for volume depletion, cooling agents, antihypertensives, benzodiazepines for sedation or control of agitation, etc.). Patients who are more ill may require more aggressive treatment, such as the use of a serotonergic antagonist (ie, cyproheptadine) and those who are severely hyperthermic (temperature >41.1°C) may require neuromuscular sedation, paralysis, and possibly endotracheal intubation.<sup>3</sup>

Management pitfalls include misdiagnosis of SS, failure to recognize its rapid rate of progression, and adverse effects of pharmacologic therapy.<sup>3</sup> The most effective treatment for SS is prevention. SS can be prevented by astute pharmacologic understanding, avoidance of polypharmacy, and physician education.<sup>3</sup>

### Neuroleptic malignant syndrome

**Possible mechanisms.** Neuromuscular malignant syndrome is thought to result from dopamine receptor antagonism leading to a hypodopaminergic state in the striatum and hypothalamus.<sup>8</sup> The pathophysiology behind NMS has not fully been elucidated; however, several hypotheses attempt to explain this life-threatening reaction. The first focuses on dopamine D2 receptor antagonism, because many of the neuroleptic (antipsychotic) medications that can precipitate NMS are involved in dopamine blockade. In this theory, blocking dopamine D2 receptors in the anterior hypothalamus explains the hyperthermia seen in NMS, while blockade in the corpus striatum is believed to lead to muscle rigidity.<sup>9</sup>

continued



## Serotonin syndrome or NMS?

### Clinical Point

**NMS can occur after a single dose, after a dose adjustment, or after years of treatment with the same medication**

**Table 5**

## Treatment for neuroleptic malignant syndrome vs serotonin syndrome

Serotonin syndrome	Neuroleptic malignant syndrome
Stop serotonergic agent	Stop causative agents
Supportive care (aim to normalize vital signs)	Supportive care (possible ICU admission)
Sedation with benzodiazepines	Medical therapy (dantrolene, bromocriptine, amantadine)
Medical therapy (cyproheptadine)	Consider ECT (unclear efficacy)
ECT: electroconvulsive therapy	
Source: Reference 17	

The second hypothesis suggests that neuroleptics may have a direct toxic effect to muscle cells. Neuroleptics influence calcium transport across the sarcoplasmic reticulum and can lead to increased calcium release, which may contribute to the muscle rigidity and hyperthermia seen in NMS.<sup>9</sup>

The third hypothesis involves hyperactivity of the sympathetic nervous system; it is thought that psychologic stressors alter frontal lobe function, with neuroleptics disrupting the inhibitory pathways of the sympathetic nervous system. The autonomic nervous system innervates multiple organ systems, so this excessively dysregulated sympathetic nervous system may be responsible for multiple NMS symptoms (hyperthermia, muscle rigidity, hypertension, diaphoresis, tachycardia, elevated CK).<sup>10</sup>

NMS can be caused by neuroleptic agents (both first- and second-generation antipsychotics) as well as antiemetics (*Table 3*,<sup>1</sup> *page 33*). The time between use of these medications and onset of symptoms is highly variable. NMS can occur after a single dose, after a dose adjustment, or possibly after years of treatment with the same medication. It is not dose-dependent.<sup>11</sup> In certain individuals, NMS may occur at therapeutic doses.

**Clinical presentation.** Patients with NMS typically present with a tetrad of symptoms: mental status changes, muscular rigidity, hyperthermia, and autonomic instability.<sup>12</sup> Mental status changes can include confusion and agitation, as well as catatonic signs and mutism. The muscular rigidity of NMS is characterized by

“lead pipe rigidity” and may be accompanied by tremor, dystonia, or dyskinesias. Laboratory findings include elevated serum CK (from severe rigidity), often >1,000 U/L, although normal levels can be observed if rigidity has not yet developed.<sup>13</sup>

**Treatment.** The first step for treatment is to discontinue the causative medication.<sup>14</sup> Initiate supportive therapy immediately to restrict the progression of symptoms. Interventions include cooling blankets, fluid resuscitation, and antihypertensives to maintain autonomic stability<sup>15</sup> or benzodiazepines to control agitation. In severe cases, muscular rigidity may extend to the airways and intubation may be required. The severity of these symptoms may warrant admission to the ICU for close monitoring. Pharmacologic treatment with dantrolene (a muscle relaxant that blocks calcium efflux from the sarcoplasmic reticulum) and bromocriptine (a dopamine agonist) have been utilized.<sup>14</sup> In case reports, electroconvulsive therapy (ECT) has been used to treat NMS<sup>15,16</sup>; however, prospective research comparing ECT with traditional treatment has not been conducted. It is also worth mentioning that if a clinician wishes to restart the neuroleptic medication, a 2-week washout period will minimize the risk of NMS recurrence.<sup>17</sup>

### Differentiating between SS and NMS

Differentiating between these 2 syndromes (*Table 4*,<sup>17</sup> *page 33*) is critical to direct appropriate intervention. *Table 5*<sup>17</sup> outlines the treatment overview for SS and NMS.



**Detailed history.** A detailed history is imperative in making accurate diagnoses. Useful components of the history include a patient's duration of symptoms and medication history (prescription medications as well as over-the-counter medications, supplements, and illicit drugs). Also assess for medical comorbidities, because certain medical diagnoses may alert the clinician that it is likely the patient had been prescribed serotonergic agents or neuroleptics, and renal or liver impairment may alert the clinician of decreased metabolism rates. Medication history is arguably the most useful piece of the interview, because serotonergic agents can cause SS, whereas dopamine blockers cause NMS. It should be noted that excess serotonin acts as a true toxidrome and is concentration-dependent in causing SS, whereas NMS is an idiosyncratic reaction to a drug.

**Physical exam.** Although there are many overlapping clinical manifestations, SS produces neuromuscular hyperactivity (ie, clonus, hyperreflexia), whereas NMS is characterized by more sluggish responses (ie, rigidity, bradyreflexia).<sup>18</sup>

**Laboratory findings.** Overlap between NMS and SS also occurs with lab findings; both syndromes can result in leukocytosis, elevated CK from muscle damage, and low serum iron levels. However, these findings are more commonly associated with NMS and are seen in 75% of cases.<sup>17,19</sup>

**Course of illness.** Duration of symptoms can also help differentiate the 2 syndromes. SS typically develops within 24 hours of starting/changing therapy, whereas NMS

## Related Resources

- Kimmel R. Serotonin syndrome or NMS? Clues to diagnosis. *Current Psychiatry*. 2010;9(2):92.
- Strawn JR, Keck Jr PE, Caroff SN. Neuroleptic malignant syndrome: Answers to 6 tough questions. *Current Psychiatry*. 2008;7(1):95-101.

### Drug Brand Names

Amantadine • Symmetrel	Linezolid • Zyvox
Amitriptyline • Elavil, Endep	Lithium • Eskalith, Lithobid
Aripiprazole • Abilify	Meperidone • Demerol
Bromocriptine • Cycloset, Parlodel	Metoclopramide • Reglan
Bupropion • Wellbutrin, Zyban	Milnacipran • Savella
Buspirone • BuSpar	Nefazodone • Serzone
Carbamazepine • Carbatrol, Tegretol	Olanzapine • Zyprexa
Chlorpromazine • Thorazine	Ondansetron • Zofran
Ciprofloxacin • Cipro	Paliperidone • Invega
Citalopram • Celexa	Palonosetron • Aloxi
Clomipramine • Anafranil	Paroxetine • Paxil
Clozapine • Clozaril	Pentazocine • Talwin, Talacen
Cyclobenzaprine • Amrix, Flexeril	Perphenazine • Trilafon
Cyproheptadine • Periactin	Phenelzine • Nardil
Dantrolene • Dantrium	Procarbazine • Matulane
Desipramine • Norpramin	Prochlorperazine • Compazine
Desvenlafaxine • Pristiq	Promethazine • Phenergan
Dextromethorphan • Benylin, Dexalone	Quetiapine • Seroquel
Dolasetron • Anzemet	Rasagiline • Azilect
Doxepin • Silenor	Risperidone • Risperdal
Droperidol • Inapsine	Safinamide • Xadago
Duloxetine • Cymbalt	Selegiline • Eldepryl, Zelapar
Escitalopram • Lexapro	Sertraline • Zoloft
Fentanyl • Actiq, Duragesic	Sibutramine • Meridia
Fluconazole • Diflucan	Tedizolid • Sivextro
Fluoxetine • Prozac	Thioridazine • Mellaril
Fluphenazine • Prolixin	Tranylcypromine • Parnate
Fluvoxamine • Luvox	Tramadol • Ultram
Granisetron • Kytril	Trazodone • Desyrel, Oleptro
Haloperidol • Haldol	Venlafaxine • Effexor
Isocarboxazid • Marplan	Vilazodone • Viibryd
Levomilnacipran • Fetzima	Vortioxetine • Trintellix
	Valproate • Depacon
	Ziprasidone • Geodon

symptoms can be present for days to weeks. Resolution of symptoms may also be helpful in differentiation because SS typically resolves within a few days of initiating treatment, whereas NMS resolves within 9 to 14 days of starting treatment.<sup>19</sup>

continued on page 42

## Clinical Point

Although both SS and NMS can result in leukocytosis, elevated CK, and low serum iron levels, these findings are more common in NMS

## Bottom Line

The clinical presentations of serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) overlap, which can make them difficult to differentiate; however, they each have distinct approaches to treatment. Features in SS that are distinct from NMS include a history of serotonergic agents, rapid onset of symptoms, hyperreflexia, and clonus. NMS is slower in onset and can be found in patients who are prescribed dopamine antagonists, with distinct symptoms of rigidity and hyporeflexia.

## Serotonin syndrome or NMS?

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### References

1. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J*. 2013;13(4):533-540.
2. Werneke U, Jamshidi F, Taylor D, et al. Conundrums in neurology: diagnosing serotonin syndrome – a meta-analysis of cases. *BMC Neurol*. 2016;16:97.
3. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120.
4. Birnes P, Coppin D, Schmitt L, et al. Serotonin syndrome: a brief review. *CMAJ*. 2003;168(11):1439-1442.
5. Sternbach H. The serotonin syndrome. *Am J Psychiatry*. 1991;148:705-713.
6. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003; 96(9):635-642.
7. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med*. 1994;331(15):1021-1022.
8. Nisijima K. Serotonin syndrome overlapping with neuroleptic malignant syndrome: A case report and approaches for differentially diagnosing the two syndromes. *Asian J Psychiatr*. 2015;18:100-101.
9. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. *Br J Anaesth*. 2000;85(1):129-135.
10. Gurrera R. Sympathoadrenal hyperactivity and the etiology of neuroleptic malignant syndrome. *Am J Psychiatry*. 1999;156:169-180.
11. Pope HG Jr, Aizley HG, Keck PE Jr, et al. Neuroleptic malignant syndrome: long-term follow-up of 20 cases. *J Clin Psychiatry*. 1991;52(5):208-212.
12. Velamoor VR, Norman RM, Caroff SN, et al. Progression of symptoms in neuroleptic malignant syndrome. *J Nerv Ment Dis*. 1994;182(3):168-173.
13. Caroff SN, Mann SC. Neuroleptic malignant syndrome. *Med Clin North Am*. 1993;77(1):185-202.
14. Pileggi DJ, Cook AM. Neuroleptic malignant syndrome. *Ann Pharmacother*. 2016;50(11):973-981.
15. San Gabriel MC, Eddula-Changala B, Tan Y, et al. Electroconvulsive in a schizophrenic patient with neuroleptic malignant syndrome and rhabdomyolysis. *J ECT*. 2015;31(3):197-200.
16. Buggenhout S, Vandenberghe J, Sienaert P. Electroconvulsion therapy for neuroleptic malignant syndrome. *Tijdschr Psychiatr*. 2014;56(9):612-615.
17. Perry PJ, Wilborn CA. Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. *Ann Clin Psychiatry*. 2012;24(2): 155-162.
18. Mills KC. Serotonin syndrome. A clinical update. *Crit Care Clin*. 1997;13(4):763-783.
19. Dosi R, Ambaliya A, Joshi H, et al. Serotonin syndrome versus neuroleptic malignant syndrome: a challenge clinical quandary. *BMJ Case Rep*. 2014;2014:bcr201404154. doi:10.1136/bcr-2014-204154.