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Research

Serotonin toxicity: Implications for clinical practice

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Abstract

Introduction

Serotonin toxicity – or serotonin syndrome – is a potentially life threatening adverse reaction to the use of one or more serotonergic drugs. Patients presenting with low-level obscure symptoms may have pathophysiology rooted in adverse dopamine and serotonergic poly-pharmacy reactions involving illegal, over-the-counter and/or prescription drugs.

Aim

This paper presents an overview of serotonin toxicity, the criteria for diagnosing serotonin toxicity, and discusses management strategies.

Conclusion

Due to the increasing prevalence of serotonergic drugs, both legal and illicit, a high index of suspicion for serotonin toxicity across a broad patient demographic is recommended. We also recommend education and further research to both raise awareness and advance the clinical competence of health care providers.

Keywords:

Serotonin toxicity; serotonin syndrome; selective serotonin reuptake inhibitors; tricyclic antidepressants; monoamine oxidase inhibitors; MDMA; ecstasy; adverse drug reactions; drug overdoses; diagnostic criteria; clinical practice; prehospital care, paramedicine

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Introduction

This paper provides clinical descriptions of a potentially dangerous and perhaps largely under-diagnosed syndrome. With the growing demand for paramedics to 'assess, treat and leave' (especially in remote and extended care situations) our intent is to provide a succinct yet detailed discussion of the syndrome. Paramedic case management in serotonin syndrome is symptomatic and relatively simple, however we advocate that a solid understanding of the underlying chemistry, pathophysiology and relevant social matters is of particular importance to paramedic practice. This paper provides a single, detailed, evidence-based reference paper for paramedics and other pre-hospital clinicians.

Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine chemical that has effects on many body systems via a range of serotonin receptors (1). Serotonin's peripheral actions include promoting platelet aggregation, regulation of atrioventricular and sinus node rates, vascular tone and gastrointestinal motility (1). Serotonin also acts centrally as a neurotransmitter. These central effects include regulation of mood, motor control, sleep, sexual behaviour, appetite, vomiting and body temperature (1).

As a neurotransmitter, serotonin is released from vesicles in the presynaptic nerve endings, crosses the synaptic cleft and activates serotonin receptors on the postsynaptic nerves, leading to an effect (2,3). Serotonin is then transported back into the presynaptic nerve for re-use or is broken down by the monoamine oxidase enzyme (2).

Pharmacological use of serotonergic drugs

Several drug classes are used pharmacologically to modify the effects of serotonin to alleviate depression (4). Selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), and non-selective tricyclic antidepressants (TCAs) inhibit the uptake of serotonin from the synaptic cleft, which is believed to incur an antidepressant effect due to a higher concentration of serotonin on recipient neurones. Similarly, monoamine oxidase inhibitors (MAOIs) are used as antidepressants by slowing the breakdown of serotonin (5). 5-HT₁ receptor agonists are used to treat migraine and 5-HT₃ receptor antagonists are used to treat nausea and vomiting.

General practitioners diagnose and treat most cases of depression in Australia, with SSRIs the most common drug prescribed for pharmacological management of patients (7). Other mental and health conditions may also be treated with SSRIs. These include anxiety, eating, obsessive compulsive disorders and select chronic pain presentations (8). Of all the drugs within this class of anti-depressants, sertraline

is most commonly used, and has been since 1996 (7). Table 1 outlines commonly prescribed SSRIs and other antidepressants.

Serotonin toxicity and prevalence

Serotonin toxicity is the result of excessive activation of serotonin receptors, and due to serotonin's widespread central and peripheral actions, results in a range of untoward effects (2). The precipitating factor can involve one or more serotonergic drugs involving a newly added drug, increased therapeutic dosage or overdose (3,9). Serotonin toxicity generally has a period of onset of 6–24 hours (10,11). The effects can be mild, for example, minor tremor and diaphoresis, to severe, with hypertonicity, hyperthermia, seizures and shock (2). There is no direct test for serotonin toxicity. Diagnosis is based on exclusion by differential diagnoses and suspicion of initiation or increased usage of a drug with serotonergic effects (2).

The prevalence of serotonin toxicity in Australia is not clear, in part because cases may not be recognised as such (9). Data from 1987 to 2003 has shown that 14% of hospital admissions from deliberate overdose of serotonergic drugs resulted in serotonin toxicity (3). The Adverse Drug Reaction Database held by Therapeutic Goods Administration reports 497 cases of serotonin toxicity between 1993 and late 2015 (12). The majority of these cases, up to early 2004, involved two or more serotonergic drugs (5).

A study in 2008 showed multiple serotonergic drug use was associated with eight percent of Australian veterans (13). The same study noted that in 2005 in excess of 7 million SSRI prescriptions and 2 million tramadol prescriptions were dispensed (13).

Patient outcomes subsequent to serotonin toxicity are sometimes poor, with one case series of 12 patients with similar presentations demonstrating a 50 percent likelihood of death or permanent disability (14).

Drugs and serotonin toxicity

Drugs acting pharmacologically on serotonin receptors can cause serotonin toxicity. These are primarily SSRIs, SNRIs, MAOIs, TCAs, 5-HT₁ agonists and 5-HT₃ antagonists (see Table 1). Additionally, illicit drugs can enhance the release of serotonin from the presynaptic nerves (eg. cocaine, amphetamine and its derivatives, including 'ice') (15). While amphetamine-based drugs act primarily on dopamine receptors, and 3,4-methylenedioxymethamphetamine (MDMA) action is serotonergic, the longer term use of amphetamines are capable of causing neurotoxicity that damages both dopamine and serotonergic receptors (16). Additionally, for consumers of SNRIs, amphetamines damage noradrenaline pathways with consequent heightened risk of toxicity (16).

Many other prescribed and over-the-counter medications have been identified in causing serotonin toxicity (see Table 1). These include tramadol, opioids, and lithium, and herbal products such as hypericum (St John's wort) and ginseng (2,17). Morphine, codeine, buprenorphine and hydrocodone are not known to be associated with serotonin toxicity (17, 18). Case reports suggest oxycodone may enhance serotonin toxicity in combination with other serotonergic drugs (18).

Consideration should be given to drugs that do not directly affect serotonin, but do interact with serotonergic drugs. Many serotonergic drugs, such as SSRIs and SNRIs, are metabolised through the cytochrome P450 (CYP) enzymes (11). Inhibition of these enzymes will cause accumulation of these serotonergic drugs and so indirectly promote serotonin toxicity, for example, fluconazole, an antifungal without serotonergic activity, may inhibit CYP3A4/5 moderately and CYP29C strongly allowing accumulation of fluoxetine, amitriptyline and ondansetron (19). Serotonergic drugs may also inhibit these enzymes further enhancing the additive potential for serotonin toxicity, for example, fluvoxamine (an SSRI) is a strong inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP3A4/5 impacting amitriptyline, clomipramine, duloxetine, citalopram, fentanyl, fluoxetine, imipramine, moclobemide, ondansetron, zolmitriptan and fluvoxamine itself (19).

Selective serotonin reuptake inhibitors and SNRIs, the most

common first-line treatments for depression, can interact with MDMA and similar substituted amphetamines causing serotonin toxicity. The risk is, however, much higher when amphetamines are taken with MAOIs (20).

Though serotonin toxicity can result from a toxic dose of a single serotonergic drug, it is most frequently the result of an adverse interaction between two or more different drugs. Of greatest risk in the illicit administration of MDMA – 'ecstasy' are concomitant serotonin-modifying agents, such as cocaine or amphetamine, which are often pressed into the same pill – (21) or an MAOI (20,22).

The composition of illicit pills is notoriously variable. For example, while MDMA might be the desired ingredient, a number of other compounds are likely to be present, with the concentration of MDMA typically 10-30%, but frequently 'ecstasy' pills contain no MDMA (21).

To aid sales, illicit pills made by local amateur chemists may appear visually identical despite containing different ingredients (21). These local pills may also be manufactured to replicate the shape of pills from overseas that have an anecdotal reputation of being high quality (23). Fortunately, the identification of the specific psychostimulants consumed is generally not clinically relevant as the management of serotonin toxicity is largely supportive (24).

Antidepressant	Opioid	Psychedelic
Amitriptyline	Dextromethorphan	Amphetamine
Citalopram	Fentanyl	Cocaine
Clomipramine	Methadone	Lysergic acid diethylamide (LSD)
Dothiepin	Oxycodone	Methamphetamine
Doxepin	Pethidine	Methylenedioxyamphetamine (MDA)
Duloxetine	Tramadol	3,4-methylenedioxy-methamphetamine (MDMA)
Escitalopram		
Fluoxetine	Antimigraine 5HT1	Other
Fluvoxamine	Eletriptan	Ginseng
Imipramine	Naratriptan	Hypericum
Mirtazapine	Rizatriptan	Linezolid
Nortriptyline	Sumatriptan	Lithium
Paroxetine	Zolmitriptan	Selegiline
Sertraline		Tryptophan
Venlafaxine	Anti-nausea 5HT3	
Phenelzine	Granisetron	
Tranylcypromine	Ondansetron	
Moclobemide		

Table 1. Medications associated with serotonin toxicity - potential varies between drugs (2)

Diagnostic tools

Two diagnostic criteria for serotonin toxicity appear frequently in literature, the Sternbach Criteria (Table 2) (25) and the Hunter Serotonin Toxicity Criteria (HSTC) (26). The Sternbach Criteria was the first diagnostic tool developed to identify

serotonin toxicity, however in emergency presentations this has been superseded by HSTC (Figure 1) due to superior sensitivity (84% vs. 76%) and specificity (97% vs. 96%). It is now almost universally employed as the diagnostic criteria for serotonin toxicity.

A.	Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present:
1)	Mental status change (confusion, hypomania)
2)	Agitation
3)	Myoclonus
4)	Hyperreflexia
5)	Diaphoresis
6)	Shivering
7)	Tremor
8)	Diarrhoea
9)	Incoordination
10)	Fever
B.	Other aetiologies (such as infections, metabolic disorders, substance abuse or withdrawal) have been ruled out
C.	A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above

Table 2. The Sternbach Criteria for serotonin syndrome (25)

Clinical features of toxicity

The clinical features of serotonin toxicity are characterised by a triad of autonomic stimulation, neuromuscular excitation and mental status changes (27). Specific signs are summarised in Table 3 (2). The clinical sequelae may include a combination

of any of the following signs, dependent on the severity of the presentation: seizure, metabolic acidosis, hyperthermia with subsequent rhabdomyolysis, kidney and liver failure, disseminated intravascular coagulopathy and eventual death.

Neuromuscular excitation	Autonomic instability	Mental status changes
Rigidity	Dilated and unresponsive pupils	Agitation
Hyperreflexia	Tachycardia	Excitement
Hypertonia	Tachypnoea	Irritability
Teeth grinding	Fever	Hyperactivity
Myoclonus	Diarrhoea	Restlessness
Ataxia	Diaphoresis	Anxiety
Tremor	Hyper/hypotension	Hypomania
Nystagmus	Flushing	Confusion
	Abdominal pain	Lethargy
		Coma

Table 3. Clinical features of serotonin toxicity (2)

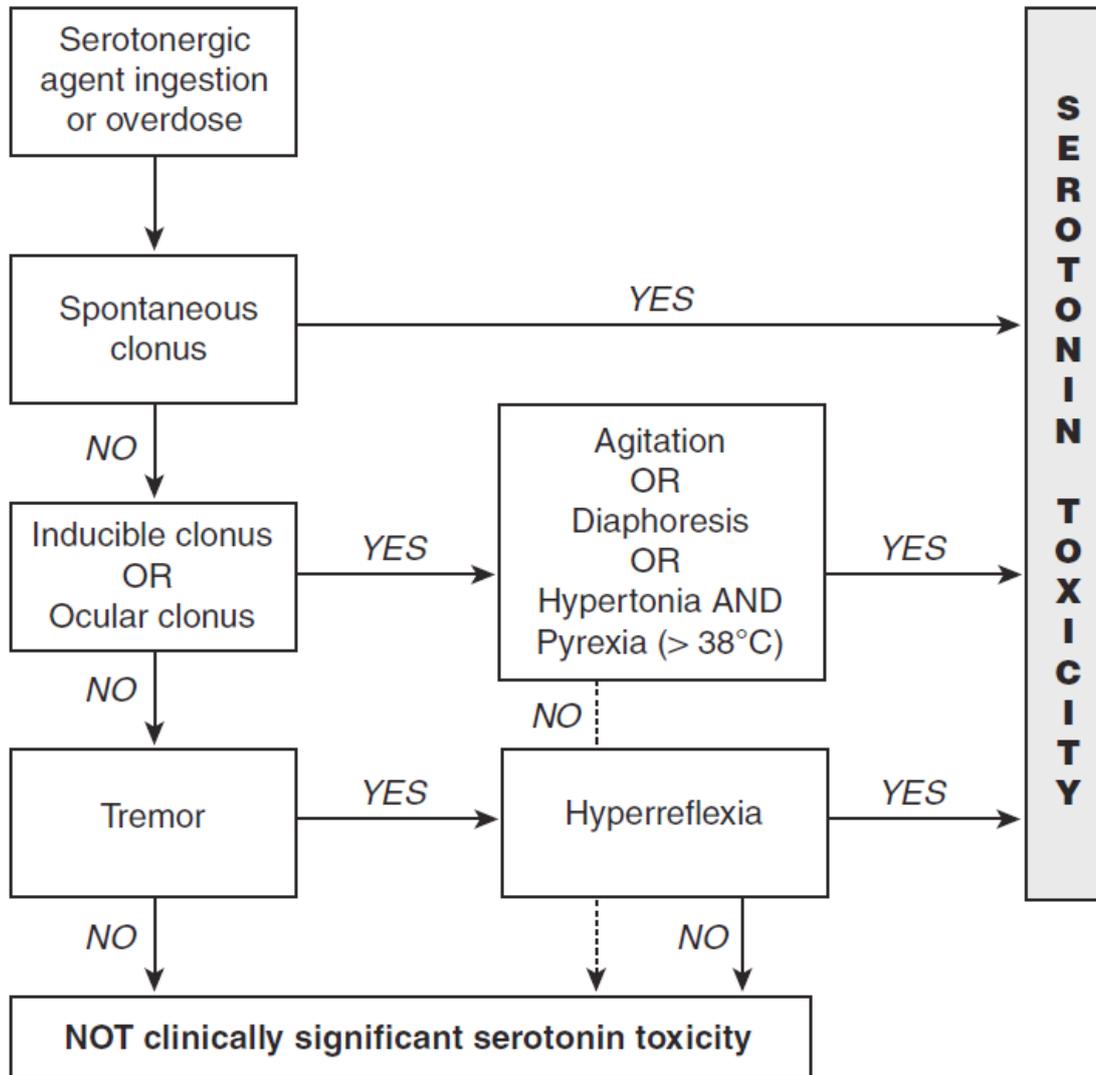


Figure 1. The Hunter Criteria for serotonin toxicity (26)

The following cases, displaying the out-of-hospital characteristic of incomplete clinical information, outline how serotonin toxicity may present as either obvious high severity (Case 1) or as subtle low severity (Case 2) presentations.

**Case 1
 Presentation**

A female, 21 years of age, was assessed and managed by paramedics at a 'rave' party after taking two 'ecstasy' tablets. Examination revealed a Glasgow Coma Score of 9, hyperreflexia, agitation, tremor, tachycardia with ischaemic changes, hypotension and tachypnoea. Blood pressure and heart rate indicated a Shock Index of 1.6. Additionally, the patient was hyperpyrexia with dry, pale skin and dilated pupils with sluggish reaction to light. Further assessment revealed myoclonus in the right calf muscle.

Outcome

Aggressive pre-hospital management including IV cooling, rapid sequence induction and tracheal intubation was instigated and the patient was transported urgently to a Category 1 hospital with intensive care facilities. Application of the Hunter Serotonin Toxicity Criteria (26) indicated the patient met the criteria for toxicity.

The patient remained comatose for approximately 24 hours before sedation was withdrawn, whereupon seizure activity developed. A cranial CT showed generalised cerebral oedema that necessitated diuretic therapy. Biomarkers in combination with a functional assessment at 36 hours indicated a degree of brain demyelination.

Case 2

Presentation

A community nurse identified mild neurological impairment and an autonomic response while assisting a socially isolated male, 70 years of age, with a back injury at home. Specifically, the patient displayed slight confusion and agitation with associated diaphoresis, mildly elevated tympanic temperature and fine muscle tremor.

The depressed patient had been taking sertraline 100 mg/day for the past several months, having lost his wife to cancer. Recently, a fall at home resulted in reduced mobility and significant pain. He was prescribed tramadol 150 mg and naproxen 500 mg twice daily. The patient was otherwise well.

Outcome

Being aware of the additive serotonergic potential of tramadol plus sertraline and suspecting a drug interaction due to a recent medication change, the nurse convinced the patient to seek further assessment at the local hospital. On arrival, application of the Sternbach Criteria (25) suggested serotonin toxicity, as other differential diagnoses were unlikely. His medication was amended and he was sent home after 2 days. A high index of suspicion by the community nurse averted a potentially serious adverse patient outcome.

Management

A high index of suspicion and the use of established and validated criteria will assist in identifying serotonin toxicity (24). While the literature supports the HSTC as being superior to the Sternbach Criteria, both potentially have a place in pre-hospital assessment of serotonin toxicity, depending on patient presentation and environmental factors.

In a subtle presentation, identification of a known serotonergic agent, in association with at least three specified clinical features and discounting other aetiologies such as infection or metabolic causes, may make the Sternbach Criteria useful. Alternatively, the HSTC requires only appropriate suspicion of serotonergic drug ingestion and key neurological features. The simpler algorithmic presentation of the HSTC may therefore be of benefit in the severe presentation.

A step-wise approach to management is supported, with aggressiveness of treatment based on clinical presentation (24). A high index of suspicion regarding recognition of potential toxicity is needed in the more subtle presentation, whereas in severe cases, aggressive management of presenting clinical issues is vital.

Differential diagnosis is the key to recognising a subtle presentation of serotonin toxicity, as evidenced in Case 2.

In this presentation, simple supportive care and removal of the offending agent is all that is necessary. The addition of a benzodiazepine to assist with tremor and agitation may be prudent, depending on severity. Activated charcoal may also be used within an hour of overdose of serotonergic medications (2,27). Transport to an appropriate medical facility and review by medical staff is a priority regardless of severity.

In suspected severe toxicity, aggressive and early management is fundamental to reducing morbidity and mortality. Key management considerations of this presentation include benzodiazepines for control of hyperreflexia, tremor and possible seizures (24).

Hyperthermia is a serious component of severe serotonin toxicity and rapid cooling is necessary for reduction of core temperature (28). This may be achieved with surface cooling and infusion of cold isotonic crystalloid, (28) which additionally will assist in managing volume depletion.

Hyperthermia should not be treated with antipyretic medications such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), as the cause of hyperthermia is increased muscle activity and not a centrally-mediated change in temperature set point (10).

Oxygenation is fundamental to offset the high metabolic demands. Again depending on severity of presentation, neuromuscular blockade, sedation and endotracheal intubation may be required (24).

A common adverse event from the induction of anaesthesia is hypotension, which occurs in 23% of cases (29). The strongest predictor of hypotension is a pre-intubation shock index greater than 0.8 (30). At the time of induction, the patient in Case 1 had a shock index two times higher at 1.6.

First-line management for rate-related myocardial ischaemia is focused on reducing the rate. In Case 1 however, the administration of a negative chronotrope would have led to vasodilation and a subsequent decrease in blood pressure (31) and a detrimental outcome.

In hospital

For patients presenting with low-level toxicity the treatment is supportive with clinically supervised reduction or removal of the drugs involved. In more severe cases direct antagonism of excess serotonin may be treated pharmacologically with 5-HT₂ antagonists such as cyproheptadine or chlorpromazine. However, chlorpromazine is not recommended if the patient is hypotensive or if neuroleptic malignant syndrome cannot be ruled out (2,27).

Conclusion

The increasing prevalence of serotonergic drugs, both legal and illicit, demands increased vigilance in the assessment of patients in various environments as fundamental to averting adverse outcomes. Whether serotonin toxicity presents subtly with ambiguous history, or as a critically ill patient requiring aggressive management, a high index of suspicion is mandatory.

We recommend clinical education and further research to both raise awareness and advance the clinical competence of health care providers.

Conflict of interest

The authors declare they have no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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