SEROTONIN SYNDROME - ADULT

TARGET AUDIENCE	Board-wide
PATIENT GROUP	For treatment – adult critical care & ED For information - All adult, including mental health

Clinical Guidelines Summary

MANAGEMENT OF SEROTONIN SYNDROME IN ADULTS [1,2,3]

- **Withdraw causative drugs** (including fentanyl patches if worn). Mild cases typically resolve within 24-48 hours, depending on drug half-life.
- **Moderate to severe cases** require acute medical facility management.

Mild Toxicity
- Oral diazepam 10mg or lorazepam 2mg (3 doses / 24h if required, then seek specialist input)

Moderate Toxicity
- Begin cooling
- IV fluids 1-2L
- IV diazepam 10mg or lorazepam 2mg (3 doses if required, then seek specialist input - further doses may be required)
- Cyproheptadine 12mg oral/NG then 8mg every 6 hours (max 32mg/day)*
- Consider olanzapine 5-10mg IM/SC – repeat once after 2 hours if req*

Severe Toxicity
- Aggressive cooling
- Treat as per moderate toxicity plus:
- Consider Rapid Sequence Induction (RSI) and paralysis
- If muscular hyperactivity, consider dantrolene 2-3mg/kg IV to max 10mg

* stock in emergency cupboard / critical care unit / ED

Supportive care may be required for:

- Pyrexia: Cooled IV fluids, ambient Bair Hugger, ice packs. ***NB.*** *Paracetamol is ineffective as the temperature is not hypothalamic in origin.*
- Hypoglycaemia, hyperkalaemia, rhabdomyolysis (*consider 1.26% bicarbonate therapy*).

RSI AND SEROTONIN SYNDROME

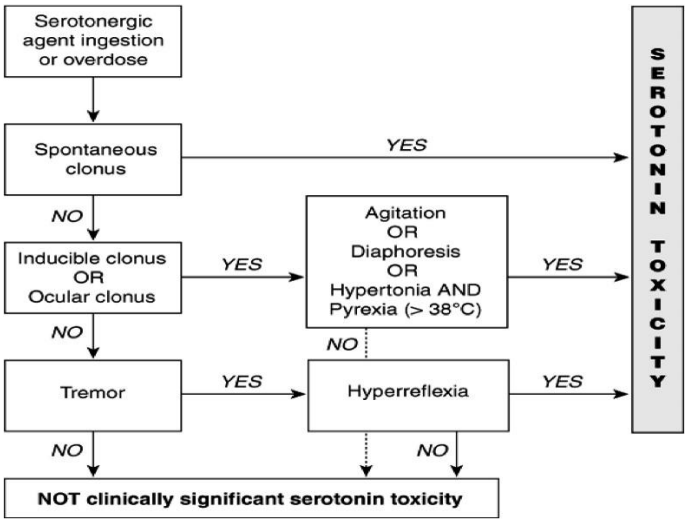
- Avoid opioids with serotonergic activity (e.g. fentanils).
- Avoid suxamethonium (risk of hyperkalaemia) - **rocuronium** is preferred.

Serotonin Syndrome – ADULT

BACKGROUND

Serotonin syndrome is a potentially life-threatening condition associated with increased intra-synaptic serotonin in the central nervous system (CNS). It is usually caused by therapeutic medication use (uncommon), drug interactions, or overdose (common). It is classically described as a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities, but actually a spectrum of toxicity ranging from mild (underreported) to life-threatening.

DIAGNOSIS (HUNTER CRITERIA)[1]



- Onset occurs within a few hours of serotonergic agent intake.
- Mild serotonin syndrome may not meet Hunter Criteria.

DIFFERENTIAL DIAGNOSIS [4]

In the absence of serotonergic exposure or neuromuscular excitation (e.g. hyperreflexia, clonus), consider alternative diagnoses, including CNS infection, neuroleptic malignant syndrome, anticholinergic/sympathomimetic toxicity, or malignant hyperthermia.

SPECTRUM OF SEROTONIN TOXICITY [1]

	SEVERITY	NEUROMUSCULAR	AUTONOMIC	MENTAL STATUS
	Serotonergic side effects	Brisk reflexes	Nausea, diarrhoea	Insomnia
	Mild	Inducible clonus, hyperreflexia	Hypertension, palpitations	Anxiety, restlessness
	Moderate	Sustained clonus, tremor	Mydriasis, flushing, diaphoresis, pyrexia, tachycardia	Agitation, hallucinations
	Severe	Rigidity, respiratory failure	Severe hyperthermia (>40°C)	Confusion, delirium

AETIOLOGY

Can occur with drugs designed to increase serotonin (e.g. SSRIs) or those with unintended serotonergic effects (e.g. linezolid). Serious toxicity is attributed to 5-HT2 receptor stimulation from combinations involving different mechanisms e.g. MAOI and SSRI combinations, necessitating washout periods to mitigate risk.[2,4] Drugs acting on other 5-HT receptors or serotonin antagonists (e.g., triptans, antipsychotics, anti-emetics, anticonvulsants) carry a lower risk.

POSSIBLE CAUSATIVE AGENTS

Numerous medications can induce serotonin syndrome alone in high doses or in combination.

Antidepressants	Opioids	CNS stimulants	Others
MAOIs e.g. phenelzine	pethidine	amphetamines	St John's wort
TCAs e.g. amitriptyline	fentanils	cocaine	Sodium valproate
SSRIs e.g. fluoxetine	oxycodone	MDMA	lithium
SNRIs e.g. venlafaxine	tramadol	LSD	linezolid
trazodone	buprenorphine	methylphenidate	
vortioxetine	tapentadol		

RESTARTING TREATMENT

Once symptoms resolve, serotonergic medication may be restarted at a lower dose under close monitoring. This should be done prior to hospital discharge in consultation with the appropriate specialty, e.g. liaison psychiatry for psychiatric medications. Alternative treatments with reduced serotonergic activity should be considered based on severity and cause of serotonin syndrome.

References/Evidence

1. Chiew AL, Management of Serotonin Syndrome. *Br J Clin Pharmacol* 2024; DOI: 10111/bcp.16152.
2. Toxbase. Serotonin Syndrome. Updated 01/21. Accessed 6/12/24.
3. UpToDate. Serotonin Syndrome. Last updated 07/24. Accessed 6/12/24.
4. BMJ Best Practice. Serotonin Syndrome. Last updated 07/10/2022. Accessed 23/8/24.

Appendices

1. Governance information for Guidance document

Lead Author(s):	Sarah Brady
Endorsing Body:	ADTC
Version Number:	2
Approval date	October 2025
Review Date:	October 2028
Responsible Person (if different from lead author)	

CONSULTATION AND DISTRIBUTION RECORD	
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Consultation Process / Stakeholders:	Iain Lang (original author) Anaesthetics teams Pharmacy surgery/critical care teams ED representative – Dr Alison Pollock, UHW
Distribution	All adult

CHANGE RECORD			
Date	**Lead Author**	**Change**	**Version**
December 2015	Iain Lang	Initial version – management of serotonin syndrome (focus on critical care)	1
May 2025	Sarah Brady	Review and extend guidance to cover more background and include non-critical care.	2
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