CLINICAL PHARMACOLOGY

THE SEROTONIN SYNDROME

The serotonin syndrome is a potentially life-threatening adverse drug reaction caused by raised serotonin levels within the CNS. This may result from an overdose, drug interaction, or occasionally following therapeutic use of serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs). It is not an idiosyncratic drug reaction, but rather a predictable consequence of excess serotonergic stimulation. This produces a spectrum of clinical manifestations ranging from barely perceptible side-effects to fatal toxicity. The increasingly used term serotonin toxicity is more descriptive of this dose-related, iatrogenic 'toxidrome' (a group of signs and symptoms found with a particular type of poisoning).

The increasing frequency of serotonin toxicity largely reflects the increased use of pro-serotonergic agents in clinical practice. Limited awareness among health care workers of this syndrome and the drugs that precipitate it, particularly the numerous potentially dangerous drug interactions, has contributed to its increasing frequency. SSRIs are understandably more frequently prescribed than tricyclic antidepressants in patients considered to be at risk of overdose, although the assumption that SSRIs are safe in overdose is increasingly being questioned. Although the exact incidence is not clear, serotonin toxicity has been reported in 14 - 16% of patients who take an SSRI overdose.

Drugs associated with serotonin toxicity

There is a wide variety of drugs associated with serotonin toxicity (Table I). It is essential that the drug history taken from a patient includes the use of over-the-counter drugs, illicit substances, dietary supplements as well as prescription medicines. Serotonin toxicity occurs most commonly when two drugs that affect serotonin levels are taken together, but it can also occur after overdose with a single drug or very rarely after a single therapeutic dose. The addition of drugs that inhibit the metabolism of the SSRIs (cytochrome P450 isoenzymes CYP2D6 and CYP3A4 inhibitors) to therapeutic SSRI doses has also precipitated the syndrome. Serotonin toxicity may also be precipitated when a new serotonergic drug is started too soon after another serotonergic medication has been discontinued. For example, a washout period of 14 days is needed when a patient changes from an SSRI to a monoamine oxidase inhibitor (MAOI). The administration of serotonergic agents within 5 weeks after stopping fluoxetine has also led to this toxicity, presumably due to the long elimination half-life of its active metabolite, norfluoxetine.

Table I. **Drugs associated with serotonin toxicity, when used alone or in combination**

Selective serotonin re-uptake inhibitors (SSRIs)
- Fluoxetine
- Citalopram
- Paroxetine
- Sertraline
- Fluvoxamine

Monoamine oxidase inhibitors
- Tranylcypromine
- Moclobemide

Tricyclic antidepressants
- Clomipramine
- Imipramine

Mood stabilisers
- Lithium

Other antidepressants
- Trazodone
- Venlafaxine
- Buspirone
- Duloxetine

Analgesics
- Pethidine
- Tramadol
- Fentanyl
- Pentazocine

Migraine treatments
- Triptans
- Ergotamine

Drugs of abuse
- Amphetamine
- Cocaine
- Methylenedioxymethamphetamine (ecstasy)
  Lysergic acid diethylamide (LSD)

Cough suppressants
- Dextromethorphan

P450 enzyme inhibitors*
- Protease inhibitors
- NNRTIs
- Linezolid (also inhibits Monoamine Oxidase)

Anticonvulsants
- Valproic acid*

Anorectic agents
- Sibutramine

Dietary supplements
- Hypericum perforatum (St John's wort)
- Panax ginseng (ginseng)
- Tryptophan

* Although these drugs are not intrinsically serotonergic, they can cause serotonin toxicity by inhibiting the metabolism and thereby increasing levels of some serotonergic drugs.

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Pathophysiology

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that binds with a serotonergic receptor on the post-synaptic neuron. Stimulation of serotonin receptors affects areas of the brain that control temperature, sleep, sexual function, appetite and mood. Serotonin also contributes to peristalsis in the gastrointestinal tract, affects platelet aggregation and enhances vascular tone. Serotonin is synthesised from dietary tryptophan, stored in the pre-synaptic nerve terminals, and released into the synapse after membrane depolarisation. Active transport back into the pre-synaptic terminal is followed by repackaging into vesicles or by degradation by monoamine oxidase (MAO). Thus, the important mechanisms of serotonin toxicity are:

- inhibition of serotonin re-uptake, e.g. SSRIs
- increased pre-synaptic release of serotonin, e.g. cocaine, amphetamines
- inhibition of the breakdown of serotonin, e.g. MAOIs (moclobemide, tranylcypromine)
- direct stimulation of serotonin receptors, e.g. buspirone, lysergic acid diethylamide (LSD).

Diagnosis

The serotonin syndrome has been described in patients of all ages including the elderly, children and newborn infants. Clinicians and patients may dismiss symptoms such as tremor, diarrhoea or hypertension as inconsequential or unrelated to drug therapy. Anxiety may be mis-attributed to the patient's mental state. Thus, the incidence of serotonin toxicity is generally underestimated as the diagnosis is often missed or delayed.

Serotonin toxicity typically exhibits neuromuscular hyperactivity (tremor, clonus, hyper-reflexia), altered mental state (agitation, excitement) and/or autonomic hyperactivity (fever, sweating, tachycardia, tachypnoea). The diagnosis relies on the presence of some of the clinical manifestations associated with serotonin toxicity (Table II) in a patient with a history of taking serotonergic agent(s) (Table I). Physical examination should include a focused assessment of deep tendon reflexes, clonus, muscular rigidity, size and reactivity of pupils, dryness of oral mucosa, bowel sounds and presence of diaphoresis (sweating). Clinical manifestations vary with the severity of serotonin toxicity, with many of the features of severe toxicity caused by poorly managed hyperthermia. The onset of symptoms is often sudden and may even occur within minutes of overdose or changing medication.

Clonus is the most important finding in establishing the diagnosis of serotonin toxicity. In a patient with a relevant drug history, clonus alone is considered sufficient for this diagnosis. There is no confirmatory laboratory test available.

Differential diagnoses to consider include:

- malignant hyperthermia (hyporeflexia, and skin may be mottled)
- anticholinergic poisoning (normal reflexes, erythematous skin and absence of bowel sounds)
- amphetamine or cocaine toxicity (toxicology screen)
- neuroleptic malignant syndrome (onset slow – 1 - 3 days)
- psychiatric illness (e.g. anxiety disorder, depression with agitation).

Management of serotonin toxicity

The management of serotonin toxicity involves the removal of the precipitating drug(s), providing supportive care (including the administration of intravenous fluids and electrolytes), the control of agitation, the administration of serotonin ($5HT_{2A}$) antagonists and the control of autonomic instability and hyperthermia. The intensity of management depends on the severity of the toxicity. The syndrome usually resolves within 24 hours of the initiation of this management, although it can persist, particularly if the drugs or their active metabolites have long elimination half-lives.

Mild cases are expected to respond to removal of the causative drug(s), supportive management and acute treatment with diazepam. Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected, and the use of serotonin antagonists considered.

In severe toxicity, in addition to the above management, the patient should immediately be sedated, administered a neuromuscular paralysing agent and intubated. Physical restraints should be avoided as they cause isometric muscle contraction that is associated with lactic acidosis and hyperthermia. Hypertension and tachycardia should be treated with short-acting agents such as intravenous nitroprusside or esmolol. Hyperthermia is controlled by eliminating excessive muscle activity.

Cyproheptadine is the recommended serotonin antagonist, although its efficacy has not yet been rigorously established. It is only available in an oral form, but the tablets can be crushed and administered via a nasogastric tube. The adult dose is 12 mg initially, followed by 2 mg every 2 hours while symptoms continue, and then a maintenance dose of 2 - 8 mg every 6 hours. Intramuscular chlorpromazine (50 - 100 mg in adults) or sublingual olanzapine administered sublingually (10 mg in adults) are alternative serotonin antagonists.

There are a number of drugs that should be avoided in cases of serotonin toxicity, including:

- propranolol, which can cause hypotension and shock and can abolish the tachycardia that can be used to determine the duration and effectiveness of therapy
- succinylcholine, because of the risk of arrhythmias in patients with hyperkalaemia associated with rhabdomyolysis
- bromocriptine and dantrolene, which may aggravate the serotonin syndrome.

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Table II. **Signs and symptoms associated with serotonin toxicity**

	Mild	Moderate	Severe
Neuromuscular hyperactivity	• Akathisia • Intermittent tremor or myoclonus • Hyperreflexia	• Tremor • Hyperreflexia and clonus (inducible and prolonged)	• Sustained clonus • Muscular rigidity and hypertonicity (lower > upper extremities) • Seizures
Autonomic hyperactivity	• Afebrile • Shivering • Tachycardia • Tachypnoea • Diaphoresis • Mydriasis • Diarrhoea	• Fever (38.5 - 41°C) • Diaphoresis (but normal skin colour) • Tachycardia • Tachypnoea • Hypertension • Mydriasis • Hyperactive bowel sounds	• Fever (> 41°C) • Severe hypertension and tachycardia that can deteriorate into shock
Mental status	• Unchanged	• Mild agitation or hypervigilance • Slightly pressured speech • Peculiar repetitive head turning behaviour	• Agitation • Excitement • Confusion • Delirium
Laboratory abnormalities			• Metabolic acidosis • Rhabdomyolysis • Elevated liver transaminases • Elevated creatinine/renal failure • Disemminated intravascular coagulopathy

Consultation with a medicines information centre, medical toxicologist, clinical pharmacologist or a poison control centre can help identify serotonergic drugs and drug interactions, and assist clinicians in anticipating and managing adverse effects. The following telephone numbers may be useful for advice on managing serotonin toxicity:

- Amayeza Info Centre: (011) 678-2332
- South African Drug and Toxicology Information Trust: (051) 444-3015
- Tygerberg Hospital Toxicology Service: (021) 938-6235
- University of Cape Town Medicines Information Centre: (021) 406-6829
- University of the Free State Poison Control and Medicine Information Centre: (051) 401-3177.

IN A NUTSHELL

Serotonin toxicity is not uncommon, and health care providers need to be able to avoid, diagnose and manage this potentially fatal syndrome which can be prevented by the modification of prescribing practices, particularly the avoidance of multi-drug regimens containing serotonergic agents.

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Recommended reading

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