

ICD-10-CM: Serotonin Syndrome Proposal Overview

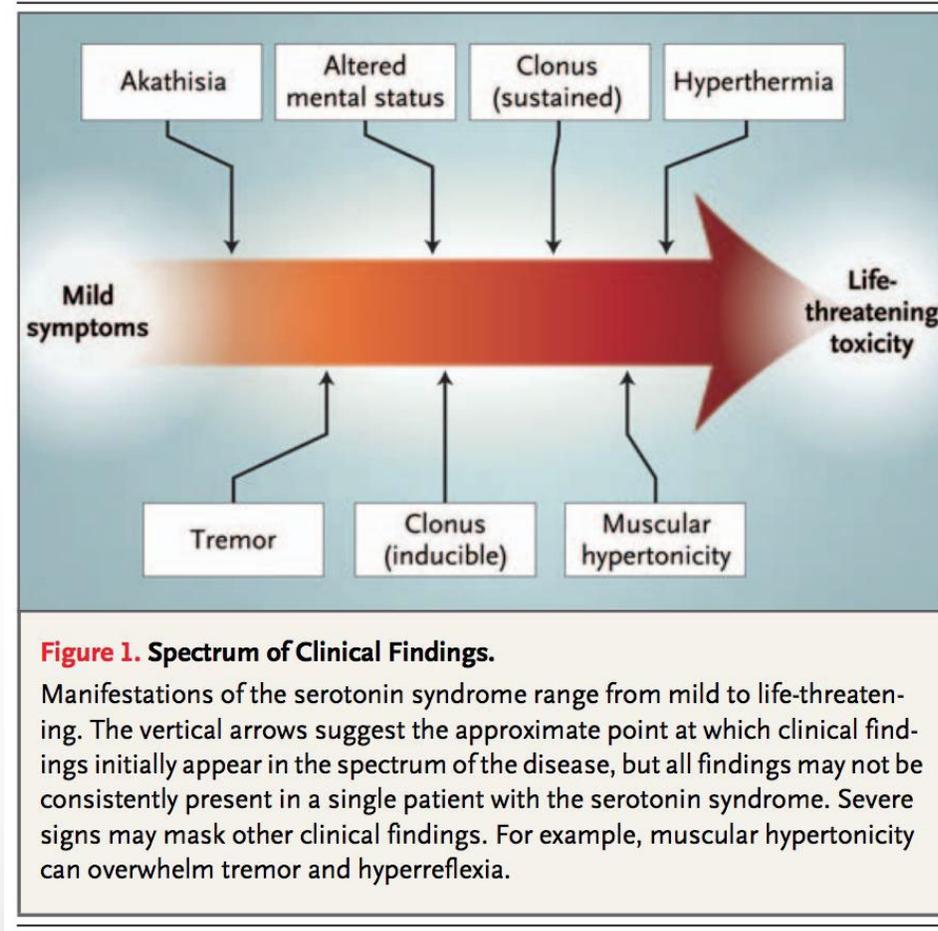
ICD-10 Coordination and Maintenance Meeting
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Spectrum of Clinical Findings

- The serotonin syndrome is characterized by a clinical spectrum of nonspecific signs and symptoms
- More mild cases are likely overlooked or missed because of overlap of clinical presentation with more common medical conditions
- If unrecognized, the serotonin syndrome can be life-threatening



- Wide range of clinical symptoms from mild tremor to life-threatening hyperthermia and shock
 - Diaphoresis, nausea/vomiting, diarrhea, headache, hallucinations, tremor
- Neuromuscular findings typically more pronounced in lower extremities
- More systemic (and severe) clinical manifestations include seizures, coma, disseminated intravascular coagulation, hypotension, ventricular tachycardia, metabolic acidosis

Examination findings:

Hyperthermia, agitation, ocular clonus, tremor, akathisia, deep tendon hyperreflexia, inducible or spontaneous clonus, muscle rigidity, dilated pupils, dry mucus membranes, increased bowel sounds, flushed skin, diaphoresis

Findings in a Patient with Moderately Severe Serotonin Syndrome

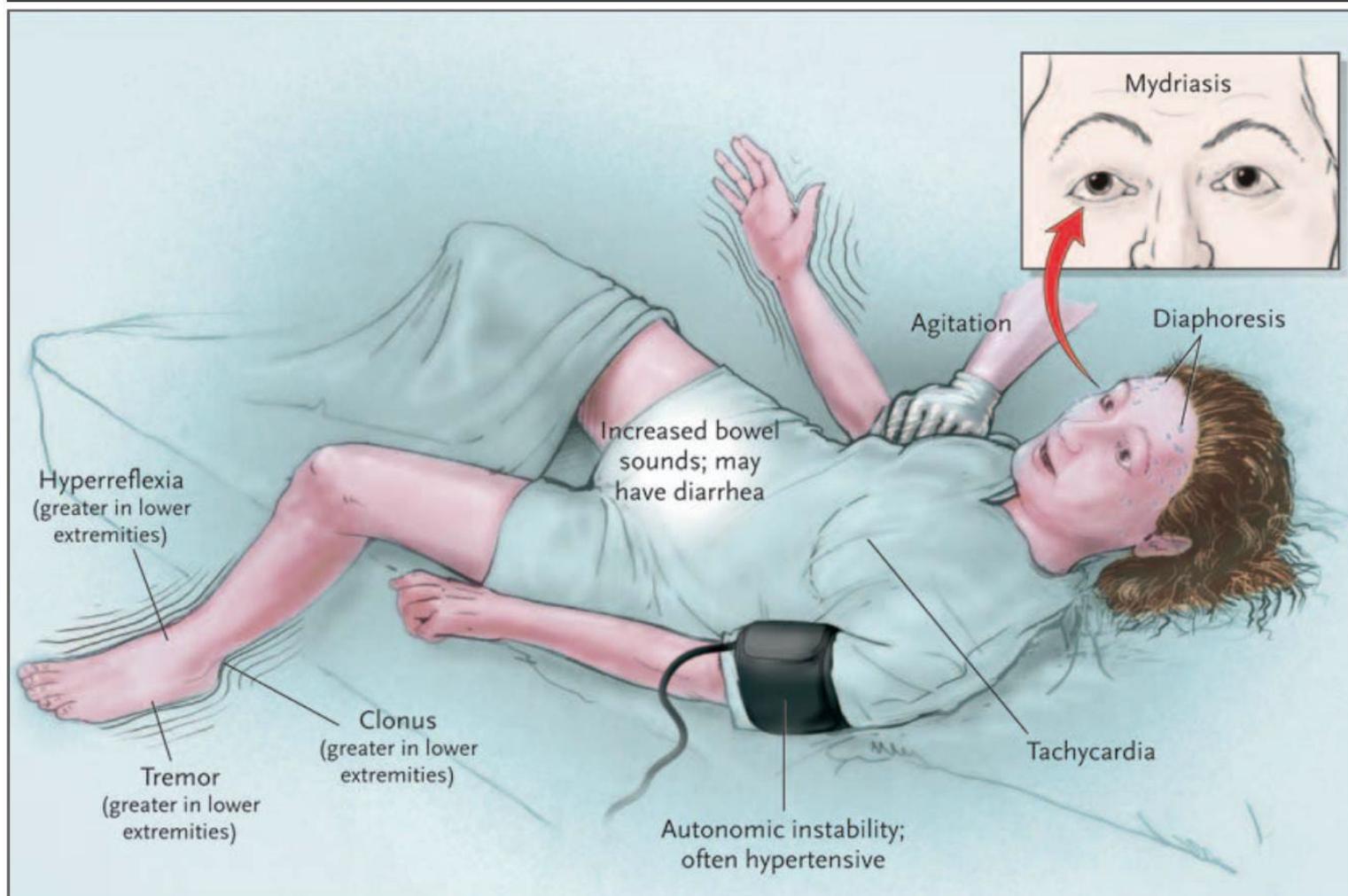


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

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

Boyer, Edward W., M.D., PhD. and Michael Shannon, M.D., M.P.H. *N Engl J Med* 2005;352:1112-20.

Increasing Incidence

- Percentage of adults taking antidepressants in the U.S. nearly doubled between 1999 and 2010
 - Increased from 6% to 10.4%
- Large case series suggest moderate Serotonin Syndrome occurs in ~15% of poisonings with SSRIs
- Common perception of multidrug etiology
- Drugs used for different medical conditions (antibiotics, pain medications, anti-emetics, migraines, etc.) can have a deleterious additive effect
- Recent study found close to half of U.S. FDA Adverse Event Reporting System Serotonin Syndrome reports involved single drug
- True incidence and severity of cases is unknown
 - Relatively uncommon condition
 - Under-recognized and under-reported
 - In one survey, majority of general physicians unfamiliar with condition
 - Mild cases often dismissed or self-limiting

Drugs and Drug Interactions Associated with the Serotonin Syndrome

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: methylenedioxymethamphetamine (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

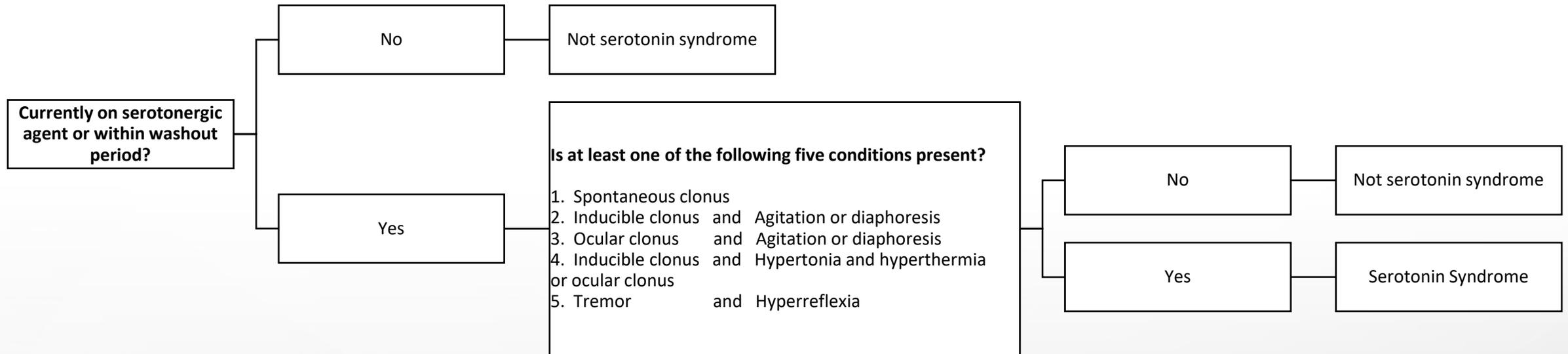
Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.

Drug interactions associated with severe serotonin syndrome

- Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, 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

Boyer, Edward W., M.D., PhD. and Michael Shannon, M.D., M.P.H. *N Engl J Med* 2005;352:1112-20.

Recognizing Serotonin Syndrome



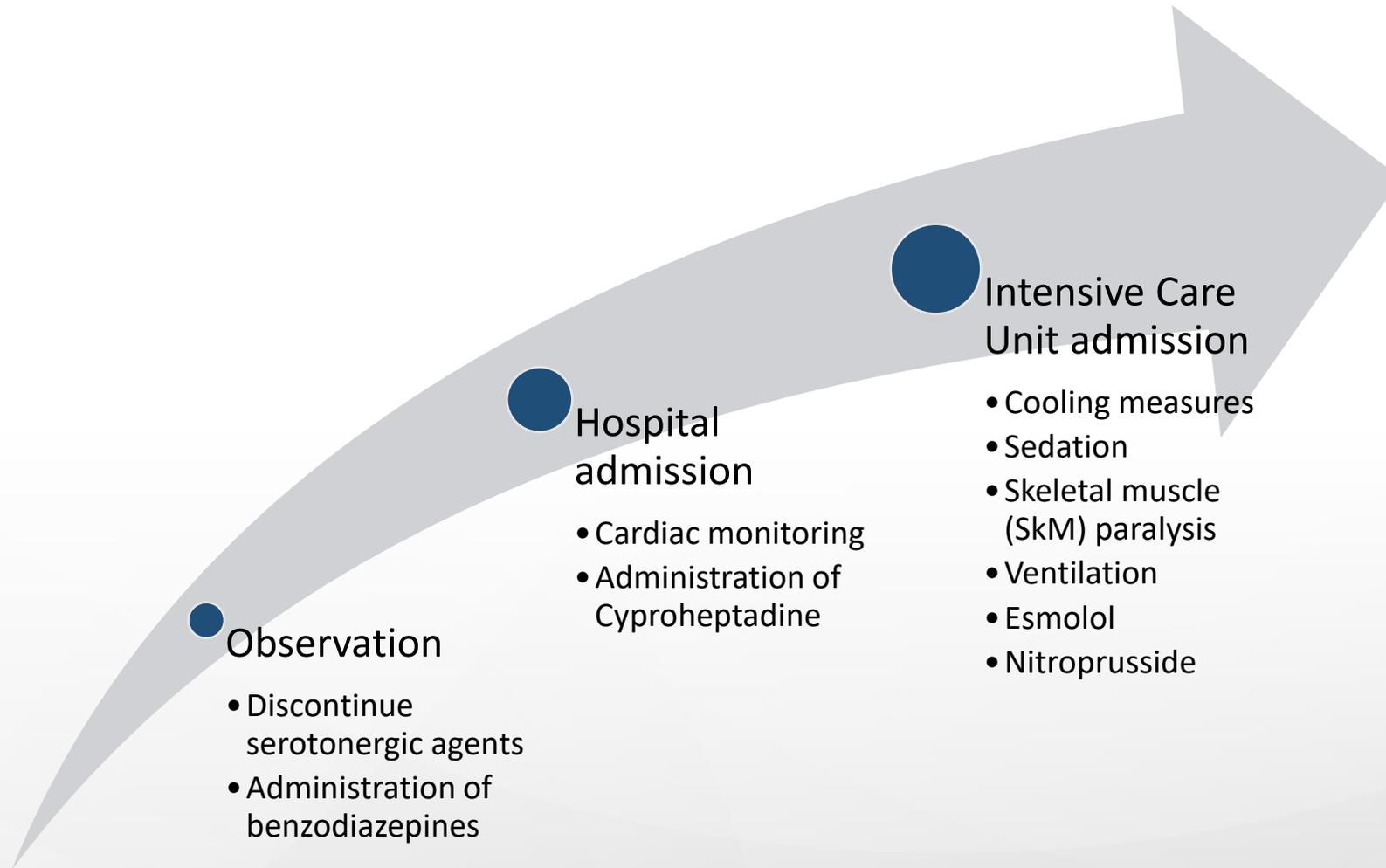
Wang RZ, Vashista V, Kaur S, Houchens NW. Serotonin syndrome: preventing, recognizing, and treating it. *Cleve Clin J Med* 2016; 83:810–817.

Similarities Between Serotonin Syndrome and Similar Conditions

	Serotonin syndrome	Neuroleptic malignant syndrome	Anticholinergic toxicity
Causative agent	Serotonergic agent	Dopamine antagonist Withdrawal from dopamine agonist	Anticholinergic agent
Onset	Within 24 hours	Within days to weeks	Within 1-2 hours
Resolution	Within 24 hours	In approximately 9 days	Within hours to days
Features similar to those of serotonin syndrome	-	Hyperthermia Altered mental state Diaphoresis Autonomic instability	Mydriasis Hyperthermia Agitation, delirium Visual hallucinations
Distinct features	Myoclonus Hyperreflexia Mydriasis Tremor Diarrhea Nausea, vomiting	Bradyreflexia Lead pipe rigidity Extrapyramidal features Absence of neuromuscular excitation	Dry skin and mucous membranes Urinary retention Decreased bowel sounds Normal muscle tone and reflexes

Wang RZ, Vashistha V, Kaur S, Houchens NW. Serotonin syndrome: preventing, recognizing, and treating it. *Cleve Clin J Med* 2016; 83:810–817.

Management of Serotonin Syndrome



Summary of Serotonin Syndrome

Definition

- Rare but potentially life-threatening condition associated with excess serotonin in the central nervous system

Epidemiology

- Observed in all age groups
- Drug mechanisms
 - therapeutic medication use
 - overdose
 - drug interactions

Symptoms

- Spectrum of clinical features range from mild to life threatening
- Clinical presentation is nonspecific and can mimic other life-threatening disorders

Diagnosis

- Clinical diagnosis, there is no laboratory test that can confirm diagnosis
- Hunter Criteria can be used if clinically suspected

Management

- Withdrawal of offending agent
- Dependent upon clinical severity
- Benzodiazepines, cyproheptadine
- Supportive management that may require critical care setting

1. (n.d.). *Serotonin syndrome (serotonin toxicity)*. UpToDate. Retrieved August 16, 2023, from <https://www.uptodate.com/contents/serotonin-syndrome-serotonin-toxicity>
2. (n.d.). *Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions*. National Library of Medicine. Retrieved August 16, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6734608/>

Conclusions

There is currently no ICD-10-CM code specific to Serotonin Syndrome

- An increasing incidence of this condition is thought to correspond with the increasing use of serotonergic agents in medical care
- Underrepresentation may correlate with lack of specific ICD-10-CM code

Adding a new ICD-10-CM code specific to Serotonin Syndrome will enable:

- More accurate capture of condition
- Representation of the significant morbidity Serotonin Syndrome carries with it
- Improved data analysis