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High risk and low prevalence diseases: Serotonin syndrome

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ABSTRACT

Introduction: Serotonin syndrome is a rare, frequently misdiagnosed, serious condition with high morbidity.
Objective: This review highlights the pearls and pitfalls of serotonin syndrome, including diagnosis, initial resuscitation, and management in the emergency department (ED) based on current evidence.
Discussion: Serotonin syndrome is a potentially deadly toxidrome marked by excess serotonin receptor activity or neurotransmission. Features of serotonin syndrome include 1) neuromuscular excitation such as tremor, hyperreflexia, and clonus; 2) autonomic dysfunction such as tachycardia, hypertension/hypotension, and hyperthermia; and 3) altered mental status such as agitation, delirium, and coma. Although serotonin syndrome may be more obvious in patients who have overdosed on serotonergic agents such as serotonin reuptake inhibitors (SSRIs), multiple other medications may also cause serotonin syndrome. Alternative diagnoses such as sepsis, neuroleptic malignant syndrome, and decompensated hyperthyroidism should be considered. The primary components of therapy include stopping the offending agent and supportive care, which focuses on agitation control, monitoring for and treating hyperthermia, and managing autonomic instability.
Conclusions: An understanding of serotonin syndrome can assist emergency clinicians in diagnosing and managing this disease.

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1. Introduction

This article series addresses high risk and low prevalence diseases that are encountered in the emergency department (ED). Much of the primary literature evaluating these conditions is not emergency medicine focused. By their very nature, many of these disease states and clinical presentations have little useful evidence available to guide the emergency physician in diagnosis and management. The format of each article defines the disease or clinical presentation to be reviewed, provides an overview of the extent of what we currently know and understand, and finally discusses pearls and pitfalls using a question and answer format. This article will discuss serotonin syndrome. This condition's low prevalence, as well as its variable atypical presentations, challenging diagnosis, and high morbidity, makes it a high risk disease.

1.1. Definition

Serotonin syndrome is a toxidrome consisting of signs and symptoms that characterize serotonin toxicity [1-4]. Serotonin toxicity was first recognized in the 1960s in animal models given serotonin agonists. It was recognized in humans with the introduction of monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA), who developed clinical symptoms similar to those in the animal models [1,4,5]. As selective serotonin reuptake inhibitors (SSRI) became more common, several diagnostic criteria were developed to better characterize serotonin syndrome [1,2,5]. Serotonin syndrome is characterized by 1) central nervous system (CNS) excitation leading to hyperreflexia, clonus, rigidity; 2) mental status changes leading to anxiety, agitation, confusion, coma; and 3) autonomic excitation with diarrhea, tachycardia, hypertension, flushing, and hyperthermia [4,6,7]. Symptoms are associated with the addition or increase in dose of a serotonergic drug and typically begin within a few hours of the inciting event [1,2,5].

There are several diagnostic criteria for serotonin syndrome, including the Sternbach, Radomski, and Hunter criteria [2,3]. These criteria were developed to create a diagnostic framework for serotonin syndrome based on common signs and symptoms. The nuances of the different criteria are discussed below. The Hunter criteria likely have the most relevance for the emergency clinician as they were derived from a patient population that is most similar to patients who are seen in the ED with serotonin syndrome currently [2,3].

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1.2. Pathophysiology

Serotonin modulates attention, behavior, and temperature control in the CNS, but in the peripheral nervous system, it regulates bronchoconstriction, gastrointestinal motility, uterine contraction, and platelet regulation [8,9]. In total, there are seven classes of serotonin receptors, 5-HT-1 through 5-HT-7, which can be further divided into subdivisions [9]. 5-HT-2a receptors are responsible for the potentially deadly signs and symptoms of serotonin syndrome such as increased muscle tone and hyperthermia [9]. 5-HT-1a receptors contribute to anxiety and hyperactivity [9]. In most cases, excess stimulation of 5-HT receptors and increased serotonergic neurotransmission can lead to serotonin syndrome [9]. This may occur due to overdose of a serotonergic medication, interaction between several serotonergic medications, and renal dysfunction resulting in accumulation of serotonergic medications [9,10].

1.3. Epidemiology

Serotonin syndrome is a rare but potentially underrecognized and life-threatening disease [3]. In one study of 112,045 hospitalized patients who were prescribed at least one serotonergic agent, six were diagnosed with serotonin syndrome, but authors noted a few cases could have been missed as they identified three additional cases that met all the criteria for serotonin syndrome and 23 cases that had partial criteria documented [11]. An observational study of patients who were co-prescribed triptans, which are thought to increase risk of serotonin syndrome, and SSRIs found an estimated incidence of serotonin syndrome of 0.6 to 2.3 cases per 10,000 person years [12]. Serotonin syndrome might be more common among the critically ill due to polypharmacy and impaired drug metabolism [13]. One observational study of 309 intensive care unit (ICU) patients found that 24 patients (7.8%) met criteria for serotonin syndrome [13]. Mortality can be severe and is primarily related to hyperthermia [3,14,15]. Studies suggest that of approximately 7300 diagnosed cases per year, approximately 100 patients die [14,15].

Failure to diagnose serotonin syndrome can lead to significant issues other than increased morbidity and mortality, as misdiagnosis may lead to inappropriate disposition (e.g., psychiatric facility) [16]. The continuation of serotoninergic home medications and potential addition of serotonergic medications while admitted can worsen serotonin syndrome leading to harm, most famously in the case of Libby Zion who died from serotonin syndrome [17]. A retrospective study of seven cases of serotonin syndrome in patients admitted to a medical floor found that five out of seven patients were initially admitted under the diagnosis of worsening of a psychiatric illness, and two out of seven were diagnosed with gastroenteritis [16]. In one study of ICU patients, 75% of patients had received a serotonergic medication after admission to ICU [13]. Given that several common medications used in the inpatient setting are potentially serotoninergic (e.g., fentanyl, ondansetron, linezolid, and tramadol), failure to diagnose serotonin syndrome or recognize potential medications reactions could lead to the development or worsening of serotonin syndrome [13].

2. Discussion

2.1. Presentation

Patients with serotonin syndrome most commonly experience symptoms within 12–24 h after medication exposure or dose adjustment. The classic triad of serotonin syndrome includes 1) neuromuscular excitation, 2) autonomic dysfunction, and 3) altered mental status (Fig. 1) [4,6,7,18-20]. Neuromuscular hyperactivity includes hyperreflexia, clonus, hyperkinesis, akathisia, and rigidity [4]. Clonus, a form of profound hyperreflexia, is a common feature of serotonin syndrome [3,4,9]. This is typically inducible and most prominent in the legs [9]. Opsoclonus and spontaneous clonus may also occur [2]. The absence of clonus is suggestive of another etiology [4,20]. Autonomic dysfunction includes hyperthermia, hypertension/hypotension, tachycardia, diaphoresis, flushing, mydriasis, nausea, vomiting, and diarrhea [5]. Mental status changes include anxiety, delirium, seizure, and coma [5]. Severe serotonin syndrome includes seizures, rhabdomyolysis, end organ injury, and extreme hyperthermia [3,21]. Mild cases of serotonin may have a more subtle presentation, with tremor, headache, dizziness, insomnia, and restlessness being the initial presenting symptom in a case series of mild cases managed in a neurology outpatient clinic [22]. All patients in this cases series demonstrated hyperreflexia and tremor, and 42% of patients demonstrated clonus, increased muscle tone, tachycardia, and nystagmus on examination [22]. A critical component of the history in suspected cases includes overdose of a serotonergic agent, recent addition of a new medication with serotonergic properties, or dose increase of a chronic medication [19,20]. As more severe cases can present with delirium and coma, history from the patient may be difficult to obtain. In cases where history is limited, it is critical to review prior records for medication history, psychiatric history, and to also obtain information from family, friends, or emergency medical services personnel.

2.2. ED evaluation

The diagnosis of serotonin syndrome is based on clinical history and physical examination. There is no diagnostic laboratory or radiologic

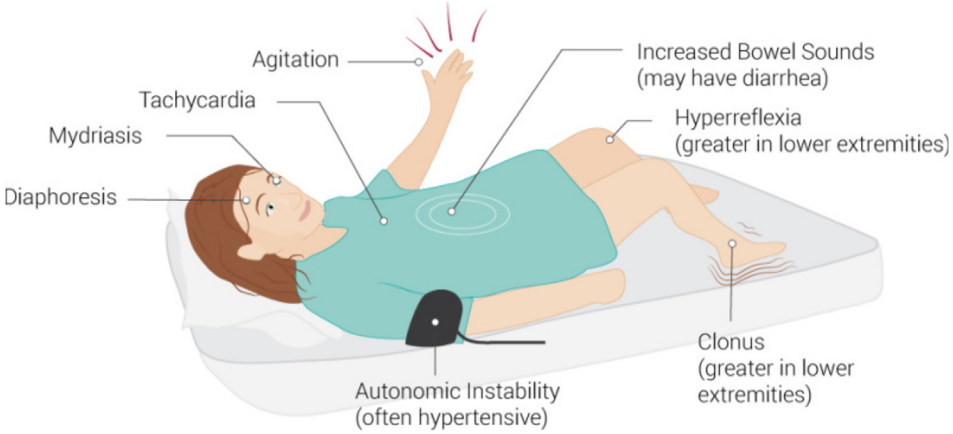

Fig. 1. Presentation of Serotonin Syndrome. From https://commons.wikimedia.org/wiki/File:SerotoninSyndrome.jpg.

test, and the history and examination determine the need for focused testing with laboratory and imaging assessment [20]. In a patient with a fever, potential alternative causes such as infectious or endocrinologic etiologies should be evaluated with complete blood cell count (CBC), electrolytes, renal and liver function, urinalysis, chest x-ray, blood cultures, and thyroid stimulating hormone (TSH) as clinically indicated [3,4,7,20]. Similarly, those with altered mental status (AMS) or evidence of head trauma should undergo non-contrast head computed tomography, while those with AMS and fever may need a lumbar puncture [20]. A drug history is important to ascertain the use of serotonergic medications, psychiatric medications, over the counter medications, and illicit drugs, as well as any changes in medications [19,20]. In patients with suspected serotonin syndrome, laboratory evaluation should include CBC, electrolytes, renal and liver function, lactic acid level, coagulation panel, and creatine kinase (CK) level (i.e., rhabdomyolysis) [20,23]. Laboratory testing may reveal leukocytosis, elevated CK, lactic acidosis, renal injury, liver enzyme elevation, hyponatremia, and disseminated intravascular coagulation. For patients with possible co-ingestions, an acetaminophen and aspirin level should be obtained [19]. An ethanol level and a urine drug screen (UDS) can be considered, although the clinician should exercise caution when interpreting the results of a UDS. A UDS does not distinguish between acute and chronic drug use, it has many false-positive or false-negative results, and it does not rule-in or rule-out serotonin syndrome [24-27]. An electrocardiogram should be obtained to evaluate QRS duration for possible signs of co-ingestions such as TCAs or diphenhydramine, as well as the QT duration for possible signs of QT prolonging medications [24,27].

2.3. ED management

The components of ED management of serotonin syndrome consist of stopping offending agents, supportive care, and decontamination [3,28]. Supportive care includes controlling agitation, monitoring for and treating hyperthermia, and treating autonomic instability. ED clinicians should consider toxicology or poison center consultation for serotonin syndrome, particularly in overdose patients [21,29]. Consultation with the psychiatric specialist may also be required after the patient is stabilized. Patients with serotonin syndrome should be placed on continuous monitoring of heart rate and pulse oximetry [19]. Mild cases, such as those with only inducible clonus and restlessness without delirium, may only require observation for symptomatic improvement [22,30]. Moderate to severe cases often require benzodiazepines and cyproheptadine for treatment of autonomic instability and agitation [3,18,29]. Intravenous fluids should be administered to treat rhabdomyolysis or hypotension if present, and electrolyte abnormalities should be corrected if present [23,29]. Antihypertensives may be required if the patient has hypertension refractory to therapy with benzodiazepines. Control of hyperthermia with physical cooling is necessary [20]. Extreme hyperthermia is life-threatening and may lead to seizure, acidosis, rhabdomyolysis, end organ injury, and disseminated intravascular coagulation [20]. Intubation for airway protection with sedation and paralysis using a non-depolarizing paralytic may be necessary, particularly if the patient is seizing or has extreme hyperthermia [9,21,30,31]. Disposition depends on the severity of the hyperthermia, mental status, ability to identify offending agents, and psychiatric needs of the patient. In patients with autonomic instability or hyperthermia, admission to an intensive care unit setting is recommended.

3. Pearls and pitfalls

3.1. What are high-risk situations or medications associated with serotonin syndrome?

The emergency clinician should consider serotonin syndrome in patients after overdose of serotonergic agents and patients with polypharmacy who have altered mental status, particularly if physical examination findings are suggestive of serotonin syndrome (see discussion below) [2,10,13,28,32]. Evidence of hyperreflexia and clonus, as well as autonomic changes, are concerning for serotonin syndrome [20]. Medications that are high risk for serotonin syndrome have changed over time as the medications used to treat depression have changed [1-3,5]. While many of the patients originally described as having serotonin toxicity were on monoamine oxidase inhibitors (MAOI), those drugs are now less common than SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRI) [1]. A 2019 review of the Toxicology Investigators Consortium (ToxIC) registry found the most common single agents associated with serotonin syndrome included sertraline, dextromethorphan, citalopram, bupropion, and fluoxetine [7]. Other drugs associated with serotonin syndrome include tramadol, trazodone, lamotrigine, and fentanyl [7]. Emergency clinicians should consider serotonin syndrome in patients with overdose of serotonergic medications including SSRIs, SNRIs, tramadol, linezolid, fentanyl, and methylene blue (Table 1), as well as in patients on multiple serotonergic medications [3,7,11,18,33-38].

The risk of developing serotonin syndrome after therapeutic ingestion of a prescribed serotonergic agent is unknown but thought to be low [7,39,40]. One study of patients taking the antidepressant nefazodone reported an incidence of 0.5–0.9 cases per 1000 person-months of treatment, while a study of patients on triptans and SSRIs or SNRIs reported an incidence of 0.6–3.9 cases per 10,000 person-years [12,41]. The incidence of serotonin syndrome after overdose of a single serotonergic agent is estimated to be around 14–16% [2,12]. As discussed, commonly used SSRIs such as sertraline, citalopram, and fluoxetine are common causes of serotonin syndrome in overdose [2]. Of the SSRIs, vilazodone in particular has high risk of causing serotonin syndrome due to its 5HT-1 partial agonism and reuptake inhibition, with case reports of pediatric patients developing serotonin syndrome from a single dose [42-45]. Bupropion, while not a true SSRI, can cause serotonin syndrome [46]. Bupropion is cathinone with structural similarity to methamphetamine and is a norepinephrine-dopamine reuptake inhibitor frequently implicated in poison center databases and case reports as a cause of serotonin syndrome [7,46,47]. Although not commonly used, MAOIs such as phenelzine and moclobemide are frequently associated with serotonin syndrome [5,31]. TCAs such as imipramine have also been associated with serotonin syndrome in polypharmacy and have a different presentation as a single-agent overdose, primarily as a anticholinergic toxidrome with wide complex tachydysrhythmias [48,49].

There are many other serotonergic agents that increase the risk of serotonin syndrome. Dextromethorphan is a common over-the-

Table 1
Drugs associated with serotonin syndrome [3,7,18,25].

Class	Medications
Psychiatric	SSRIs and SNRIs: citalopram*, fluoxetine*, sertraline*, venlafaxine, vilazodone MAOIs: phenelzine, rasagiline, selegiline TCAs: clomipramine, imipramine Others: bupropion*, trazodone, buspirone, lithium
Antiepileptics	Lamotrigine, carbamazepine, valproate
Antiemetics^	Ondansetron, granisetron, metoclopramide
Anti-migraine	Triptans, ergotamine, methylergonovine
Opioids	Fentanyl, meperidine, methadone, dextromethorphan, tramadol*
Illicit Drugs	Methamphetamine, amphetamine, ecstasy (MDMA), psilocybin, LSD
Miscellaneous	Linezolid, cyclobenzaprine, methylene blue, St. John's Wort, fluconazole, chlorpheniramine

Abbreviations: selective serotonin reuptake inhibitors (SSRI); serotonin-norepinephrine reuptake inhibitors (SNRI); monoamine oxidase inhibitors (MAOI); tricyclic antidepressants (TCA); 3,4-Methylenedioxymethamphetamine (MDMA); lysergic acid diethylamide (LSD).
* Indicates the top 5 agents implicated in serotonin syndrome.
^ It is controversial whether or not 5HT-3 antagonists like ondansetron cause serotonin syndrome.

counter cough suppression medication that can cause serotonin syndrome with polypharmacy [36,50,51]. Tramadol has been associated with serotonin syndrome in isolated overdoses as well as polypharmacy [51-54]. Tramadol can inhibit serotonin reuptake, and its metabolism by CYP450 may impact the risk of serotonin syndrome [36,51-54]. In 2006 the FDA released an advisory about the risk of serotonin syndrome in patients on triptans and SSRIs/SNRIs, since triptans were noted to have some affinity for 5HT receptors [12]. A database study of over 19,000 patients co-prescribed triptans and an SSRI or SNRI identified 17 cases of serotonin syndrome [12]. Only seven cases occurred during a year when the medications were co-prescribed, with the other ten cases occurring during a time frame when the patient was on a single agent, suggesting an overall low risk of serotonin syndrome when triptans and SSRIs/SNRIs are taken together [12]. Ondansetron has been associated with serotonin syndrome, as 5HT-3 antagonism may lead to increased serotonin reuptake, although some have argued this mechanism is theoretical and the association unclear [3]. Some antiepileptics, such as lamotrigine, are also associated with serotonin syndrome, although risk in population-based studies is low [37].

There are several serotonergic medications used in the ED or critical care setting that increase the risk of serotonin syndrome. Fentanyl and meperidine are piperidine opioids that are thought to have serotonin reuptake inhibition properties [11,25,51,55]. A retrospective study compared 107,507 admitted patients at a tertiary hospital who received a serotonergic agent but did not receive fentanyl and 4538 patients receiving a serotonergic agent and fentanyl [11]. Authors identified four patients in the fentanyl and serotonergic agent group meeting Hunter's criteria for serotonin syndrome (incidence of 0.09%) and five patients in the serotonergic agent alone group (incidence of 0.005%) [11]. Although this suggests a low-overall incidence of serotonin syndrome from fentanyl, there is likely an increased risk of development in patients on multiple serotonergic agents [11]. Linezolid is an oxazolidinone antibiotic with reversible MAOI properties that can cause serotonin syndrome [35,56]. A study of the FDA Adverse Event Reporting System (AERS) identified 29 cases of serotonin toxicity in patients on linezolid, though all patients were on other serotonergic agents [35]. An oxazolidinone muscle relaxant, metaxalone, which is structurally related to linezolid, has also been reported to cause serotonin syndrome in overdose [57,58]. Methylene blue, which is used to treat postoperative vasoplegia and methemoglobinemia, has MAOI properties and has been reported to cause serotonin syndrome [38].

Illicit drugs that increase serotonin release and uptake can also cause serotonin syndrome, either with recreational use or in overdose [7]. Amphetamines, methamphetamine, cocaine, and “bath salts” have been associated with serotonin syndrome, likely due to indirect signaling of dopamine and norepinephrine [7,26,59]. Ecstasy (MDMA) and psilocybin are thought to increase the risk of serotonin toxicity as they directly act on the serotonin receptor [7,59].

Some drugs with CYP inhibitor properties such as St. John's Wort and fluconazole may increase the concentration of serotonergic drugs [60,61]. Additionally, lithium may increase serotonin receptor sensitivity, which may result in serotonin syndrome [18,19,62].

3.2. What are physical examination findings that suggest serotonin syndrome?

The physical examination findings in serotonin syndrome include spontaneous or inducible clonus, ocular clonus, tremor, hyperreflexia, increased muscle tone, and agitation (Table 2) [2]. Clonus is usually inducible and most prominent in the legs, though it can involve the whole body [9,30]. Opsoclonus is defined by involuntary, multidirectional eye movements and is common in serotonin syndrome [9,10]. These can be triggered by eye movement or be continuous, and they may be fine or coarse [9,10]. Spontaneous clonus includes rhythmic, large muscle contractions [10]. The absence of clonus suggests against the diagnosis of serotonin syndrome, though in severe cases, clonus can lead to severe rigidity [9,30]. Patients with underlying neurologic disease may not demonstrate clonus, and in those with tremor, clonus can be difficult to ascertain [63]. One study found mydriasis and tachycardia are common, occurring in approximately 32% and 40% of patients, respectively [2]. However, these are common in other toxidromes, including anticholinergic and sympathomimetic toxidromes, and thus they were not included the original Hunter criteria [2]. Tachycardia may not be useful as a diagnostic sign in serotonin syndrome but is useful in determining prognosis and response to treatment [2]. A retrospective study of 1010 cases from the ToxIC database found that clonus and hyperreflexia were the most common physical examination findings present in 60% of patients [7]. Other common findings include agitation in 33%, coma in 25%, and rigidity in 14% of patients [7]. In this study, 16% of patients required intubation, and 3% demonstrated temperatures over 40 °C (104.4 °F), though the mortality was 0.1% [7]. This study also noted that seizures were more common in bupropion, citalopram, and fluoxetine overdoses compared to dextromethorphan and sertraline [7]. A prospective observational study of patients admitted to the ICU, none of whom diagnosed with serotonin syndrome by the treating clinician, evaluated for patients meeting the Hunter criteria and the presence of serotonergic agents [13]. Hyperreflexia and tachycardia were the most common clinical characteristics, present in 92% of patients [13]. Less common physical examination findings were nystagmus (13%) and diarrhea (4%) [37]. A systematic review of published serotonin syndrome cases found that fever is not universally present, with up to 27% of severe cases remaining afebrile [3].

3.3. What are the strengths and weaknesses of the diagnostic criteria?

Several criteria are available for use in evaluating serotonin syndrome. The Sternbach criteria were first created in 1991 based upon a literature review of the published case reports at that time [1]. Cases were primarily among inpatients in psychiatric facilities who were on multiple medications. The criteria included clinical signs and symptoms such as hyperreflexia, tremor, diarrhea, agitation, and hyperthermia [1]. The criteria excluded patients with recent neuroleptic administration and required that other causes of symptoms be excluded [1]. Issues with the Sternbach criteria include the non-specific nature of the criteria, including components such diaphoresis, fever, and agitation that may be present in other diseases and toxidromes of catecholamine excess [63]. Review of an additional 24 cases led to the development of the Radomski criteria [5]. Symptoms were categorized into mental, neurological, and vegetative with major and minor criteria for each to better characterize the spectrum of serotonin syndrome [5]. Advantages of the Radomski criteria include major and minor criteria to stratify the severity of serotonin syndrome [63]. A weaknesses of both the Sternbach and Radomski criteria is that many of the patients used to derive these criteria were on MAOI medications that are less commonly used, and thus these criteria do not reflect the current epidemiology of serotonin syndrome [63]. The Hunter Criteria were later derived from 473 patients who had overdosed on a single SSRI [2]. Although rigidity was not present in any of the patients evaluated for the Hunter Criteria, the authors included it in their decision rule because it was felt to be clinically important [2,21]. After the criteria were developed, they were compared

Table 2
Physical examination findings in serotonin syndrome [3,4,7,1] [3].

Physical Examination Findings	Frequency of Occurrence (%)
Tachycardia	35–92
Clonus	60–79
Hyperthermia (Temp >100.4F)	64–75
Rigidity	14–45
Seizure	14–36
Coma	25–33
Mydriasis	17–32
Diarrhea	4–9

Table 3
Comparison of the diagnostic criteria for serotonin syndrome.

	Sternbach	Radomski			Hunter
Patients studied	38 patients from case reports	62 patients from case reports			473 patients from a single center after overdose of a single SSRI
Signs / Symptoms	At least three of the following: • Confusion • Agitation • Incoordination • Diaphoresis • Shivering • Tremor • Fever • Hyperreflexia • Clonus • Diarrhea	At least four minor symptoms or three major plus two minor			If any of the following criteria are met: 1. Spontaneous clonus 2. Inducible clonus and agitation OR diaphoresis 3. Ocular clonus and agitation OR diaphoresis 4. Tremor and hyperreflexia 5. Hypertonic/rigid and temp >38C and ocular clonus or inducible clonus
			Major	Minor	
		Mental	• Coma • Impaired mental status • Elevated mood	• Restlessness • insomnia	
		Neurologic	• Myoclonus • Hyperreflexia • Shivering • Tremor • Rigidity	• Discoordination • Dilated Pupils • Akathisia	
		Vegetative	• Fever • Sweating	• Diarrhea • Tachycardia • Tachypnea • Hypertension or hypotension	

among a larger set of patients who had overdosed on at least one serotonergic agent [2]. They found that when compared to a gold standard of diagnosis by a toxicologist, the Hunter Criteria had a sensitivity of 84% and specificity of 97% compared to the Sternbach criteria which had a sensitivity of 75% and specificity of 96% [2]. Of note, the Hunter criteria may be inaccurate in patients with peripheral neuropathies as they may not display many of the upper motor neuron signs in the criteria like hyperreflexia [63]. Another disadvantage of the Hunter criteria is that it shares many features with neuroleptic malignant syndrome such as hyperthermia and rigidity [63]. Table 3 compares the different criteria for the diagnosis of serotonin syndrome [1,2,5].

3.4. What are other alternative diagnoses that must be considered?

Serotonin syndrome has clinical features that overlap with several other potentially life threatening toxicologic, psychiatric, neurologic, infectious, and endocrinologic disorders (Table 4) [10,13,19,20,27,32]. Infectious etiologies of fever and altered mental status (e.g., sepsis, spinal infection, meningitis, and encephalitis) should be considered [27,64]. Thorough medication histories, including any illicit drug use and potential toxin exposures, should be obtained as there are several toxicologic causes of hyperthermia and altered mental status [20,27]. Neuroleptic malignant syndrome may be confused with serotonin syndrome, particularly in patients on multiple psychiatric medications [20,23,28]. The time course of neuroleptic malignant syndrome is much slower, developing over a few weeks of antipsychotic exposure and is associated with more rigidity and no hyperreflexia or clonus compared to serotonin syndrome that develops in hours to days after overdose or after a new serotonergic agent is introduced [20,27,28]. Hyperthyroidism may also cause hyperthermia, autonomic dysfunction, and brisk reflexes [30,66,67]. While stroke rarely cause hyperthermia, it should be considered particularly in altered patients. Psychiatric illness such as malignant catatonia can cause altered mental status and abnormal movements that may overlap with serotonin syndrome [10,32]. Mild cases of serotonin syndrome might be misdiagnosed as generalized anxiety, viral syndrome, or migraine [22].

3.5. What are the key components of management?

Supportive care and discontinuation of offending agents are the key components of management of serotonin syndrome. Treating agitation, monitoring for and treating hyperthermia, and managing autonomic instability are the cornerstones of supportive care. Benzodiazepines are a mainstay of treatment for agitation, seizures, and hyperthermia in serotonin syndrome [21,27-29]. Mechanistically benzodiazepines counteract the serotonin-induced adrenergic signaling which reduces autonomic instability, suppresses seizure foci, and relaxes muscle contractions that generate heat [3,30]. Benzodiazepines have many advantages such as multiple routes of administration and fast time of onset if given intravenously [19,20]. There are no guidelines or randomized trials to guide the dosing of benzodiazepines in serotonin syndrome [30]. If seizures develop benzodiazepines can be dosed similarly to benzodiapines [72]. Additional options for control of agitation include dexmedetomidine, as it has sedative properties and may modulate serotonin activity, although there might be limited availability of this agent in the ED. [73] A case series of three pediatric patients who had persistent hyperreflexia and hypertension despite being on midazolam infusions had improvement once transitioned to dexemedatomidine [73]. Another case report of a vilazodone overdose in a pediatric patient used dexmedetomidine as a benzodiazepine sparing agent, and the authors noted they were able to adequately treat agitation without having to intubate the patient [45]. Dexmedetomidine used to treat serotonin syndrome was used as an infusion typically in the range of 0.2–1.0 μg/kg/h [73].

The mechanism of hyperthermia in serotonin syndrome in animal models is thought to be due to brown fat thermogenesis and excessive muscle contractions from increased serotonergic and adrenergic signaling [20]. Cyproheptadine has anticholinergic properties that may theoretically worsen hyperthermia and as discussed below has limited utility in the critically ill patient with serotonin syndrome [29]. Evidence from the general management of drug induced hyperthermia suggests that decreased time to normothermia improves survival [27,74]. Benzodiazepines will improve mild hyperthermia due to muscle relaxation [20]. Antipyretics such as acetaminophen do not have a role in drug induced hyperthermia as the elevated temperature is not mediated by the hypothalamus, unlike in fever from an infectious cause [20,74]. For mild hyperthermia (38–40 °C), physical cooling with cooling blankets, ice packs, fans should be performed [74]. Temperatures in excess of 41 °C are life threatening and require rapid cooling including ice-immersion [74,75]. Intubation may be necessary in the setting of extreme agitation or hyperthermia [25,30,46,67,76]. The timing of these interventions depends on the clinical scenario and the resources available at the treating ED. [74,75] External cooling should be started immediately in all patients with severe hyperthermia [74,75]. While ice-baths are often regarded as superior and experts have recommended that IV access, benzodiazepine administration, and even intubation can all occur while in an ice-bath, depending on clinician experience and comfort level, evaporative cooling may be logistically easier to perform if these other interventions are necessary [74,75]. Based on other hyperthermic conditions, external cooling should be performed with a goal core temperature of 39 °C [74]. If hyperthermia

Table 4
Differential diagnosis of serotonin syndrome.

Disease	Distinguishing Features
Neuroleptic Malignant Syndrome	-Occurs within days to weeks of exposure to dopamine antagonists and dopamine withdrawal [10]. -Presents with "lead-pipe" rigidity, slow movements, bradyreflexia, and mutism [10,32]. -Patients have neuromuscular hypoactivity and normal pupils or mydriasis [10,32].
Malignant Hyperthermia*	-Acute development after inhaled anesthetics like halothane or depolarizing paralytics such as succinylcholine [67]. -Presents with hyperthermia with temperatures >104 F, rigidity is common, but pupils are normal [67]. -Patients have rigor-mortis like rigidity and hyporeflexia [67]. -Laboratory analysis demonstrates metabolic acidosis and elevated CK [67].
Malignant Catatonia*	-Patients will have slow movements and rigidity without history of antipsychotic exposure [10]. -"Waxy flexibility" with the limbs able to be passively manipulated into postures that the patient will hold for prolonged periods [10]. -Fever, tachycardia, and labile blood pressure can all be present [10].
Acute Dystonic Reaction	-Usually develops within 5 days of receiving a dopamine antagonist (e.g., antipsychotic, metoclopramide, prochlorperazine). -Oculogyric crisis can present with fixed stare [10,32]. -May present with opisthotonos, blepharospasm, and/or laryngeal spasm but no opsoclonus [10]. -Patients typically do not demonstrate tachycardia, hyperreflexia, or tachycardia [10].
Anticholinergic Toxicity	-Anticholinergic medication exposure with bladder retention, hyperthermia with dry skin, dry mucous membranes, tachycardia, and hypertension but no hyperreflexia and normal muscle tone [27]. -Patients may demonstrate hypervigilance, hallucinations, and delirium with mumbling speech [27]. -Many drugs have anticholinergic effects such as antihistamines, antiparkinsonian drugs, belladonna alkaloids, and atropine [27].
Sympathomimetic Toxicity	-Presents after ingestion of sympathomimetic substance with fever, tachycardia, hypertension, confusion, diaphoresis, and mydriasis [27]. -Patients do not typically have hyperreflexia or clonus [6]. -Some sympathomimetics like MDMA are also serotonergic, and some sympathomimetics may be used with a serotonergic agent (e.g., cocaine and fentanyl) [27].
Strychnine Toxicity*	-Uncommon poisoning associated with rodenticides and some Chinese herbal remedies (e.g., Miqianzi) [68]. -Presents with uncontrolled muscle contractions, hyperthermia, and tachycardia [68]. -Mental status preserved until critical hyperthermia and lactic acidosis develop [68].
Tetanus*	-Uncontrolled muscle spasms, lockjaw, autonomic instability, and alternating tachycardia and bradycardia [69]. -In adults typically develops from infected wounds [69].
Sedative-Hypnotic Withdrawal	-Baclofen, benzodiazepine, and alcohol withdrawal can produce tachycardia, hypertension, anxiety, diaphoresis, nausea/vomiting, and altered mental status [26,70]. -Seizures more common in withdrawal [26]. -Baclofen withdrawal can cause spasticity [70]. -Fevers can be present but are uncommon. -Patients should not have clonus [70].
Sepsis	-Fever, tachycardia, and altered mental status can be present in sepsis [27]. -Typically presents with evidence of an infection focus [27]. -Unlikely to have clonus or hyperreflexia [27].
Meningitis/Encephalitis	-Fever, tachycardia, altered mental status, and neck stiffness are common presentations [19,27]. -Unlikely to have clonus or hyperreflexia [27].
Stroke	-Neurologic deficit and hyperreflexia will present in a focal neurologic distribution [71]. -Fever can occur from stroke, although it usually develops after acute presentation [66]. -History of acute onset and other symptoms such as weakness or numbness [66,71].
Thyroid Storm	-Tachycardia, altered mental status, and hyperthermia are common [65]. -May have brisk reflexes [65]. -Opsoclonus and spontaneous clonus are uncommon [65].

Abbreviations: creatine kinase (CK); 3,4-Methylenedioxymethamphetamine (MDMA).
* Indicates rare diseases that can mimic serotonin syndrome, but they are uncommon ED diagnoses.

is refractory to external cooling and benzodiazepines, intubation and paralysis should be performed, even in the absence of airway compromise, in order to control repeated muscle contractions that contribute to hyperthermia [27,74]. Non-depolarizing agents for paralytics are preferred (e.g., rocuronium), as succinylcholine may theoretically worsen muscle contraction and rhabdomyolysis [30]. Fentanyl should be avoided for induction and post-intubation sedation as it may theoretically worsen serotonin syndrome, and other agents such as propofol, midazolam, ketamine, or dexmedetomidine should be used instead [25,55]. Other than severe hyperthermia, intubation should be considered in serotonin syndrome in cases of uncontrollable agitation, status epilepticus, or respiratory failure from chest wall rigidity [21].

Autonomic instability can manifest as hypotension, hypertension, or tachycardia [15]. Benzodiazepines and dexmedetomidine will blunt the catecholamine response that drives some of the autonomic instability from serotonin syndrome, and benzodiazepines are the recommended first-line therapy for patients with hypertension and tachycardia associated with serotonin syndrome [30,73]. Beta-blockers, calcium channel blockers, and nitroglycerin have limited roles in treating hypertension and tachycardia in serotonin syndrome based on available literature but may be considered in patients refractory to other therapies (e.g., benzodiazepines) [77]. One systematic review consisting primarily of case reports found little to no effect with beta-blockers such as metoprolol or labetalol on treating hypertension in serotonin syndrome [77]. This systematic review did discuss several case reports that found diltiazem to be effective at treating hypertension, while other calcium channel blockers such as nicardipine had less of an effect [77]. There is little evidence to guide the treatment of hypotension in serotonin syndrome. Intravenous fluids should be administered initially, but in patients with hypotension refractory to IV fluids, a vasopressor such as norepinephrine should be initiated [77].

3.6. What role do antidotes such as cyproheptadine possess in serotonin syndrome?

Cyproheptadine is an oral antihistamine with some serotonin antagonistic properties that can be used for serotonin syndrome, but it is not necessarily an integral component of management [29]. Recommendations for dosing of cyproheptadine range from initial doses of 4–12 mg (administered orally), followed by 1–4 mg every 2–4 h until symptoms resolve or a maximum dose of 32 mg in 24 h is administered [29,46]. There are several limitations to cyproheptadine. Because it is only available via the oral route, it may be difficult to administer in an altered patient [3,29,30]. Additionally, critically ill patients may have delayed gastric absorption, and cyproheptadine reaches peak serum levels 6–9 h after ingestion in healthy volunteers, implying its action may be

Table 5
Serotonin syndrome pearls.

- Serotonin syndrome is characterized by 1) neuromuscular excitation such as tremor, hyperreflexia, and clonus; 2) autonomic dysfunction such as tachycardia, hypertension/hypotension, and hyperthermia; and 3) altered mental status such as agitation, delirium, and coma.
- Serotonin syndrome can develop after overdose of a single serotonergic agent or therapeutic doses of multiple serotonergic agents.
- Common physical examination findings include hyperthermia, tachycardia, hyperreflexia, and clonus, though mild cases may present in a subtle manner with tremor, headache, dizziness, insomnia, and restlessness.
- The differential diagnosis includes neuroleptic malignant syndrome, malignant hyperthermia, sympathomimetic toxicity, anticholinergic toxicity, sedative-hypnotic withdrawal, sepsis, stroke, and thyrotoxicosis.
- While there are a variety of criteria, the Hunter criteria are the most relevant in the ED setting.
- Components of treatment include controlling agitation, monitoring for and managing hyperthermia, and treating autonomic instability.
- Cyproheptadine is not associated with improved outcomes in critically ill patients with serotonin syndrome, though it may be used in mild to moderate cases. Benzodiazepines can assist with treatment of neuromuscular excitation, autonomic dysfunction, and agitation.

delayed in the critically ill patient [29]. Cyproheptadine also has antihistaminic and anticholinergic side effects that may obscure clinical improvement when treating serotonin syndrome, by causing some tachycardia and hyperthermia [29]. A retrospective study including cases of possible serotonin syndrome did not show any association between cyproheptadine administration and improved outcomes, although this study possesses multiple limitations including bias and confounders [29]. Cyproheptadine is a reasonable choice for mild cases but has limited utility in moderate to severe cases.

Anti-serotonergic medications such as olanzapine and risperidone have been utilized to treat serotonin syndrome, but conflicting reports suggest they may cause serotonin syndrome and are not recommended [33,78]. Chlorpromazine may be used to treat serotonin syndrome due to serotonin antagonist properties, but it may cause hypotension and thus is not a preferred agent [20,30]. Dantrolene has not been proven to be effective in serotonin syndrome and should not be used [20,30]. Table 5 provides a summary of pearls concerning serotonin syndrome.

4. Conclusion

Serotonin syndrome is an uncommon diagnosis defined by neuromuscular excitation such as tremor, hyperreflexia, and clonus; autonomic dysfunction such as tachycardia, hypertension/hypotension, and hyperthermia; and altered mental status such as agitation, delirium, and coma. It is associated with increased serotonin receptor activity or neurotransmission. A variety of medications are associated with serotonin syndrome, including sertraline, bupropion, tramadol, dextromethorphan, fentanyl, and linezolid. Physical examination findings such as spontaneous clonus, hyperreflexia, altered mental status, and hyperthermia suggest the disease, but there are a variety of mimics. Components of therapy include stopping the offending agent and supportive care, which focuses on agitation control, monitoring for and treating hyperthermia, and managing autonomic instability. Severe cases will require external cooling, sedation, and possibly muscle paralysis and intubation. Mild cases may present with just tremor, restlessness, dizziness, or headache. Unfortunately, delays in identification may lead to misdiagnosis and disease progression to worsening hyperthermia, rhabdomyolysis, seizures, and death, and thus emergency clinicians must consider this diagnosis in the ED.

CRediT authorship contribution statement

Anthony Spadaro: Writing – review & editing, Writing – original draft. **Kevin R. Scott:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Alex Koyfman:** Visualization, Supervision, Conceptualization. **Brit Long:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization.

Declaration of Competing Interest

None.

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