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PRACTICE

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Serotonin syndrome

Serotonin syndrome is a potentially fatal and largely avoidable adverse drug reaction caused by serotonergic drugs. The steady increase in use of such drugs means all doctors need to be aware of what drugs increase serotonin and how to promptly recognise the syndrome and determine if it is potentially life threatening.

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What is serotonin syndrome?

Serotonin syndrome is a drug induced syndrome characterised by a cluster of dose related adverse effects that are due to increased serotonin concentrations in the central nervous system. It is also known as serotonin toxicity as it covers a spectrum from mild through to severe adverse effects depending, presumably, on the extent of increased serotonin.[1 2] Severe toxicity usually occurs only with a combination of two or more serotonergic drugs (even when each is at a therapeutic dose), one of which is generally a monoamine oxidase inhibitor.[1 3] Moderate toxicity has been reported with an overdose of a single drug and occasionally from increasing therapeutic doses.[1 3 4] Its incidence is difficult to assess, but in large case series of overdoses, moderate serotonin toxicity occurred in 15% of poisonings with selective serotonin reuptake inhibitors (SSRIs).[5]

In the central nervous system, serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter with many effects, including modification of mood, sleep, vomiting, and pain. Many drugs influence serotonergic neurotransmission, including some antidepressants, appetite suppressants, analgesics, sedatives, antipsychotics, anxiolytics, antimigraine drugs, and antiemetics.[1 2]

Severe or life threatening effects (rigidity and hyperthermia) seem to result only from stimulation of 5-HT_2 receptors, and only drugs that generally increase serotonergic effects are expected to cause serotonin toxicity. Thus antipsychotics, anxiolytics, antimigraine drugs, and antiemetics, which are serotonin antagonists or have effects on other specific receptors (5-HT_{1A}, 5-HT_{1D}, 5-HT_3), do not carry a significant risk of serotonin toxicity.[1 4 6] Drug classes that are implicated in serotonin toxicity (see box 1) are largely restricted to serotonin precursors, serotonin agonists, drugs causing serotonin release, serotonin reuptake inhibitors, and monoamine oxidase inhibitors.[4] However, some drugs from other classes also have these effects, including some herbal medicines (box 1). A few drug interactions are clearly linked to apparently classic cases of serotonin toxicity where the mechanism remains unclear.[7] These drugs generally have effects on other neurotransmitters and may have secondary effects on serotonin release or reuptake.

How does it present?

Serotonin toxicity starts within hours of ingesting drug(s) that cause an increase in serotonin. The classic triad of clinical features are neuromuscular excitation (such as clonus, hyperreflexia, myoclonus, rigidity), autonomic nervous system excitation (such as hyperthermia, tachycardia), and altered mental state (such as agitation, confusion) (fig 1⇓). The acute onset of these features should trigger a search for a toxic explanation (along with consideration of other conditions such as alcohol or drug withdrawal, non-convulsive seizures, and encephalitis).

Although case series showed moderate serotonin toxicity occurred in 15% of SSRI overdoses, there were no severe cases.[5] Serotonin toxicity did not occur in overdoses of the reversible monoamine oxidase inhibitor moclobemide alone. However, if a second serotonergic drug was ingested, serotonin toxicity was nearly always present and was severe in about half of these cases.[15]

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Box 1: Drugs that have been associated with moderate to severe serotonin toxicity*

Monoamine oxidase inhibitors

- Irreversible inhibitors—Phenelzine, tranylcypromine, iproniazid, isocarboxazid
- Reversible inhibitors of monoamine oxidase A—Moclobemide
- Non-psychotropic drugs—Linezolid, methylene blue (methylthioninium chloride)

Serotonin releasing agents

- Fenfluramine, sibutramine
- Amphetamine, methamphetamine, methylphenidate, phentermine
- Synthetic stimulants—Ecstasy, "bath salts" (cathinones, phenylethylamines)
- Serotonin reuptake inhibitors
- Selective serotonin reuptake inhibitors—Fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram
- Serotonin-noradrenaline reuptake inhibitors—Venlafaxine, desvenlafaxine, duloxetine
- Tricyclic antidepressants—Clomipramine, imipramine
- Opioid analgesics—Pethidine, tramadol, fentanyl, dextromethorphan
- St John's wort (*Hypericum perforatum*)

Miscellaneous

- Lithium
- Tryptophan
- Buspirone

*Severe serotonin toxicity generally involves a combination of agents from different drug classes[3 4 8-12]

How do we diagnose it?

The diagnosis of serotonin syndrome is clinical, and is plausible only in the setting of starting or increasing the dose (or overdose) of a potent serotonergic drug, or shortly after a second serotonergic drug is added leading to a drug interaction. Difficulties sometimes arise in identifying contributing agents because some drugs have persistent activity (irreversible monoamine oxidase inhibitors) or long half lives (fluoxetine) and may have been stopped weeks earlier. There should be a careful history of illicit drug use (stimulants such as cathinones and other synthetic stimulants, ecstasy, amphetamines, or cocaine) and of herbal medicines (such as St John's wort, ginseng, tryptophan, and pharmaceutical adulterants in appetite suppressants). Serotonergic actions of drugs that are not marketed as serotonergic (such as tramadol, fentanyl, linezolid, and methylene blue) are another trap for the unwary (see box 1).

Some pathognomonic features of serotonin syndrome and combinations of clinical signs are rarely seen in other conditions, and, with a supporting drug history, these can allow a confident diagnosis. The classic features in the diagnosis are generalised clonus (inducible, spontaneous, ocular), and these form the key components of the Hunter serotonin toxicity criteria, which have been validated and can be used to confirm the diagnosis of moderate or severe toxicity (fig 2⇓).[13] Clonus is usually most marked, and easily elicited, with ankle dorsiflexion: spontaneous clonus differs from rapid myoclonic jerks by being rhythmic, large muscle contractions, and is often triggered by minor movements or vibrations.

The term ocular clonus covers a range of abnormal involuntary movements that involve fine or coarse oscillations of gaze in all directions (examples at http://curriculum.toxicology.wikispaces.net/Serotonin_video).[16] These can be continuous or triggered by rapid eye movement. Other abnormal eye movements such as "ping pong gaze" (short cycle, periodic, alternating lateral gaze) may also be seen.

Severe serotonin toxicity is characterised by a rapidly rising temperature and rigidity and is again diagnosed on clinical grounds. Investigations are not of diagnostic value, except to diagnose complications (such as effects of hyperthermia—disseminated intravascular coagulation, multiorgan failure, rhabdomyolysis), other drug effects in overdose (electrocardiographic changes), or to exclude other diagnoses such as encephalitis or cerebral vasculitis (most commonly head scans, electroencephalography, lumbar puncture). Among patients also taking antipsychotic drugs it may be necessary to differentiate from neuroleptic malignant syndrome. The key differentiating features are that neuroleptic malignant syndrome is of relatively slow onset over days, and marked by extrapyramidal features and rigidity, but clonus is not a feature.

A different problem relates to mild serotonin toxicity, which can be difficult to distinguish from many medical conditions or other adverse drug effects. Patients taking therapeutic SSRIs commonly have features such as lower limb hyperreflexia or a few beats of ankle clonus without toxicity. A diagnosis of mild serotonin syndrome may be tempting for any febrile, tachycardic, agitated, or confused person taking psychiatric drugs (there are many reports along these lines quoting the presence of non-specific "Sternbach criteria"[14] but without the classic features of the Hunter serotonin toxicity criteria[13]). A diagnosis of adverse reactions to serotonergic drugs in such circumstances is largely a presumptive diagnosis after exclusion of other explanations and is possible only for drugs that are known to increase serotonin (both criteria are often ignored but explicitly specified as necessary in the Sternbach criteria[14]). The diagnosis is further supported by resolution on stopping serotonergic drugs, but whether the mechanism is mild serotonin toxicity or some other drug effect in such cases is moot. Mild serotonergic adverse effects in therapeutic use will not progress to severe toxicity in the absence of dose escalation or drug interactions. For some patients with a good therapeutic response, continuation of the drug at the same or a lower dose may be justifiable.

How can we treat it?

Serotonin syndrome in mild to moderate cases usually resolves in one to three days after stopping the serotonergic drugs. Severe toxicity is a medical emergency and may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular

coagulation, and adult respiratory distress syndrome,[17] and thus requires intensive supportive care.

Supportive care largely consists of sedation as required. Ensuring adequate hydration and careful monitoring of temperature, pulse, blood pressure, and urine output are necessary. Preventing hyperthermia and subsequent multiorgan failure is a key goal in severe serotonin toxicity. In animal models lowering temperature also indirectly down regulated $5HT_{2A}$ receptors in the central nervous system and reduced serotonin levels.[2] Sedation to reduce muscle hyperactivity (such as midazolam infusion or oral diazepam), active cooling (fans with water sprays, ice packs, or cooling blankets), and even paralysis and ventilation may be useful in severe cases.

Serotonin antagonists and in particular $5HT_{2A}$ receptor antagonists reduce hyperthermia and other severe manifestations in animal studies.[1 2 8] For severe serotonin toxicity, intravenous chlorpromazine is the most commonly used serotonin antagonist, but intravenous fluid loading is essential to prevent hypotension.[8] Oral cyproheptadine has been used to treat moderate serotonin toxicity, with doses of 8-16 mg up to a daily maximum of 32 mg. Whether its sedative or serotonin antagonist effects are more important remains unclear. In moderate serotonin toxicity agitation is generally the most troublesome symptom, and sedation with oral diazepam may be all that is required. There are no clinical trials or other strong evidence supporting any of the above approaches to treatment,[8] but recovery is usual and mortality low (<1%) when such approaches have been applied.[5 15]

How can we prevent it?

Several systematic reviews clarify the extent to which severe serotonin syndrome may result from drug interactions.[3 4 6 9-11] However, spurious associations and cautions have proliferated elsewhere in the medical literature, and product information is a major impediment to sensible decision support in this area. Clinicians prescribing an SSRI (and their patients) can expect to be warned of up to 1000 interacting drugs (for example, on www.drugs.com/), with hundreds of these warning of "rare but serious" serotonin syndrome. Interactions of an SSRI with any monoamine oxidase inhibitor might be lethal and should be avoided at all cost. However, interactions with other serotonin reuptake inhibitors are likely to be minor (additive effect), and interactions with serotonin releasing agents (such as amphetamines) might even attenuate toxicity.[18] Further, many listed interactions—such as with carbamazepine, most tricyclic and atypical antidepressants,[4 12] and triptans[6]—have little or no evidence to support the contention that serotonergic effects are increased by coadministration. However, clomipramine and imipramine are much more serotonergic than other tricyclic antidepressants and have caused serotonin toxicity.

An awareness of drugs with potent serotonergic effects is the key to preventing drug interactions. It is apparent from systematic reviews of case reports[3 4 6 9-11] that nearly all severe serotonin syndromes involve a monoamine oxidase inhibitor, and the relatively small number of these can easily be committed to memory (box 1). Washout periods should be observed when switching antidepressants. If possible avoid the use of serotonergic drugs for non-psychiatric conditions (such as tramadol for analgesia). Patients also need to be aware of the potential for serious drug interactions, especially given the existence of over the counter drugs and herbal medicines with serotonergic activity (box 1).

Some individuals seem to be more susceptible, but it is unclear if pharmacokinetic (such as decreased drug metabolism) or pharmacodynamic (such as serotonin receptor polymorphism) differences explain this, and strong consistent pharmacogenetic associations have not been found.[19] No evidence has been found to support theories that potent dietary monoamine oxidase inhibitor compounds are a cause of serotonin toxicity in highly susceptible individuals.[20]

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Summary points

- Serotonin syndrome is the clinical manifestation of excess serotonin in the CNS, resulting from therapeutic use or overdose of serotonergic drugs. The most severe cases involve drug interactions, particularly between MAO inhibitors and serotonin reuptake inhibitors or serotonin releasing drugs.
- The diagnosis is clinical, and should be suspected if this triad of clinical features is present: neuromuscular excitation (e.g. clonus, hyperreflexia, myoclonus, rigidity), autonomic excitation (e.g. hyperthermia, tachycardia), and altered mental status (e.g. agitation, confusion). Confirmation of the diagnosis should be based largely on pathognomonic neuromuscular features (as per the Hunter Serotonin Toxicity Criteria) as the other features are non-specific.
- The spectrum of toxicity ranges from mild to life threatening; management can escalate from simple cessation of the drug(s), to intensive care and active cooling. Anti-serotonergic drugs may be used but there is little evidence to support this.

Figures

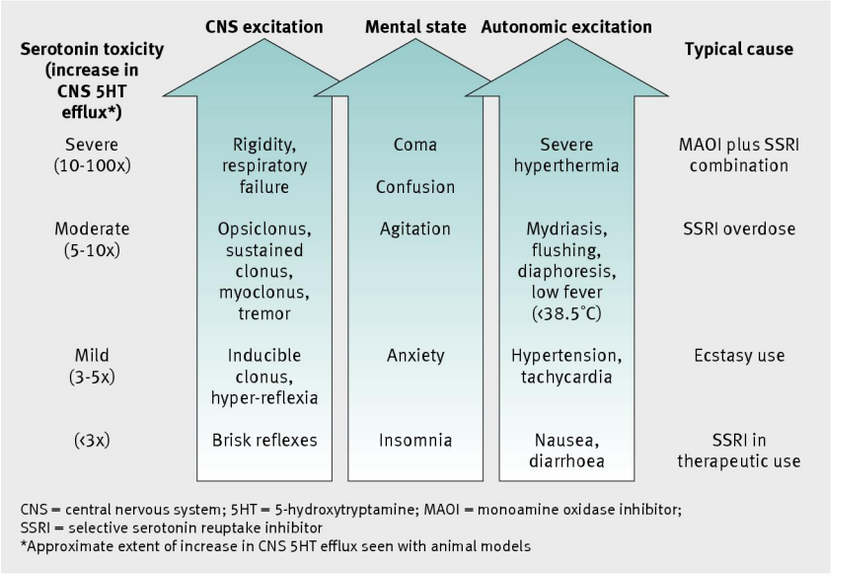

Fig 1 Spectrum of effects according to the triad of common clinical features in serotonin syndrome[2-4 8 13 14]

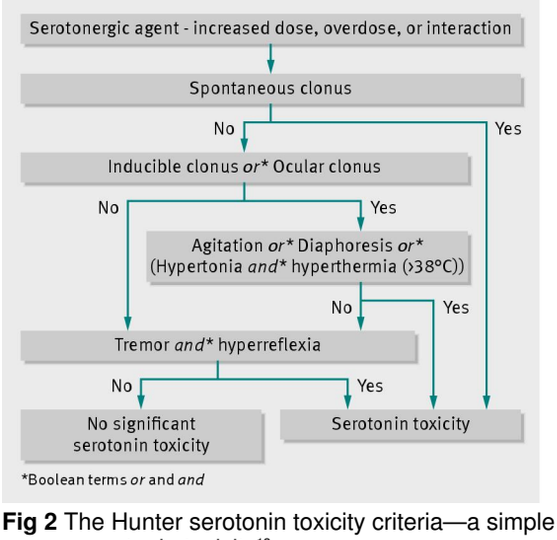

Fig 2 The Hunter serotonin toxicity criteria—a simple flowchart to guide clinical confirmation of diagnosis of moderate or severe serotonin toxicity[13]