Mental Health Services
Prescribing Management Group

Serotonin Syndrome

Background

Serotonin syndrome is the clinical manifestation of an increase in serotonin levels in the central nervous system characterised as a triad of features; alteration in mental state, neuromuscular abnormalities and autonomic hyperactivity. Serotonin syndrome is perhaps better described as a spectrum of serotonin toxicity from mild serotonergic features that may cause minimal concern to the patient or clinician, to severe life-threatening toxicity that should be considered a medical emergency .[1]

Incidence

In its mildest form, serotonin syndrome is probably relatively common, but under reported. Approximately 15% of patients taking an acute overdose of selective serotonin reuptake inhibitors (SSRIs) develop moderate serotonin syndrome.[2]

Aetiology

Serotonin syndrome can occur from any exposure to medication that increases intrasynaptic serotonin concentration in the central nervous system. This includes medications where the therapeutic aim is to increase serotonin levels e.g. SSRI antidepressants and medications where this effect is unintended e.g. linezolid. In practice, it is usually encountered as a result of overdose of serotonergic drugs or as a consequence of drug interactions e.g. via inhibition of metabolism of serotonergic drugs or when more than one drug affecting serotonin is taken. Occasionally, it can occur when one serotonergic agent is prescribed alone in susceptible individuals.

Drugs associated with serotonin syndrome [1-3]

Serotonin-reuptake inhibitors	Monoamine oxidase inhibitors	Serotonin-releasing agents	Others
Selective serotonin-reuptake inhibitors (SSRIs) e.g. fluoxetine, sertraline	Phenelzine, tranylcypromine	Amphetamines	Lithium
Serotonin noradrenaline reuptake inhibitors (SNRIs) e.g. venlafaxine, duloxetine	Moclobemide	Methylphenidate	Tryptophan
Tricyclic antidepressants (TCAs) e.g. clomipramine, amitriptyline	Linezolid	Synthetic stimulants e.g. ecstasy, cathinones	Buspirone
St John's wort	Parkinson's treatment e.g. selegiline, rasagiline		Vortioxetine
Opioid analgesics e.g. pethidine, tramadol, fentanyl	Methylene blue		

Severe serotonin syndrome toxicity is usually as a result of a combination of serotonergic agents that act via separate mechanisms.[3] Life-threatening cases have been reported with the use of MAOIs in combination with SSRIs, therefore washout periods must be observed to minimise this risk.

Serious toxic effects are thought to result from stimulation of $5HT_2$ receptors, [2,4] therefore drugs that act on other 5HT receptors or are serotonin antagonists have a low risk of serotonin toxicity e.g. triptans, antipsychotics, antiemetics, anticonvulsants.

Diagnosis of serotonin syndrome

Onset of serotonin syndrome is usually within a few hours of drug initiation or dose changes and diagnosis of serotonin syndrome is primarily clinical.[2,3] Absence of exposure to a serotonergic agent, excludes serotonin syndrome as a diagnosis.

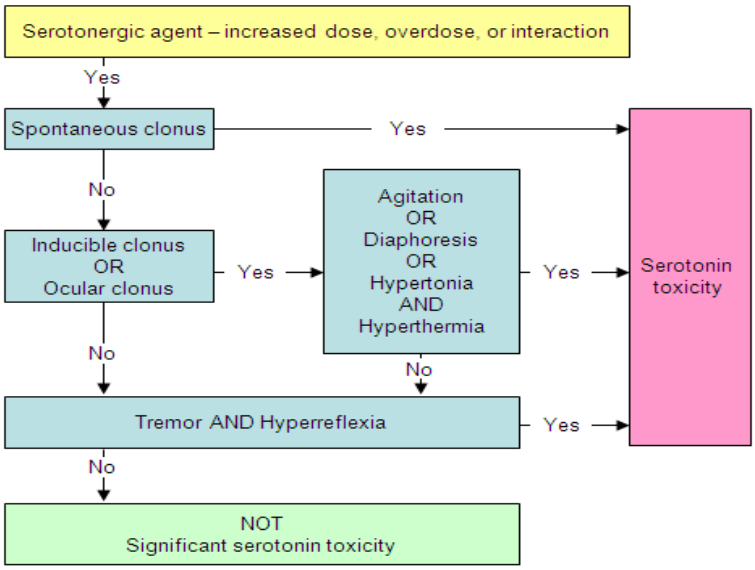
Symptoms of serotonin syndrome[1]		
Alterations in mental state	**Neuromuscular abnormalities**	**Autonomic hyperactivity**
Agitation	Tremors	Hypertension
Anxiety	Clonus	Tachycardia
Disorientation	Hyperreflexia	Tachypnea
Restlessness	Muscle rigidity	Hyperthermia
Excitement	Bilateral Babinksi signs	Mydriasis
		Diaphoresis
		Flushed skin
		Shivering
		Vomiting
		Diarrhoea
		Hyperactive bowel sounds
		Arrhythmias

Severe cases may result in complications such as seizures, rhabdomyolysis, multi-organ failure, coma and death.[2]

The Hunter Serotonin Toxicity Criteria (HSTC) are the most specific and sensitive diagnostic criteria and are less likely to miss early, mild or subacute forms of serotonin syndrome (although very mild symptoms of serotonin syndrome may not meet the HSTC).[3]

Serotonin toxicity exists in the presence of a serotonergic agent plus one of the following criteria: [5]

- Spontaneous clonus
- Inducible clonus AND agitation or diaphoresis
- Ocular clonus AND agitation or diaphoresis
- Tremor AND hyperreflexia
- Hypertonia AND pyrexia (temp> 38 °C) AND ocular or inducible clonus



Increasing severity of serotonin syndrome[3,6]

Mild	Moderate	Severe
Restlessness Nausea Diarrhoea Hyperreflexia	Agitation / anxiety Tachycardia Clonus Tremor Low fever / shivering Diaphoresis	Hyperthermia Rigidity Confusion Spontaneous clonus Convulsions

Differential diagnoses [3,7]

Differential diagnosis	Distinguishing features
Neuroleptic malignant syndrome	Absence of neuromuscular excitation* Presence of bradykinesia, lead-pipe rigidity and EPSE Slower onset of action History of exposure to antipsychotics (unless also on serotonergic drugs)
Anticholinergic toxicity	Absence of neuromuscular excitation* Bowel sounds absent, dry skin History of exposure to anticholinergic
Malignant hyperthermia	Absence of neuromuscular excitation* History of exposure to anaesthetic agent
CNS infection	Absence of neuromuscular excitation*
*hyperreflexia & clonus	

Management

Treatment of serotonin syndrome consists of discontinuing the serotonergic medication(s), assessing the severity of toxicity, providing supportive care and potentially the use of antiserotonergic treatment. In mild symptoms of

serotonin syndrome, discontinuing the implicated medication(s) usually resolves the presentation within 24-48 hours (the time course will depend on the clearance of the causative agent e.g. fluoxetine with a long half life will be much longer).[2]

Moderate to severe cases should be managed in an acute medical facility.

In moderate to severe toxicity, depending on the symptoms, the following should be considered: [2,3]

- assessment of airways, breathing and circulation
- hyperthermia should be treated with rapid cooling
- benzodiazepines for symptomatic relief of anxiety and agitation, muscle rigidity, myoclonus
- cyproheptadine (serotonin receptor antagonist)
- chlorpromazine as a serotonin receptor antagonist (reserved for severe cases and to clinicians with experience in its use for managing serotonin syndrome)

Restarting treatment

Once the symptoms have resolved and depending on the severity of the presentation and the likely explanation for the serotonin syndrome (e.g. increased dose, overdose, drug-drug interaction), it may be appropriate to consider recommencing a serotonergic medication at a lower dose under close monitoring. Alternative treatment with less serotonergic activity may need to be considered.

References:

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