Medication Safety Series: MSS 36

Serotonin Syndrome

What?	• Serotonin syndrome (SS) is used to describe significant serotonin toxicity. The two terms may be used interchangeably to describe a life-threatening adverse drug reaction which is growing in incidence; although overall incidence is unclear, due to under-reporting / under-diagnosis, it has been observed in around 15% of patients taking an overdose of SSRIs.
Why?	• SS is due to high concentrations of serotonin (5-HT) at some receptor subtypes in the CNS with mechanisms including: increase in serotonin synthesis or release; inhibition of serotonin metabolism or uptake; activation of serotonergic receptors. Note different drugs have different half-lives - affects time to build up concentration/remain in system on stopping.
Who?	• Higher risk is associated with ↑ age, ↑ dose of serotonergic agents, serotonergic agents in combination with drugs that have a high CYP2D6 inhibitory function, comorbidities such as chronic pain or Parkinson's disease which may result in combinations of serotonergic drugs & patients undergoing haemodialysis / with end-stage renal disease.
When?	• Onset of symptoms is usually rapid, often within hours of drug or dose changes (60% of cases occur within 6 hours of the new drug or dose), with cases usually resolving within 24 hours of stopping the serotonergic drug(s). • Can occur with a single serotonergic drug (see table 1) at a therapeutic dose, due to a drug interaction (including food interactions e.g. grapefruit juice), in overdose or more frequently when combinations of serotonergic drugs are used. • Not just psychotropic drugs, also other drugs or substances including some over-the-counter medicines and illicit substances. • Caution is required when combining serotonergic drugs e.g. when switching or augmenting antidepressants. Most risky antidepressant combination is MAOI + SSRI.

Diagnosis	• SS can be difficult to differentiate from other conditions including, Neuroleptic Malignant Syndrome, anticholinergic toxicity, alcohol or antidepressant withdrawal and malignant hyperthermia. • SS or toxicity consists of a triad of features (see figure 1): alteration of mental status (around 40% of patients) e.g. anxiety, agitation or confusion, neuromuscular abnormalities/hyperactivity (around 50% of patients) e.g. clonus, raised CK and autonomic instability (around 50% of patients) e.g. hyperpyrexia, that do not necessarily present together and can vary in severity from mild to life threatening (death is usually due to hyperpyrexia-induced multi-organ failure). • Several systems of diagnostic criteria exist, but the Hunter Serotonin Toxicity Criteria (HSTC, figure 2) are currently recommended as the most accurate and specific criteria and are less likely to miss early, mild or subacute forms of serotonin syndrome. • Severe serotonin toxicity may present early as moderate toxicity with some drug formulations e.g. extended-release venlafaxine.
Management	• **EPMA:** Prescribers will be alerted to any risk of SS from interacting medication when prescribing & can take appropriate action to review prescription or monitor. Any alerts generated & accepted for an individual prescription can be viewed within EPMA prescribing by clicking 'view details' & in drug administration via 'Safety Warnings' tab. In addition, in EPMA Drug Administration, the prescriber or pharmacist can add a medication note to alert nurses to any patient at significant risk of SS. • Treatment is guided by the severity of toxicity. STOP the serotonergic medication, assess the severity of toxicity and provide supportive care. • In moderate & severe cases, the use of specific anti-serotonergic agents may be required- urgent medical review is needed, and patients can deteriorate rapidly, ensure patient attends Accident and Emergency. • Patients may need acute inpatient monitoring over 12-24 hours.

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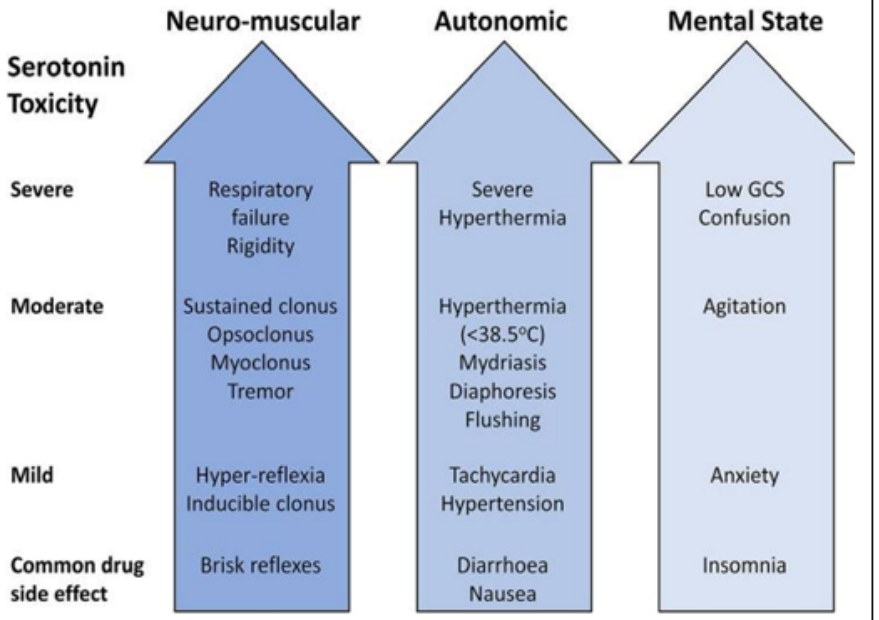
Restarting treatment	• Depending on the situation that has led to the serotonin toxicity (e.g., increased dose, overdose, drug-drug interaction), a single serotonergic medication may be restarted at a lower dose after the condition has resolved, while the patient is monitored closely. • If the serotonin syndrome resulted from a drug-drug interaction, specifically use/overdose of an illicit substance, patient's prescribed medication can be restarted at their normal dose.
Advice for patients	• When starting or adjusting risk medications, advise patients to report any signs of shakes, shivers or high temperatures promptly. • **For TEWV staff to use with patients and carers**: Choice and Medication have a short and longer handy fact sheet on serotonin syndrome • **Open access**: Side effects - Selective serotonin reuptake inhibitors (SSRIs) - NHS

Figure 1 - The spectrum of clinical features in serotonin syndrome:

Source: Buckley et al



Definitions:

Clonus - an abnormal reflex response that involves involuntary and rhythmic muscle contractions

Diaphoresis - excessive sweating without an obvious cause

GCS - Glasgow Coma Scale estimates impaired consciousness and coma severity

Hyper-reflexia - overactive or overresponsive bodily reflexes

Mydriasis - dilation of the pupil in the eye

Myoclonus - sudden, brief involuntary twitching or jerking of a muscle or group of muscles

Opsoclonus - uncontrolled, irregular, and nonrhythmic eye movement

Figure 2 - Hunter Serotonin Toxicity Criteria

Presence of serotonergic agent:

- Recent addition
- Increased dose or overdose
- Interaction

AND meet one of the following conditions:

- Spontaneous clonus
- Inducible clonus AND agitation OR diaphoresis
- Ocular clonus AND agitation OR diaphoresis
- Ocular clonus OR inducible clonus AND Hypertonia AND Temperature > 38°C*
- Tremor AND Hyperreflexia

**The presence of temperature ⩾38.5°C and/or marked hypertonia or rigidity (especially truncal) indicates severe SS with a risk of progression with respiratory compromise.*

Table 1 - Common Serotonergic Drugs and possible interactions (information from references listed below, BNF and EMC (SmPC search)		
Psychotropic drugs	***SSRIs***	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, (Dapoxetine)
	SNRIs	Duloxetine, venlafaxine
	MAOI *(greatest risk)*	Isocarboxazid, moclobemide (reversible MAO-A inhibitor), phenelzine, tranylcypromine
	TCAs	Amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine
	Other antidepressants	Bupropion, L-tryptophan, mirtazapine, reboxetine, trazodone, vortioxetine
	ADHD medication	Atomoxetine, dexamfetamine, lisdexamfetamine, methylphenidate
	Others	Aripiprazole, buspirone, carbamazepine, fenfluramine, lithium, lurasidone, quetiapine.
Opioids		Buprenorphine, codeine, dextromethorphan, fentanyl, methadone, oxycodone, pentazocine, pethidine, tapentadol, tramadol.
Parkinson's Disease		MAO-B inhibitors: rasagiline, safinamide, selegiline. Amantadine, L-Dopa.
Antibacterials		Linezolid, tedizolid (reversible MAOI activity)
Anti-cancer		Procarbazine (weak MAO inhibitor)
Anti-emetic		Metoclopramide, ondansetron, granisetron, palonosetron
Antihistamines		Chlorphenamine, diphenhydramine
Migraine treatments		Triptans e.g. frovatriptan, almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan. Dihydroergotamine.
Diagnostic Dye		Methylthioninium Chloride (Methylene blue) – MAOI activity
Herbal/complementary Medicines		St John's Wort (Hypericum Perforatum)
Illicit substances		Amphetamines, cocaine, novel psychoactive substances, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
Food Interactions with serotonergic drugs		***Grapefruit juice*** with drugs metabolised by CYP3A4 e.g. sertraline – increases bioavailability by up to 50%; consumption of large quantities of ***caffeine*** particularly with drugs metabolised by CYP1A2 e.g. fluvoxamine, reduces caffeine clearance by up to 80% which may result in caffeine toxicity; inhibition of CYP1A2 by caffeine may increase available levels of other drugs e.g. TCAs. It is also noted that some compounds found in ***coffee*** demonstrate (reversible) inhibitory effects on both monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B).

References:

- Serotonin syndrome - Symptoms, diagnosis and treatment | BMJ Best Practice
- Buckley N A, Dawson A H, Isbister G K. Serotonin syndrome BMJ 2014; 348 :g1626 doi:10.1136/bmj.g1626
- Ellahi R. Serotonin syndrome: a spectrum of toxicity. *BJPsych Advances*. 2015;21(5):324-332. doi:10.1192/apt.bp.114.013037
- Red Whale – Serotonin Syndrome guide (published May 2023)
- Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. Int J Tryptophan Res. 2019 Sep 9;12:1178646919873925. doi: 10.1177/1178646919873925.
- Toxbase: Serotonin toxicity, last updated 1/21; accessed online 4/3/25.
- UKMI Q&A: What is serotonin syndrome? 2020.