Serotonin Syndrome - A Focused Review

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Abstract

Background: Serotonin syndrome is a potentially life-threatening syndrome with manifestations spanning from mild adverse effects to life-threatening toxicity. The syndrome is caused by overstimulation of serotonin receptors by serotonergic drugs. Since the use of serotonergic drugs is increasing, primarily due to the widespread use of selective serotonin reuptake inhibitors, cases of serotonin syndrome have likely seen a parallel increase. The true incidence of serotonin syndrome remains unknown due to its diffuse clinical presentation. Objectives: This review aims to provide a clinically focused overview of serotonin syndrome, covering its pathophysiology, epidemiology, clinical manifestations, diagnostic criteria, differential diagnosis, and treatment as well as classifying serotonergic drugs and their mechanism of action. The pharmacological context is emphasized, as it is crucial for detection and management of serotonin syndrome. Methods: Focused review based on a literature search using the PubMed database. Findings and conclusion: Serotonin syndrome can occur through therapeutic use or overdose of a single serotonergic drug, or as a drug interaction between two or more serotonergic drugs. Central clinical features consist of neuromuscular excitation, autonomic dysfunction and altered mental status, occurring in a patient undergoing new or altered serotonergic therapy. Early clinically recognition and treatment are crucial to prevent significant morbidity.

Serotonin Syndrome

A Focused Review

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Abbreviations: *selective serotonin reuptake inhibitors (SSRI); serotonin-norepinephrine reuptake inhibitors (SNRI); monoamine oxidase inhibitors (MAOI); tricyclic antidepressants (TCA); 3,4-Methylenedioxy methamphetamine (MDMA); lysergic acid diethylamide (LSD); 5-HT (5-Hydroxytryptamine); CYP (Cytochromes p450).*

1. Introduction

Serotonin syndrome is a syndrome - or drug toxidrome - precipitated by the use of serotonergic drugs, leading to excessive activation of both central and peripheral serotonin postsynaptic receptors. As a consequence, patients with serotonin syndrome experience varieties of altered mental status, autonomic hyperactivity and neuromuscular aberrations with risk of fatal outcomes [1–5].

Many drugs – be it in therapeutic doses, overdoses, intoxications or as a complex drug interaction between two or more serotonergic agents – can result in serotonin syndrome. At the same time, the actual incidence of serotonin syndrome is unknown due to its diffuse clinical presentation. As a result, serotonin syndrome is often not recognized or formally diagnosed [4].

The objective of this review is to enhance clinicians' awareness of serotonin syndrome by providing an overview of the condition with an emphasis on serotonergic drugs and their impact on serotonergic pathways as this knowledge is essential for detecting as well as managing the syndrome.

2. Method

This focused review is based on a literature search using the PubMed database. The keywords used in the search were: 'serotonin syndrome', 'serotonin toxicity' and 'serotonergic syndrome' in combination with 'serotonin/serotonergic agents', 'pharmacology', 'serotonin receptors', 'drug effects', 'diagnosis' and 'treatment'. A cross-reference search based on the examined literature was performed.

3. Serotonin syndrome

3.1 Pathophysiology

Serotonin (5-Hydroxytryptamine, 5-HT) functions as a biochemical mediator both peripherally and centrally.

Its peripheral actions include stimulating vasoconstriction, uterine contraction, bronchoconstriction, gastrointestinal motility, and platelet aggregation. In the central nervous system, serotonin is present in the raphe nuclei of the brainstem, where it inhibits excitatory neurotransmission and modulates wakefulness, attention, mood, appetite, thermoregulation, motor tone, and emesis[6,7]. Thus, Serotonin is involved in numerous complex physiological processes and many drugs have been developed to manipulate serotonin concentrations [8,9].

Serotonin syndrome arises from an excessive stimulation of serotonin receptors in both the central and peripheral nervous systems, triggered by drugs that elevate synaptic serotonin levels . Serotonin can bind to multiple families of 5-HT receptors. While no single receptor is solely responsible for serotonin syndrome,

it is acknowledged in the literature that the subtypes 5-HT1A and 5-HT2A (particularly the latter) play a significant role [2,10].

Serotonin syndrome is by definition a drug-induced syndrome. It is also referred to as 'serotonin toxicity', which accurately reflects that the syndrome covers a dose-dependent spectrum or a continuum of serotonergic effects from mild adverse effects to life-threatening cases of toxicity[1,4,9,11,12].

3.2 Epidemiology

The true incidence of serotonin syndrome remains unknown, and the number of cases is likely significantly higher than reported. The clinical manifestation of serotonin syndrome varies, and its symptoms can resemble those of several other medical conditions. Mild cases are frequently overlooked or dismissed thus making serotonin syndrome likely to be underdiagnosed in clinical practice [1,4,13]. At the same time, reported cases of serotonin syndrome appears to be on the rise; likely as a result of the widespread usage of serotonergic medications, in particular selective serotonin reuptake inhibitors (SSRIs) [1,11,13–15].

As a rough estimate, the Toxic Exposure Surveillance System, a major US database, reported 54,410 cases of SSRI poisoning in 2016, with 102 resulting deaths. It is speculated that approximately 15% of these poisonings meet criteria for serotonin syndrome [11].

4. Serotonergic drugs and their pharmacological mechanism of action

4.1 Serotonergic drugs

Numerous drugs affect the serotonergic neurotransmission[1,4,8,9,16]. Table 1[16] provides a list of drugs commonly used (or misused) that have been associated with serotonin syndrome.

The involvement of antipsychotics in serotonin syndrome is discussed in the literature. Case reports suggest an association between specifically second-generation antipsychotics and serotonin syndrome[17]. These drugs antagonize dopamine (D2) and serotonin (5-HT2A) receptors, but many of them also act as partial agonists of 5-HT1A receptors [18,19]. The exact mechanism is not fully comprehended, but a common hypothesis in the literature is that the 5-HT2A receptor antagonism by these second-generation antipsychotics may result in serotonin accumulation and cumulative activation of 5-HT1A receptors [1,2,4,6,10,17,20].

Paradoxically, there is also anecdotal evidence supporting the effectiveness of second-generation antipsychotics – specifically olanzapine and chlorpromazine – in the *treatment* of serotonin syndrome. Safety and efficacy has not been thoroughly evaluated, and second-generation antipsychotics are not considered part of the recommended treatment [1,2].

The drugs commonly associated with the development of serotonin syndrome differs by their mechanism of action with respect to serotonin. In table 2[1], these drugs are classified based on their pharmacological mechanism of action.

The inhibition of specific cytochrome P450 (CYP450) enzymes are a matter of potential great clinical importance as it can result in increased systemic exposure of some serotonergic drugs. For instance, concomitant use of an SSRI (e.g. sertraline) and tramadol – the most common cause of serotonin syndrome – may create a vicious cycle where the SSRI inhibits the metabolism of tramadol, which is a pro-drug that is activated by the CYP2D6 enzyme, causing increased serotonergic activity[1,4].

4.2 Clinical implications

Serotonin syndrome can occur with the use of a single serotonergic drug – in therapeutic doses or in overdose – but is seen most frequently and with a greater degree of toxicity when combining several serotonergic drugs. The most severe cases described in the literature often involve an monoamine oxidase inhibitor (MAOI) in combination with another serotonergic drug, typically an SSRI[4,8,11,21]. Concomitant administration of an SSRI and tramadol is the most frequent cause of serotonin syndrome[4,22].

Individuals exhibit varying sensitivity to serotonergic influence. Whether this is due to individual pharmacokinetic conditions (e.g. reduced drug metabolism) or individual pharmacodynamic circumstances (e.g. serotonin receptor polymorphism) is not known [8]. Although a critical level of serotonin appears to be necessary for the development of serotonin syndrome, patients can present with the syndrome at varying drug dosages and combinations, indicating considerable individual variability in that critical value[4,23]

While it is not contraindicated to combine drugs with serotonergic effects, clinical caution should be exercised[8]. The key to preventing – and managing – serotonin syndrome is recognizing the syndrome and paying appropriate attention to the prescription of serotonergic drugs as well as an understanding of the clinical symptoms and diagnostic criteria.

5. Diagnosis

5.1 Clinical manifestations

Serotonin syndrome occurs within hours of taking one or more drugs with a serotonergic effect. The classic triad of symptoms consists of: Neuromuscular abnormalities *(* clonus, myoclonus, tremor, hyperreflexia, hypertonicity), autonomic hyperactivity (hyperthermia, tachycardia, hypertension, diarrhea) and altered mental status (agitation, confusion, anxiety, coma) [1,4,8]. In table 3[21], these symptoms are tentatively categorized according to severity.

5.2 Diagnostic criteria

Serotonin syndrome is a clinical diagnosis based primarily by evaluation of the patient's medical history (use of serotonergic drugs or illicit substances, change in dose or addition of new drugs) and a physical examination [2–4]. No biomarkers have been identified for serotonin syndrome, although certain nonspecific laboratory abnormalities, such as leukocytosis, low bicarbonate level, elevated creatinine level, and elevated transaminases, have been reported[4].

Several diagnostic criteria have been suggested for the categorization of serotonin syndrome. The most accurate are the Hunter Serotonin Toxicity Criteria that have replaced the older Sternbach Criteria. The Hunter Criteria have 84% sensitivity and 97% specificity for moderate and severe serotonin syndrome when compared to the diagnostic gold standard for serotonin syndrome: a diagnosis by a medical toxicologist. Mild cases of serotonin syndrome are difficult to distinguish from numerous other medical conditions and side effects, which is why the Hunter Criteria cannot be used for this [3,8].

The Hunter Serotonin Toxicity Criteria appear in figure 1[3] below.

5.3 Differential diagnosis

Relevant differential diagnoses for serotonin syndrome includes neuroleptic malignant syndrome, anticholinergic toxicity, serotonergic discontinuation syndrome, sympathomimetic drug intoxication, malignant hyperthermia, meningitis and encephalitis [16].

Neuroleptic malignant syndrome, a life-threatening neurological disorder most often caused by an adverse reaction to antipsychotic drugs[24], may be confused with serotonin syndrome, especially in patients taking multiple psychiatric drugs. Neuroleptic malignant syndrome progresses more slowly and is associated with rigidity, but not hyperreflexia or clonus, compared to serotonin syndrome [4,8,11,16]. As shown in table 4[4,8,11], clinical features, drug usage and time course provides useful information for distinguishing between the syndromes.

6. Treatment

The primary approach to treating serotonin syndromes involves immediate discontinuation of all serotonergic drugs and providing supportive care to maintain stable vital signs. With proper treatment, serotonin syndrome usually resolves within 24 hours without sequelae[1,11].

In mild cases, discontinuation of serotonergic drugs, observation, supportive care and, if needed, benzodiazepines for sedation are generally sufficient. Moderate cases of serotonin syndrome has been suggested to be treated with a serotonin antagonist in the form of cyproheptadine, a histamine-1 receptor antagonist with 5-HT1A and 5-HT2A antagonistic properties [25], but the level of evidence for this treatment is poor [1,26]. Severe, life-threatening cases – often presenting with hyperthermia >41°C – demands urgent treatment in the intensive care unit [1,4,8,11].

The prognosis of serotonin syndrome is favorable if the patient is diagnosed and treated. In cases of uncertain diagnosis, discontinuation of any serotonergic agents and initiation of supportive care is advisable [4].

7. Conclusion

Serotonin syndrome is a drug-induced syndrome resulting from increased serotonin activity. The syndrome can evolve from standard treatment, overdose, intoxication or any combination of serotonergic drugs – including pharmacodynamic and pharmacokinetic interactions – that increases serotonergic neurotransmission. The central symptoms are neuromuscular excitation, autonomic dysfunction and altered mental status, occurring in a patient undergoing new, altered or enhanced serotonergic therapy. The Hunter Serotonin Toxicity Criteria are widely accepted as the most accurate diagnostic criteria.

A variety of drugs – of which this focused review provides an overview and classification – are associated with serotonin syndrome. Due to the widespread use of serotonergic drugs, clinicians must maintain a high level of clinical suspicion for serotonin syndrome, as early recognition and treatment are crucial to prevent significant morbidity and mortality.

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Tables

Table 1. Drugs associated with serotonin syndrome

Class Examples of associated drugs

Psychiatric SSRIs: citalopram*, fluoxetine*, sertraline*, escitalopram, paroxetine

SNRIs: venlafaxine, duloxetine

TCAs: amitriptyline, clomipramine, imipramine MAOIs: phenelzine, rasagiline, selegiline Others: bupropion*, buspirone, lithium

Antiepileptics Lamotrigine, carbamazepine, valproate

Antiemetics Ondansetron, granisetron, metoclopramide

Anti-migraine Triptans, ergotamine, methylergonovine

Opioids Fentanyl, meperidine, methadone, dextromethorphan, tramadol*

Illicit Drugs Methamphetamine, amphetamine, ecstasy (MDMA), psilocybin, LSD

Miscellaneous Linezolid, cyclobenzaprine, methylene blue, St. John's Wort, fluconazole, chlorpheniramine

Modified from: Anthony Spadaro, Kevin R Scott, Alex Koyfman, Brit Long [16]*. * Top 5 agents implicated in serotonin syndrome.*

Table 2: Drugs associated with development of serotonin syndrome categorized according to their mechanism of action

Mechanism of action	**Selected drug examples**
Increase serotonin release	Amphetamines, MDMA Antidepressants: mirtazapine Opioids: oxycodone, tramadol, dextromethorphan
Inhibit serotonin uptake	Amphetamines, MDMA, cocaine SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline SNRIs: duloxetine, venlafaxine TCAs: amitriptyline, clomipramine, imipramine Opioids: methadone, tramadol, dextromethorphan
Inhibit serotonin metabolism	Anxiolytics: buspirone MAOI: phenelzine, rasagiline, selegiline
Activate Serotonin Receptors Inhibit Cytochrome P450	Hallucinogen: LSD Antidepressants: trazodone Opioids: fentanyl Mood stabilizers: lithium *CYP2D6* Inhibitors: fluoxetine, sertraline Substrates: dextromethorphan, oxycodone, risperidone, tramadol *CYP3A4* Inhibitors: ciprofloxacin, ritonavir Substrates: methadone, oxycodone, venlafaxine *CYP2C19* Inhibitors: fluconazole Substrates: citalopram

Modified from: James Francescangeli, Kunal Karamchandani, Meghan Powell, Anthony Bonavia [1]*.*

Table 3. Symptoms of serotonin syndrome by severity

Severity Symptoms

Mild Anxiety, hypertension, tachycardia, hyperreflexia, diarrhea

Moderate Agitation, clonus, tremor, hyperthermia

Severe Life-threatening hyperthermia, confusion, hypertonicity, respiratory failure, coma, death

Credit: The Maudsley Prescribing Guidelines in Psychiatry[21]*.*

Table 4. Distinguishing features between serotonin syndrome and neuroleptic malignant syndrome

	Serotonin syndrome	**Neuroleptic malignant syndrome**
Trigger drug	Drug with serotonergic effect	Drug with dopaminergic effect, often antipsychotics
Onset	Onset usually within 24 hours	Onset over days to weeks
Remission of symptoms	Rapid remission following discontinuation of the trigger drug	Gradual remission following discontinuation of the trigger drug
Neurological symptoms	*Neuromuscular hyperactivity:* Tremor, clonus, hyperreflexia	*Neuromuscular hypoactivity: Extrapyramidal symptoms; hypokinesia and lead tube rigidity*

Modified from: Buckley NA, Dawson AH, Isbister GK [8]; Scotton WJ, Hill LJ, Williams AC, Barnes NM [11]; Volpi-Abadie J, Kaye AM, Kaye AD [4]