

## REVIEW ARTICLE

## CURRENT CONCEPTS

## The Serotonin Syndrome

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**T**HE SEROTONIN SYNDROME IS A POTENTIALLY LIFE-THREATENING ADVERSE drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs. Three features of the serotonin syndrome are critical to an understanding of the disorder. First, the serotonin syndrome is not an idiopathic drug reaction; it is a predictable consequence of excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors.<sup>1,2</sup> Second, excess serotonin produces a spectrum of clinical findings.<sup>3</sup> Third, clinical manifestations of the serotonin syndrome range from barely perceptible to lethal. The death of an 18-year-old patient named Libby Zion in New York City more than 20 years ago, which resulted from coadministration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition.<sup>4</sup>

## DEFINITION AND EPIDEMIOLOGY

The serotonin syndrome is often described as a clinical triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder (Fig. 1).<sup>5,6</sup> Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration.

The incidence of the serotonin syndrome is thought to mirror the increasing number of proserotonergic agents being used in clinical practice.<sup>7</sup> In 2002, the Toxic Exposure Surveillance System, which receives case descriptions from office-based practices, inpatient settings, and emergency departments, reported 26,733 incidences of exposure to selective serotonin-reuptake inhibitors (SSRIs) that caused significant toxic effects in 7349 persons and resulted in 93 deaths.<sup>8,9</sup> The assessment of the serotonin syndrome in therapeutic drug dosing has relied on post-marketing surveillance studies, one of which identified an incidence of 0.4 case per 1000 patient-months for patients who were taking nefazodone.<sup>10</sup> Performing a rigorous epidemiologic assessment of the serotonin syndrome, however, is difficult, since more than 85 percent of physicians are unaware of the serotonin syndrome as a clinical diagnosis.<sup>10</sup> The syndrome occurs in approximately 14 to 16 percent of persons who overdose on SSRIs.<sup>8</sup>

Although the serotonin syndrome has occurred in a broad range of clinical environments, several barriers limit the ability of clinicians to diagnose the condition. First, the syndrome may be missed because of its protean manifestations. Clinicians and patients may dismiss symptoms such as tremor with diarrhea or hypertension as inconsequential or unrelated to drug therapy; anxiety and akathisia may be misattributed to the patient's mental state.<sup>5,10</sup> Second, a strict application of the diagnostic criteria proposed

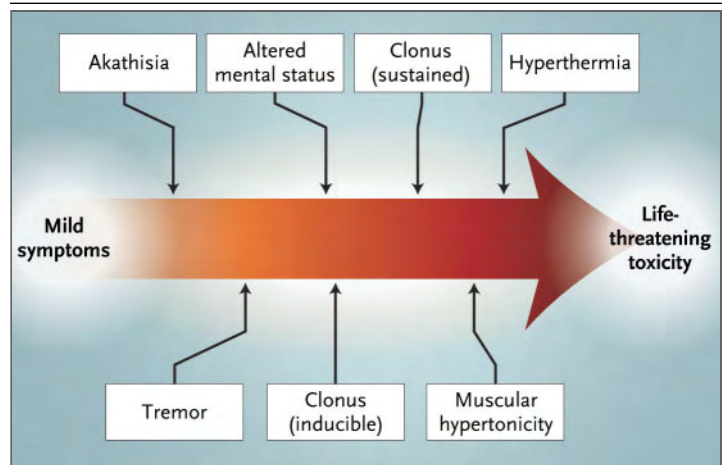
by Sternbach potentially rules out what are now recognized as mild, early, or subacute cases of the disorder.<sup>1,11</sup> Third, clinicians cannot diagnose a condition of which they are unaware, even though the serotonin syndrome is not rare and has been identified in patients of all ages, including the elderly, children, and newborn infants.<sup>10,12-14</sup>

A striking number of drugs and drug combinations have been associated with the serotonin syndrome (Table 1). These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, SSRIs, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products; the withdrawal of medications has also been associated with the syndrome.<sup>1,4,12,15-23</sup> A single therapeutic dose of an SSRI has caused the serotonin syndrome.<sup>12</sup> Moreover, the addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the condition.<sup>16,24,25</sup> Administration of serotonergic agents within five weeks after the discontinuation of fluoxetine therapy has produced a drug interaction culminating in the serotonin syndrome, presumably the result of the demethylation of fluoxetine to norfluoxetine, a serotonergic metabolite with a longer serum half-life than its parent compound.<sup>13</sup> Specific drugs, such as MAOIs that are irreversible or nonselective or that inhibit monoamine oxidase subtype A, are strongly associated with severe cases of the syndrome, especially when these agents are used in combination with meperidine, dextromethorphan, SSRIs, or methylenedioxymethamphetamine (MDMA, or “ecstasy”).<sup>4,8,15,26,27</sup>

#### MANIFESTATIONS

The serotonin syndrome encompasses a range of clinical findings. Patients with mild cases may be afebrile but have tachycardia, with a physical examination that is notable for autonomic findings such as shivering, diaphoresis, or mydriasis (Fig. 2). The neurologic examination may reveal intermittent tremor or myoclonus, as well as hyperreflexia.

A representative example of a moderate case of the serotonin syndrome involves such vital-sign abnormalities as tachycardia, hypertension, and hyperthermia. A core temperature as high as 40°C is common in moderate intoxication. Common features of the physical examination are mydriasis, hyperactive bowel sounds, diaphoresis, and normal



**Figure 1. Spectrum of Clinical Findings.**

Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

skin color. Interestingly, the hyperreflexia and clonus seen in moderate cases may be considerably greater in the lower extremities than in the upper extremities; patellar deep-tendon reflexes often demonstrate clonus for several seconds after a single tap of the tendon, whereas the brachioradialis reflex is only slightly increased. Patients may exhibit horizontal ocular clonus. Changes in mental status include mild agitation or hypervigilance, as well as slightly pressured speech. Patients may easily startle or adopt a peculiar head-turning behavior characterized by repetitive rotation of the head with the neck held in moderate extension.

In contrast, a patient with a severe case of the serotonin syndrome may have severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity. Again, the increase in muscle tone is considerably greater in the lower extremities. The muscle hyperactivity may produce a core temperature of more than 41.1°C in life-threatening cases. Laboratory abnormalities that occur in severe cases include metabolic acidosis, rhabdomyolysis, elevated levels of serum aminotransferase and creatinine, seizures, renal failure, and disseminated intravascular coagulopathy. Many of these abnormalities arise, however, as a consequence of poorly treated hyperthermia.

**Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.****Drugs associated with the serotonin syndrome**

Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram  
 Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine  
 Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid  
 Anticonvulsants: valproate  
 Analgesics: meperidine, fentanyl, tramadol, and pentazocine  
 Antiemetic agents: ondansetron, granisetron, and metoclopramide  
 Antimigraine drugs: sumatriptan  
 Bariatric medications: sibutramine  
 Antibiotics: linezolid (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)  
 Over-the-counter cough and cold remedies: dextromethorphan  
 Drugs of abuse: methylenedioxyamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)  
 Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)  
 Other: lithium

**Drug interactions associated with severe serotonin syndrome**

Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anaf-ranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron  
 Phenelzine and meperidine  
 Tranylcypromine and imipramine  
 Phenelzine and selective serotonin-reuptake inhibitors  
 Paroxetine and buspirone  
 Linezolid and citalopram  
 Moclobemide and selective serotonin-reuptake inhibitors  
 Tramadol, venlafaxine, and mirtazapine

To better delineate the signs and symptoms that define the serotonin syndrome, the clinical findings in 2222 consecutive cases of self-poisoning with serotonergic drugs were rigorously assessed on the basis of information from a detailed toxicology registry.<sup>2</sup> These findings were then compared with the "gold standard," the assignment of a diagnosis of the serotonin syndrome by a medical toxicologist.<sup>2</sup> The clinical findings that had a statistically significant association with the diagnosis of the syndrome were primarily neuromuscular, including hyperreflexia, inducible clonus, myoclonus, ocular clonus, spontaneous clonus, peripheral hypertonicity, and shivering.<sup>2</sup> Autonomic derangements were tachycardia on admission, mydriasis, diaphoresis, and the presence of bowel sounds and diarrhea.<sup>2</sup> Abnormalities in mental status that were significantly associated with the serotonin syndrome were agitation and delirium.<sup>2</sup> Hyperthermia that was caused by muscular hypertonicity, defined in this

study as a temperature of more than 38°C, was not as strongly associated with the diagnosis of the serotonin syndrome but occurred in severely intoxicated patients.<sup>2</sup>

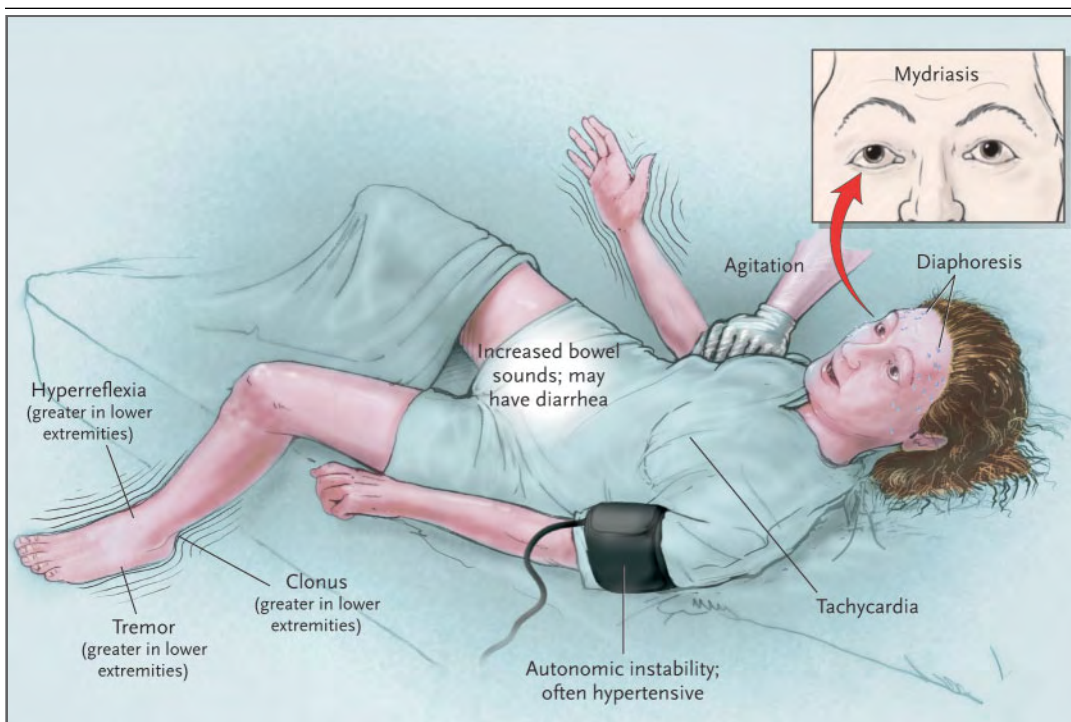
The onset of symptoms is usually rapid, with clinical findings often occurring within minutes after a change in medication or self-poisoning.<sup>28</sup> Approximately 60 percent of patients with the serotonin syndrome present within six hours after initial use of medication, an overdose, or a change in dosing.<sup>28</sup> Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death. The serotonin syndrome is not believed to resolve spontaneously as long as precipitating agents continue to be administered.

#### PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Serotonin is produced by the decarboxylation and hydroxylation of L-tryptophan. Its quantity and actions are tightly regulated by a combination of reuptake mechanisms, feedback loops, and metabolizing enzymes (Fig. 3). Serotonin receptors are divided into seven 5-hydroxytryptamine (5-HT) families (5-HT<sub>1</sub> to 5-HT<sub>7</sub>), several of which have multiple members (e.g., 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1C</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub>, and 5-HT<sub>1F</sub>). Further structural and operational diversity is achieved by allelic polymorphisms, splice variants, receptor isoforms, and the formation of receptor heterodimers.<sup>29</sup>

Serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla.<sup>30</sup> The rostral end of this system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior.<sup>30</sup> The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone.<sup>30</sup> In the periphery, the serotonin system assists in the regulation of vascular tone and gastrointestinal motility.<sup>30</sup>

No single receptor appears to be responsible for the development of the serotonin syndrome, although several lines of evidence converge to suggest that agonism of 5-HT<sub>2A</sub> receptors contributes substantially to the condition.<sup>31-35</sup> Additional subtypes of serotonin receptors, such as 5-HT<sub>1A</sub>, may contribute through a pharmacodynamic interaction in which increased synaptic concentrations of serotonin agonist saturate all receptor subtypes. Nora-



**Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.**

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

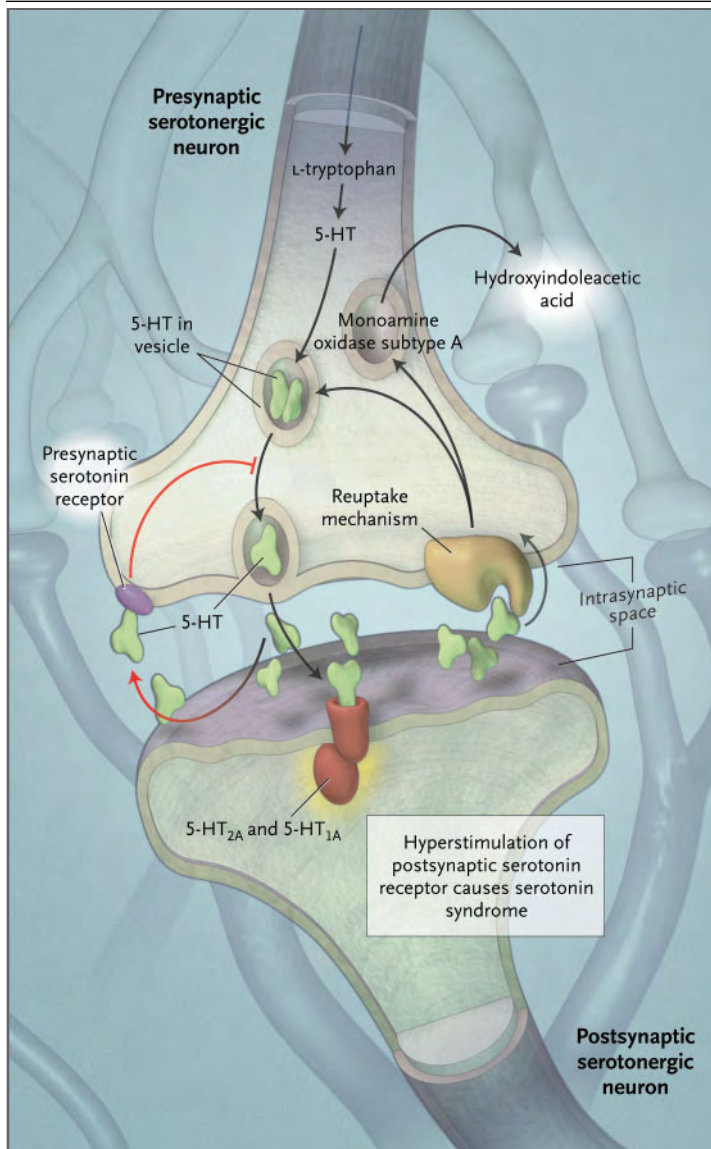
adrenergic CNS hyperactivity may play a critical role, since the degree to which CNS norepinephrine concentrations are increased in the serotonin syndrome may correlate with the clinical outcome.<sup>33,35,36</sup> Other neurotransmitters, including *N*-methyl-*D*-aspartate (NMDA) receptor antagonists and  $\gamma$ -aminobutyric acid (GABA), may affect the development of the syndrome, but the role of these agents is less clear.<sup>33,37</sup> Dopaminergic receptors have been implicated, but this association may arise from pharmacodynamic interactions, direct interactions between serotonin and dopamine receptors, other mechanisms, or a misdiagnosis of the serotonin syndrome as the neuroleptic malignant syndrome.<sup>26,33,38,39</sup>

#### DIAGNOSIS

No laboratory tests confirm the diagnosis of the serotonin syndrome. Instead, the presence of tremor, clonus, or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis, which must be inferred from the patient's history and physical examination. When obtaining

the patient's history, clinicians should inquire about the use of prescription and over-the-counter drugs, illicit substances, and dietary supplements, since all of these agents have been implicated in the development of the serotonin syndrome. The evolution of symptoms and their rate of change should also be reviewed. Physical examination should include a focused assessment of deep-tendon reflexes, clonus, and muscle rigidity, in addition to an evaluation of the size and reactivity of the pupils, the dryness of the oral mucosa, the intensity of bowel sounds, skin color, and the presence or absence of diaphoresis.

Although several diagnostic criteria have been developed, we prefer the decision rules described in Figure 4.<sup>2,11,14,40</sup> These rules, when compared with the original diagnostic criteria, are simpler, more sensitive (84 percent vs. 75 percent), and more specific (97 percent vs. 96 percent) for diagnosing the serotonin syndrome.<sup>1,2</sup> Clonus (inducible, spontaneous, and ocular) is the most important finding in establishing the diagnosis of the serotonin syndrome.<sup>2,27,41</sup> Clinicians should always be aware



**Figure 3. Serotonin Biosynthesis and Metabolism.**

Serotonin is produced in presynaptic neurons by hydroxylation and decarboxylation of L-tryptophan. Serotonin is then incorporated into vesicles, where it resides until it is needed for neurotransmission. After axonal stimulation, serotonin is released into the intrasynaptic space; presynaptic serotonin receptors function as a feedback loop to inhibit exocytosis of vesicles (shown in red). Serotonin then binds to postsynaptic receptors to effect neurotransmission. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron, where it is reintroduced into vesicles. Serotonin is then metabolized by monoamine oxidase subtype A to hydroxyindoleacetic acid.

that hyperthermia and hypertonicity occur in life-threatening cases, but muscle rigidity may mask the highly distinguishing findings of clonus and hyperreflexia and therefore cloud the diagnosis.<sup>2,42</sup>

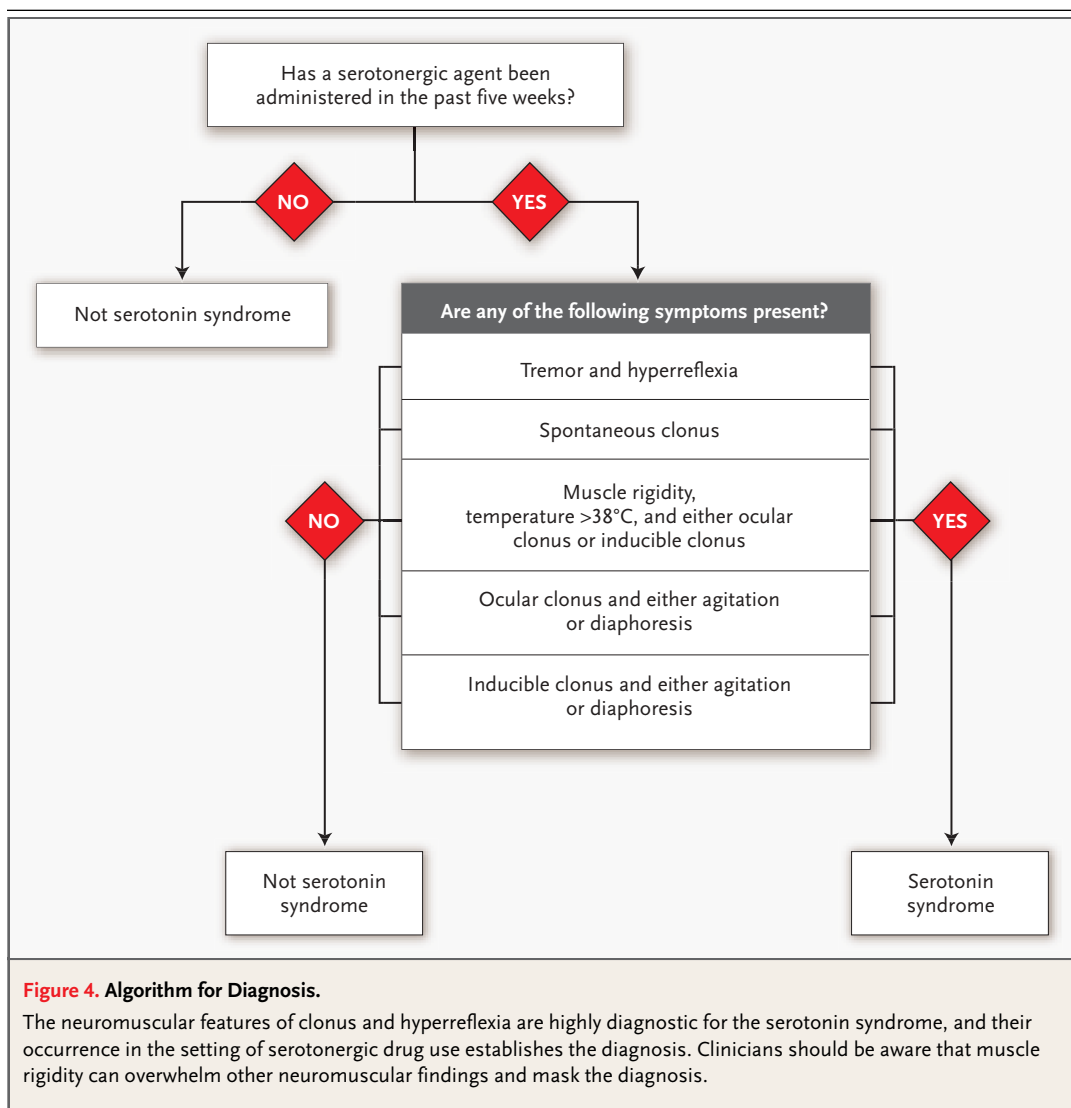
The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and the neuroleptic malignant syndrome, each of which can be readily distinguished from the serotonin syndrome on clinical grounds and on the basis of the medication history (Table 2). Patients with the anticholinergic syndrome have normal reflexes and show the “toxidrome” of mydriasis; agitated delirium; dry oral mucosa; hot, dry, erythematous skin; urinary retention; and an absence of bowel sounds. Hyperactive bowel sounds — along with neuromuscular abnormalities, diaphoresis, and normal skin color — distinguish the serotonin syndrome from the anticholinergic toxidrome.<sup>2</sup>

Malignant hyperthermia is a pharmacogenetic disorder characterized by increasing concentrations of end-tidal carbon dioxide, hypertonicity, hyperthermia, and metabolic acidosis. The disorder occurs within minutes after exposure to inhalational anesthetic agents.<sup>43</sup> On physical examination, the skin is often mottled, with cyanotic areas contrasting with patches of bright red flushing.<sup>43</sup> The rigor mortis-like rigidity of skeletal muscles and hyporeflexia that are seen in malignant hyperthermia further distinguish this condition from the serotonin syndrome.<sup>43</sup>

The neuroleptic malignant syndrome is an idiopathic reaction to dopamine antagonists, a condition that is defined by a slow onset, bradykinesia or akinesia, “lead pipe” muscular rigidity, hyperthermia, fluctuating consciousness, and autonomic instability.<sup>44</sup> Signs and symptoms of the neuroleptic malignant syndrome typically evolve during several days, in contrast to the rapid onset and hyperkinesia of the serotonin syndrome. Knowledge of the precipitating drug also helps in distinguishing between syndromes: dopamine antagonists produce bradykinesia, whereas serotonin agonists produce hyperkinesia.<sup>45</sup>

#### MANAGEMENT

Management of the serotonin syndrome involves the removal of the precipitating drugs, the provision of supportive care, the control of agitation, the administration of 5-HT<sub>2A</sub> antagonists, the control of autonomic instability, and the control of hyperthermia.<sup>45</sup> Many cases of the serotonin syndrome typically resolve within 24 hours after the initiation of therapy and the discontinuation of serotonergic drugs, but symptoms may persist in patients taking drugs with long elimination half-lives, active metab-



olites, or a protracted duration of action. Supportive care, comprising the administration of intravenous fluids and correction of vital signs, remains a mainstay of therapy. However, an abrupt deterioration in the condition of a patient who has been conservatively treated indicates the need for an immediate, aggressive response.<sup>1,2,45</sup>

The intensity of therapy depends on the severity of illness. Mild cases (e.g., with hyperreflexia and tremor but no fever) can usually be managed with supportive care, removal of the precipitating drugs, and treatment with benzodiazepines. Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected and may benefit from the administration of 5-HT<sub>2A</sub> antagonists. Hyperthermic patients (those whose

temperature is more than 41.1°C) are severely ill and should receive the above therapies as well as immediate sedation, neuromuscular paralysis, and orotracheal intubation.

Control of agitation with benzodiazepines is essential in the management of the serotonin syndrome, regardless of its severity. Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome.<sup>37,45</sup> Physical restraints are ill-advised and may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.<sup>46</sup> If physical restraints are used, they must be rapidly replaced with chemical sedation.

Pharmacologically directed therapy involves the

**Table 2. Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions.**

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Pupils	Mucosa	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental Status
Serotonin syndrome	Proserotonergic drug	<12 hr	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Mydriasis	Sialorrhea	Diaphoresis	Hyperactive	Increased, predominantly in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mydriasis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonist	1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Normal	Sialorrhea	Pallor, diaphoresis	Normal or decreased	"Lead-pipe" rigidity present in all muscle groups	Bradyreflexia	Stupor, alert mutism, coma
Malignant hyperthermia	Inhalational anesthesia	30 min to 24 hr after administration of inhalational anesthesia or succinylcholine	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled appearance, diaphoresis	Decreased	Rigor mortis-like rigidity	Hyporeflexia	Agitation

administration of 5-HT<sub>2A</sub> antagonists.<sup>7,45</sup> Cyproheptadine is the recommended therapy for the serotonin syndrome, although its efficacy has not been rigorously established.<sup>7,45</sup> Treatment of the serotonin syndrome in adults may require 12 to 32 mg of the drug during a 24-hour period, a dose that binds 85 to 95 percent of serotonin receptors.<sup>47</sup> Clinicians should consider an initial dose of 12 mg of cyproheptadine and then 2 mg every two hours if symptoms continue. Maintenance dosing involves the administration of 8 mg of cyproheptadine every six hours. Cyproheptadine is available only in oral form, but tablets may be crushed and administered by nasogastric tube. Atypical antipsychotic agents with 5-HT<sub>2A</sub>-antagonist activity may be beneficial in treating the serotonin syndrome. The sublingual administration of 10 mg of olanzapine has been used successfully, but its efficacy has not been rigorously determined.<sup>48</sup> Clinicians desiring a parenteral agent should consider the intramuscular administration of 50 to 100 mg of chlorpromazine.<sup>45</sup> Even though chlorpromazine is an outdated therapy that has been replaced in psychiatric practice by newer agents, its use may nonetheless be considered in severe cases.<sup>45</sup>

Control of autonomic instability involves stabilization of fluctuating pulse and blood pressure. Hypotension arising from MAOI interactions should be treated with low doses of direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, and epinephrine). Direct agonists do not require intracellular metabolism to generate a vasoactive amine, but their concentration in the synapse is regulated by catecholamine-O-methyltransferase. Indirect agents such as dopamine are metabolized to epinephrine and norepinephrine. Under normal conditions, monoamine oxidase limits the intracellular concentration of these metabolites. When inhibited, however, monoamine oxidase cannot control the amount of epinephrine and norepinephrine produced, and an exaggerated hemodynamic response may ensue. Patients in whom hypertension and tachycardia develop, either as a result of pressor therapy or from poisoning itself, should be treated with short-acting agents such as nitroprusside and esmolol.

Control of hyperthermia involves eliminating excessive muscle activity. Although benzodiazepines have a beneficial effect in moderate cases, in severely ill patients with hyperthermia (a temperature of more than 41.1°C) immediate paralysis should be induced with nondepolarizing agents such as vec-

uronium, followed by orotracheal intubation and ventilation. Clinicians should avoid succinylcholine because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. Recent case reports have shown that premature termination of neuromuscular paralysis was associated with a recrudescence of hyperthermia.<sup>49</sup> There is no role for antipyretic agents in the management of the serotonin syndrome; the increase in body temperature is due to muscular activity, not an alteration in the hypothalamic temperature set point.

Potential pitfalls for clinicians include misdiagnosis of the serotonin syndrome, a failure to comprehend its rapidity of progression, and adverse effects of pharmacologically directed therapy. The diagnosis may be clouded by the presence of severe muscle rigidity that obscures myoclonus and hyperreflexia. If the correct diagnosis is not obvious, a prudent course is to withhold antagonist therapy and provide aggressive supportive care, sedation with benzodiazepines, and, if necessary, intubation and paralysis.<sup>7</sup> Because of the speed with which the condition of patients declines, physicians should anticipate the need for aggressive therapy before clinical indications are reached.

Therapies such as propranolol, bromocriptine, and dantrolene are not recommended.<sup>7,45</sup> Propranolol, a 5-HT<sub>1A</sub> antagonist with a long duration of action, may cause hypotension and shock in patients with autonomic instability. Furthermore, propranolol can abolish tachycardia that can be used to determine the duration and effectiveness of therapy.<sup>2</sup> Bromocriptine, a dopamine antagonist, and dantrolene are not useful therapies; case reports citing their use probably involved a misdiagnosis of another condition as the serotonin syndrome.<sup>7,35,45</sup> Bromocriptine has been implicated in the development of the serotonin syndrome, and its use in patients in whom the neuroleptic malignant syndrome is misdiagnosed may worsen serotonergic signs.<sup>27,50</sup> According to one report, the administration of bromocriptine and dantrolene to a patient with the serotonin syndrome caused an abrupt increase in temperature, culminating in death.<sup>39</sup> This finding is supported by the observation that dantrolene has no effect on survival in animal models.<sup>34,35</sup>

Antagonist therapy with the use of cyproheptadine and chlorpromazine may have unintended effects. The dosage of cyproheptadine used to treat the serotonin syndrome may cause sedation, but this effect is a goal of therapy and should not deter clinicians from using the drug. Chlorpromazine is an outmoded drug that has been associated with severe orthostatic hypotension and has been thought to aggravate hyperthermia. Patients who require acute parenteral therapy for the serotonin syndrome are often hypertensive and are not ambulatory, so that the risk of orthostatic hypotension is minimized. Hyperthermia in response to neuroleptic administration is an idiopathic response; the normal outcome is hypothermia. Nonetheless, chlorpromazine should not be administered to a patient with hypotension or the neuroleptic malignant syndrome, since the drug could potentially exacerbate clinical findings.

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#### PREVENTION

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The serotonin syndrome can be avoided by a combination of pharmacogenomic research, the education of physicians, modifications in prescribing practices, and the use of technological advances. The application of pharmacogenomic principles can potentially protect patients at risk for the syndrome before the administration of serotonergic agents. Once toxicity occurs, consultation with a medical toxicologist, a clinical pharmacology service, or a poison-control center can identify proserotonergic agents and drug interactions, assist clinicians in anticipating adverse effects, and provide valuable clinical decision-making experience. The avoidance of multidrug regimens is critical to the prevention of the serotonin syndrome. If multiple agents are required, however, computer-based ordering systems and the use of personal digital assistants can detect drug interactions and decrease reliance on memory in drug ordering. Post-marketing surveillance linked to physician education has been proposed to improve awareness of the serotonin syndrome.<sup>10</sup>

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