

Serotonin Syndrome / Serotonin Toxicity

Serotonin toxicity can develop from large doses of a single pro-serotonergic drug, or when combinations of serotonergic agents are used together. Switching between antidepressants without an adequate "washout" period, can also lead to additive serotonin effects, resulting in toxicity. Symptoms are dose-related, rather than as a result of an idiosyncratic adverse drug reaction. The clinical manifestation can range from barely perceptible to lethal.

Serotonin syndrome refers to a collection of cognitive, autonomic and neuromuscular changes caused by an increase of serotonin in the central nervous system (CNS).

It has been recently suggested that the preferred term for this condition is "serotonin toxicity", as this emphasises a progressive increase in serotonin concentrations and resultant progression of toxic symptoms.

Clinical features of serotonin toxicity / syndrome

Neuromuscular effects	Autonomic effects	Mental status changes
hyperreflexia, myoclonus, tremor, ataxia, rigidity, restlessness, nystagmus, trismus	shivering, sweating, fever, hypertension, tachycardia, nausea, diarrhoea, salivation, tachypnoea	confusion, hypomania, agitation, headache, coma

Pathophysiology

Serotonin influences mood, sleep, vomiting and pain perception in the CNS, while affecting muscles, nerves and platelets in the periphery.

Serotonin toxicity can occur with excessive doses of a single serotonergic drug. However severe toxicity usually occurs from a combination of two or more agents, even when each is used at a 'normal' therapeutic dose, particularly when these drugs act to increase serotonin via different mechanisms. Increased serotonin concentrations can occur for a variety of reasons, including combinations of serotonin precursors, agonists, serotonin 'releasers', serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs) and some herbal medicines [see table].

Mechanism of overstimulation of serotonin receptors

Mechanism	Associated drugs
Excess concentration of precursors of serotonin or its agonists	buspirone, levodopa, lithium, L-tryptophan, sumatriptan (Imigran®), naratriptan (Naramig®), LSD
Increased release of serotonin	amphetamines, cocaine, ecstasy, phentermine, BZP
Reduced reuptake of serotonin	SSRIs (eg. fluoxetine, paroxetine, citalopram), TCAs (eg. amitriptyline, nortriptyline, imipramine, doxepin), venlafaxine, sertraline, pethidine, tramadol, dextromethorphan
Reduced serotonin metabolism	MAOIs: eg. selegiline, tranylcypromine, moclobemide, linezolid
Other agents implicated in serotonin toxicity	Dextropropoxyphene (Digesic® / Paradex®), ergotamines, pentazocine

LSD = lysergic acid diethylamide, BZP = benzylpiperazine, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors.

Diagnosis

This is largely based on the clinical features of serotonin toxicity (see above) and knowledge of drugs ingested.

Potential differential diagnoses include:

Anticholinergic poisoning. Patients show normal reflexes, mydriasis, agitated delirium, dry mouth, hot/dry erythematous skin, urinary retention and an absence of bowel sounds. By comparison, patients with serotonin toxicity have hyperactive bowel sounds, neuromuscular abnormalities, sweating and normal skin colour.

Neuroleptic malignant syndrome (NMS). This is traditionally regarded as an idiopathic reaction to dopamine antagonists, although NMS is often very difficult to distinguish from serotonin toxicity. It is important to realise that enhanced serotonin activity promotes dopamine antagonism, so the pharmacology is closely linked. It has a slow onset (tends to develop over several days), and causes bradykinesia or akinesia, "lead pipe" rigidity in all muscles, hyperthermia, fluctuating consciousness and autonomic instability. Serotonin syndrome/toxicity tends to occur more rapidly and is associated with hyperkinesia. Knowing the agent involved will help distinguish NMS from serotonin syndrome.

Malignant hyperthermia. This genetically-determined disorder occurs within minutes (though up to 24h) of exposure to inhalational anaesthetics, causing hypertonicity, hyporeflexia, hyperthermia and metabolic acidosis. The skin is often mottled with cyanotic and red-flushed areas. The clinical setting, rigor mortis-like rigidity of the skeletal muscles and hyporeflexia from malignant hyperthermia distinguish it from the less pronounced rigidity and hyperreflexia of serotonin syndrome.

Management

The aggressiveness of management depends on the severity of symptoms. Resolution is generally prompt following discontinuation of the precipitating agent(s). However symptoms can persist where drugs with a long elimination half-life, active metabolites or a prolonged duration of action are involved. Management is largely supportive by controlling agitation, hyperthermia and autonomic instability. Serotonin antagonists such as cyproheptadine may be useful in moderate to severe cases, but should only be used under specialist guidance.

Prevention

Combinations of serotonergic drugs, especially involving SSRIs (eg. fluoxetine, paroxetine) and/or MAOIs, should generally be avoided. The SSRIs as well as being serotonergic also inhibit the metabolism of CYP2D6 and 3A4 substrates (which include most centrally acting drugs). If a combination is unavoidable, specialist guidance is recommended. The new drug should be started at a low dose using slow titration to the desired effect. If possible, choose a short half-life drug, as it will clear quicker should problems occur.

Summary

Combining different serotonergic drugs in a patient can result in a well recognised spectrum of adverse effects, which can range from minor effects through to severe, life-threatening conditions. These combinations should be avoided where possible, or used under carefully monitored conditions. Usually, a more suitable, safer alternative is available. The Drug Information Service or your ward pharmacist is available to assist if needed.