IAEM Clinical Guideline

Serotonin Syndrome

Version 1.0

April 2024

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In Collaboration with IAEM Clinical Guideline Committee

To reference this document please reference as:

Lynch J, Hennessy A. Serotonin Syndrome. IAEM Guidelines 2024. https://iaem.ie/professional/clinical-guidelines/ (accessed 16th March 2024)

DISCLAIMER

Revision History

Date	Version	Section	Summary of changes	Author
April 2024	V1.0	All	Final version	JL/AH

ACKNOWLEDGEMENT

Special thank you to the following stakeholders for their contribution in developing this guideline

- Dr Cormac Kennedy, Consultant Pharmacologist at St. James's Hospital
- Eileen Relihan, Medication Safety Facilitator at St. James's Hospital
- Dr Sean Keane, Consultant Intensivist at St. James's Hospital

CONTENTS

GLOSSARY OF TERMS

Opsoclonus	Oculomotor dyskinesia characterised by involuntary, arrhythmic, multidirectional eye movements

GLOSSARY OF ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
AKI	Acute Kidney Injury
CT	Computed Tomography
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
EEG	Electroencephalogram
ED	Emergency Department
GCS	Glasgow Coma Score
ICP	Intracranial Pressure
IV	Intravenous
LSD	Lysergic Acid Diethylamide
MAOIs	Monoamine Oxidase Inhibitors
MDMA	3,4-Methylenedioxymethamphetamine
NMS	Neuroleptic Malignant Syndrome
MSU	Mid-stream Urine
SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Serotonin & Norepinephrine Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
VBG	Venous Blood Gas

Serotonin Syndrome

INTRODUCTION

Serotonin syndrome is a potentially life-threatening drug-induced condition. It is characteristically described as combination of recent ingestion of a drug likely to alter post-synaptic serotonin levels and a clinical triad of:

1. Mental status changes
2. Neuromuscular features
3. Autonomic instability

These symptoms do not necessarily occur concomitantly, with mental status changes and autonomic instability present in approximately 40% of cases, and neuromuscular features in approximately 50%.

Serotonin syndrome is rare, although incidence is increasing, which is thought to be due to the increased use of serotonergic agents in clinical practice. The true incidence is likely under-reported due to a number of factors: Mild cases are often dismissed or overlooked; there is a lack of specific diagnostic test or confirmatory laboratory findings; and clinical manifestations may be wrongly attributed to an alternative cause, particularly in severe cases.

PARAMETERS

Target audience	This guideline is intended for use by all ED staff managing patients with serotonin syndrome.
Patient population	Adult patients (over 18 years of age) presenting to the ED with: - Mental status changes, - Neuromuscular features and/or - Autonomic instability which may be contributable to serotonin syndrome.

AIMS

To provide an evidence-based guideline on the management of ED patients with serotonin syndrome.

CAUSATIVE AGENTS

Drugs that cause serotonin toxicity can be divided into two main groups:

1. Those that increase pre-synaptic serotonin sources through:
    - Augmentation of serotonin production (serotonin agonists/precursors)
    - Inhibitors of serotonin metabolism
2. Those that amplify serotonergic effects by increasing the amount in the synapse:
    - Enhancers of serotonin release
    - Blockers of serotonin reuptake

Please refer to Table 1 below for causative agents of serotonin syndrome.

Group of drugs	List of agents/drugs
Serotonin agonists or precursors	-LSD -L-Tryptophan -Triptans
Inhibitors of serotonin metabolism	-Linezolid -Methylene blue -MAOIs -Ayahuasca -St. John's wort -Syrian rue
Enhancers of serotonin release	-Substituted amphetamines e.g., MDMA, cathinones, phenylethylamines -Buspirone -Cocaine -Lithium -Mirtazapine
Blockers of serotonin reuptake	-Clomipramine, imipramine (TCAs) -Dextromethorphan -Fentanyl -Meperidine (Pethidine) -SSRIs -Tramadol -Trazodone -Venlafaxine (SNRI)

Others	-Anti-convulsant medications: Carbamazepine, lamotrigine, valproic acid, topiramate, gabapentin, pregabalin -Ginseng -Ondansetron

Table 1. Causative Agents of Serotonin Toxicity. Adapted from Goldfrank's Toxicologic Emergencies.

DIAGNOSTIC CRITERIA

Three sets of diagnostic criteria have been proposed for the diagnosis of serotonin syndrome:

1. Sternbach criteria
2. Radomski criteria
3. Hunter criteria

The Hunter Criteria (please refer to figure 1) are the most accurate, with a specificity of 97% and sensitivity of 84% compared with diagnosis by a medical toxicologist. These criteria were based on signs & symptoms in acute serotonin ingestion and therefore may not be applicable to all presentations. These criteria should also not supersede clinical judgement, and if there is a high index of suspicion for serotonin toxicity in a patient not meeting the criteria, treatment for serotonin syndrome should be initiated.

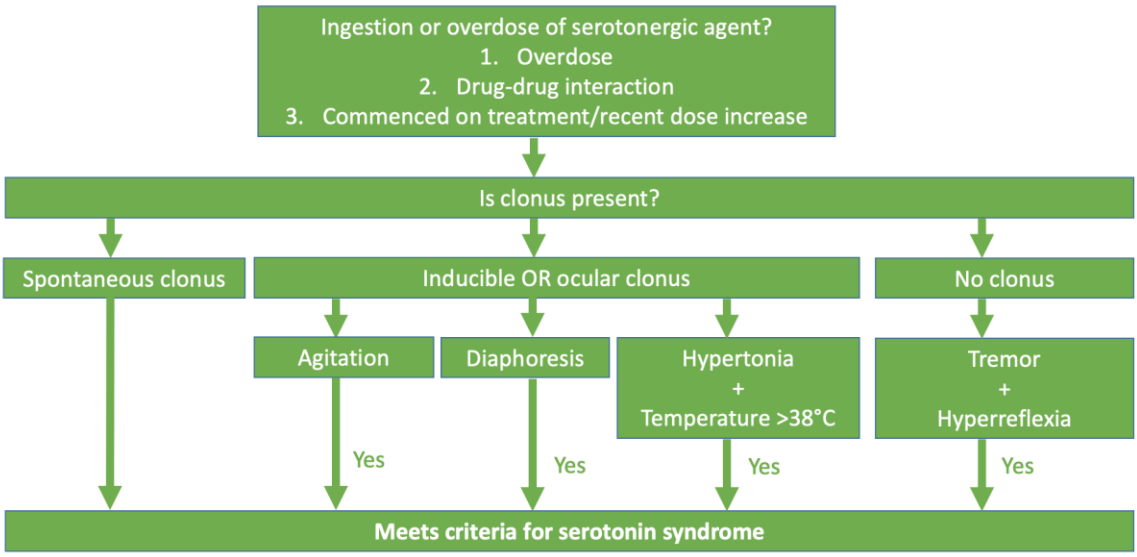

Figure 1: Hunter Criteria for Serotonin Toxicity

DIFFERENTIAL DIAGNOSIS

Differential diagnoses which should be considered in assessment of a patient with suspected serotonin syndrome include:

- Other toxidromes, including:
    - Sympathomimetic intoxication
    - Anticholinergic toxicity
    - Alcohol, Baclofen, Benzodiazepine or barbiturate withdrawal
- Sepsis
- Meningitis
- Viral or autoimmune encephalitis
- Hyperthermia syndromes e.g., neuroleptic malignant syndrome or heat stroke
- Thyrotoxicosis
- Sympathetic storm (rare, can occur as a paroxysmal clinical syndrome or after traumatic brain injury)

COMPARISON OF SEROTONIN TOXICITY AND NEUROLEPTIC MALIGNANT SYNDROME

The key features to look for in differentiating serotonin toxicity from Neuroleptic Malignant Syndrome include the presence of clonus and hyperreflexia, the presence of GI symptoms, the absence of bradykinesia and lead pipe rigidity, and the more insidious onset of symptoms.

NMS typically occurs days to weeks after exposure to a causative agent, whereas symptoms of toxicity occur within an hour of exposure to a causative agent in 30% of patients with serotonin toxicity, and within 6 hours in 60%.

	Neuroleptic Malignant Syndrome	**Serotonin Toxicity**
Class of causative drug	Dopamine antagonist	Serotonin agonist
Onset of symptoms post exposure	Days – weeks	Hours
Duration of symptoms	Days – 2 weeks	Approx. 24 hours
Altered consciousness	Common	Common
Agitation or hyperactivity	Common	Common
Autonomic instability	Common	Common
Hyperthermia	Common	Common
Gastrointestinal symptoms	Not seen	Common
Lead pipe rigidity	Common	Rare
Bradykinesia	Common	Not seen
Shivering	Not seen	Common
Tremor, hyperreflexia, clonus	Rare	Common

Table 2. Comparison of Serotonin Toxicity and Neuroleptic Malignant Syndrome (NMS). Adapted from Goldfrank's Toxicologic Emergencies

ASSESSMENT OF THE PATIENT WITH SUSPECTED SEROTONIN SYNDROME

Clinical features

The characteristic symptoms of mental status changes, neuromuscular features and autonomic instability do not always occur simultaneously, and patients with serotonin toxicity can present with a wide range of symptoms of varying severity. The presence of severe hyperthermia, severe rigidity or convulsions is associated with significantly increased morbidity and mortality.

Refer to Table 3 below for clinical features and severity of serotonin syndrome.

Mild toxicity	Moderate toxicity	Severe toxicity
Anxiety	Agitation	Low GCS
Hyperreflexia	Hyperthermia	Confusion
Inducible clonus	Mydriasis	Severe hyperthermia
Tachycardia	Diaphoresis	(>40°C)
Hypertension	Flushing	Respiratory failure
	Sustained clonus	Rigidity
	Opsoclonus	Convulsions
	Myoclonus	
	Tremor	

Table 3: Clinical features and severity of serotonin syndrome.

Complications of severe serotonin toxicity include:

- Cardiac arrhythmia
- Left ventricular dysfunction
- Circulatory collapse
- Rhabdomyolysis

- Pulmonary oedema
- ARDS
- Acute renal failure
- DIC
- Multi-organ failure
- Cardiorespiratory arrest

History

A detailed drug history should be taken including the use of prescription, over the counter, or illicit drugs, as well as dietary supplements.

A detailed medical history should be taken, including the presence of conditions which may indicate use of serotonergic agents such as depression or chronic pain syndromes. The timescale of ingestion of a serotonergic agent(s) is also necessary as most cases develop within hours of ingestion. Consideration should also be given to the potential ingestion of delayed release preparations as these may cause delayed onset toxicity.

Investigations

Necessary investigations should be based on clinical presentation, the following may be considered:

- VBG to assess for metabolic acidosis, raised lactate, hyperkalaemia, hypoglycaemia
- Full blood count and CRP to assess for infection
- Renal profile and liver function test to assess for organ dysfunction
- Creatine kinase to assess for rhabdomyolysis
- Coagulation studies to assess for DIC

- ECG to assess for prolonged QTc, widened QRS or arrhythmia
- Paracetamol and salicylate levels if intentional overdose
- Screening for source if sepsis suspected
- Lumbar puncture if meningitis/encephalitis suspected
- CT brain if signs of raised ICP

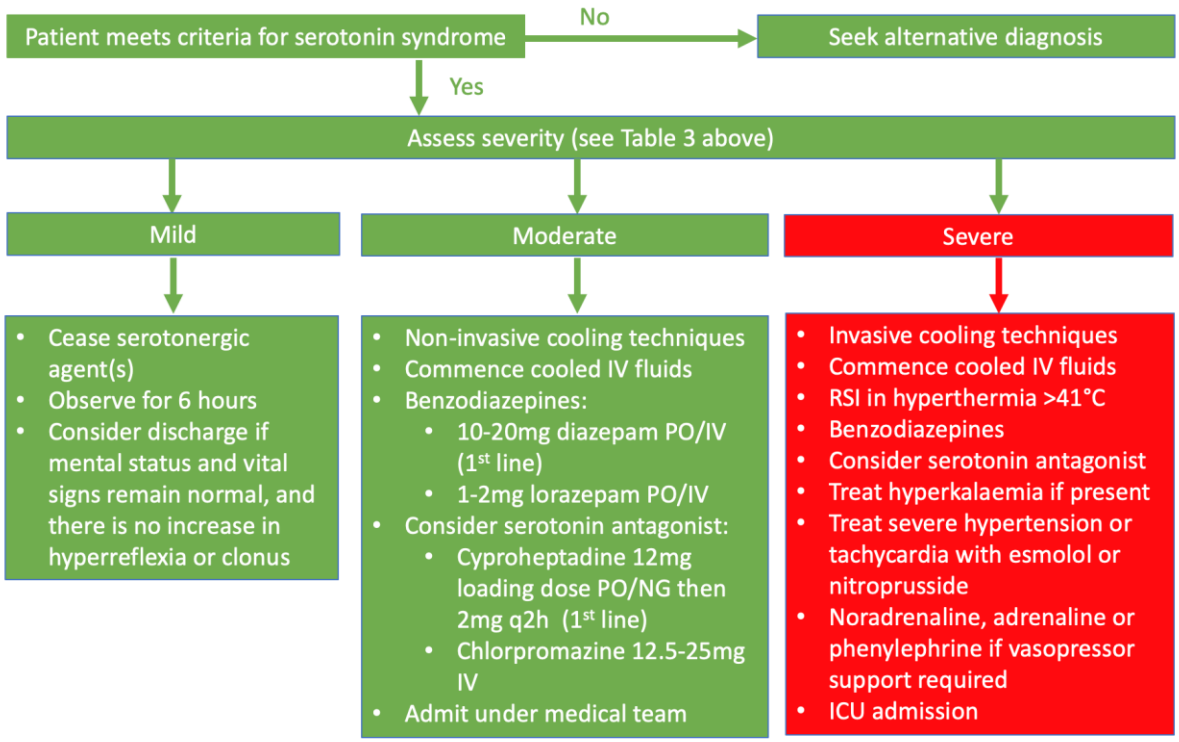

Figure 2: Algorithm for the management of serotonin syndrome

MANAGEMENT

The basic principles of management of serotonin syndrome are:

1. **Cessation of all serotonergic agents.**
2. **Supportive care aimed at normalising vital signs including management of hyperthermia, if necessary.**
3. **Sedation with benzodiazepines.**
4. **Administration of serotonin antagonists.**

Approach in patients with suspected serotonin toxicity

1. Patients must be on continuous cardiac monitoring with frequent or continuous monitoring of core temperature dependent on severity of hyperthermia.
2. Supplemental oxygen should be initiated if SpO2 <94%.
3. Commence IV fluids, aiming for a urine output of ≥0.5ml/kg/hour, or ≥1ml/kg/hour in the presence of rhabdomyolysis.
4. Hyperkalaemia should be treated with IV calcium gluconate/chloride and insulin/dextrose according to local protocols.
5. Physical restraint should be avoided as it will worsen metabolic demand and hyperthermia.
6. Administer benzodiazepines:
    - 10-20mg diazepam PO or IV (1st line) - Preferred due to shorter duration of action
    - 1-2mg lorazepam PO or IV
    - 1-2mg lorazepam IM or 5-10mg midazolam IM may be used if IV access not possible and patient is too agitated to take oral medications
    - Further doses as required, monitoring for respiratory depression
7. Treat hyperthermia:

- **Mild to moderate hyperthermia** - may be treated with non-invasive cooling techniques such as ice packs in the groin and axillae, mist or fan techniques, or external cooling devices
- **Severe hyperthermia** (body temperature >40°C or rapidly rising body temperature despite non-invasive cooling techniques) - may require more invasive cooling measures such as administration of cooled IV fluids or cooled fluid lavage (e.g. gastric, bladder)
- Immediate RSI is required for patients with a core body temperature of >41°C or a rapidly rising body temperature despite cooling
    - **Suxamethonium should be avoided in patients with AKI or rhabdomyolysis due to risk of hyperkalaemia.**
    - Ensure sedation maintained with benzodiazepine infusion and paralysis maintained with long acting non-depolarizing neuromuscular blockade such as atracurium.
    - Consider continuous EEG monitoring in paralysed patients (though the risk of seizures is low in serotonin syndrome).
- Antipyretics such as paracetamol have no role as the hyperthermia is not hypothalamic in origin.

8. Consider use of serotonin antagonists in moderate to severe cases:
    - Cyproheptadine PO or NG (1st line)
        - 12mg loading dose
        - Then 4-8mg q6h
    - Chlorpromazine 12.5-25mg IV
        - Can cause significant hypotension
9. Autonomic instability:
    - Severe hypertension and tachycardia may be treated with short-acting agents such as esmolol (1st line) or nitroprusside.

    - avoid hydralazine as this may increase serotonin levels.
- Fluid refractory hypotension (most commonly seen in patients with serotonin toxicity secondary to MAOIs) requiring vasoactive support may be treated with adrenaline, noradrenaline or phenylephrine (a peripheral phenylephrine or metaraminol infusion may be considered while central venous access is secured).
    - **Dopamine should be avoided.**

Caution

Avoid use of fentanyl as it blocks serotonin reuptake and may worsen toxicity.

Treatment with dantrolene, propranolol or bromocriptine is NOT recommended.

- Dantrolene is only effective in hyperthermia caused by skeletal muscle receptor abnormalities
- Propranolol may cause hypotension, and may mask tachycardia thus making assessment of treatment effectiveness more difficult
- Bromocriptine may exacerbate serotonin toxicity due to its serotonin agonist properties

DISPOSITION

- Patients with severe serotonin toxicity require admission to a critical care setting.
- Patients with moderate toxicity require admission for observation and cardiac monitoring until symptoms resolve.
- Patients with mild toxicity may be considered for discharge after an observation period of 6 hours, provided their mental status and vital signs remain normal, and there is no increase in hyperreflexia or clonus.

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- Royal College of Emergency Medicine and National Poisons Information Service Guideline on Antidote Availability for Emergency Departments (July 2022) APPENDIX 1: Stocking Guidance