Recognition and management of serotonin syndrome

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Given the widespread use of serotonergic agents and the associated risk of potentially life threatening illness as a result of their use, it is important that prescribers have a sound understanding of serotonin syndrome, its consequences and management.

Serotonin syndrome is the clinical manifestation of serotonergic hyperactivity in the CNS either directly or indirectly in response to ingested serotonergic agents. Its presentation ranges from mild and transient through to severe and life threatening, and it can progress rapidly if not detected and managed appropriately. The increase in CNS serotonin activity may be the result of serotonergic medications taken at prescribed dose, intentional or accidental overdose, or interactions between prescribed or over-the-counter (OTC) medications resulting in potentiation of serotonin within the CNS and consequent pathological effects.

Causes of serotonin syndrome
Serotonergic agents (see Table 1) have become a routine aspect of prescribing in recent years in both primary and secondary-care settings, particularly for psychiatric conditions. The most commonly known reason for their use is perhaps the use of SSRIs in depressive disorders, however multiple classes of psychiatric medication have significant serotonergic effects and may be prescribed in a range of clinical conditions including anxiety disorders, obsessive compulsive disorders and eating disorders among others. Non-psychiatric conditions are also commonly treated with medications that possess serotonergic activity, including analgesics, antibiotics, antimigraine drugs and anti-emetics. Some illicit drugs such as amphetamine and LSD are also known to potentiate serotonin, but a further concern is the ever-changing new wave of “legal highs”, which have been less extensively studied. Case reports indicate that these novel substances may also be implicated in serotonin syndrome.

Serotonergic agents may act in any of the following ways to contribute to a clinical picture of serotonin syndrome: increased synthesis of serotonin; increased release of serotonin from cells; decreased reuptake of serotonin by cells; inhibition of the enzymes responsible for metabolising serotonin.
The exact incidence of serotonin syndrome is difficult to estimate, possibly due to a lack of recognition and awareness in prescribers, but also due to the spectrum of clinical presentations that may develop, some of which overlap with the milder and more common side-effects that many patients experience when starting serotonergic medication. Isbister et al’s 2004 study did, however, estimate that up to 15 per cent of SSRI overdose patients developed serotonin syndrome.11

Given the widespread use of serotonergic agents in psychiatry, other fields of medicine, OTC medications and illicit substances, combined with the associated risk of acute and potentially life-threatening illness as a result of their use, it is important that prescribers have a sound understanding of serotonin syndrome, its consequences and management. This in turn promotes informed and shared prescribing decisions made with patients, and facilitates patient education in monitoring for any adverse effects.12

**Signs and symptoms**

Signs and symptoms of serotonin syndrome (summarised in Table 2) can be considered under three main groups resulting in the recognisable triad of: altered mental state, neuromuscular abnormalities and autonomic excitation.

Changes in mental state may include agitation, anxiety, disorientation, restlessness and confusion. Neuromuscular signs may include hyperreflexia, clonus, tremor, muscle rigidity, bilateral Babinski sign. Hyperreflexia and clonus are often more pronounced in the lower extremities.13 Autonomic signs may include hyperthermia, hypertension, tachycardia, diaphoresis, mydriasis, skin flushing, increased bowel sounds, nausea, vomiting and diarrhoea.5,6,14

Patients will not necessarily display signs and symptoms in all three domains outlined above, with an estimated 40 per cent showing evidence of altered mental state, 50 per cent with neuromuscular changes and 40 per cent with autonomic abnormalities.15

Consequently, given the range of potential presentations, the Hunter diagnostic criteria for serotonin syndrome have been developed to aid clinicians in reaching a diagnosis (See Figure 1).3 Use of the Hunter criteria in diagnosing serotonin syndrome yields 84 per cent sensitivity and 97 per cent specificity, making it preferable to the previously used Sternbach criteria.16

Differential diagnoses for serotonin syndrome include neuroleptic malignant syndrome, anticholinergic toxicity, malignant hyperthermia, stimulant intoxication, sedative withdrawal, encephalitis and meningitis.5
Vulnerable patient groups
Serotonin syndrome has been in observed in children, adults and the elderly. 
Theoretically, any patient taking a serotonergic agent may potentially develop serotonin syndrome; however, prescribers should be particularly vigilant in any patient taking more than one serotonergic agent, for psychiatric conditions or otherwise. Buckley et al (2014) emphasise that severe serotonin syndrome is generally seen only in the context of ingestion of multiple serotonergic agents, the most common cause being the combining of an MAOI with one or more other serotonergic drug. As such, MAOIs should not be used in combination with other serotonin potentiating medications.3

As outlined, the signs and symptoms of serotonin syndrome emerge rapidly, often within hours of a change in dose or new medication being started. Prescribers should therefore be vigilant for emerging symptoms of serotonin syndrome in such patients, and also consider that long half-life drugs such as fluoxetine may still exert serotonergic effects via their metabolites for up to two weeks after discontinuation.19

Patients who have experienced accidental or intentional overdose of serotonergic agents must also be considered at risk of developing serotonin syndrome. Some intentional overdoses may be perceived as low risk in terms of suicidal intent, however careful history of both prescribed and overdose medication should be taken (from collateral source when possible) to ensure that a potentially fatal serotonin toxicity is not imminent.

First- and second-line treatment options
Serotonin syndrome is in effect a continuum of the effects of serotonin toxicity. In the most benign cases of serotonin syndrome, the systemic and end organ effects of serotonin toxicity may include rhabdomyolysis, acidosis, renal failure and disseminated intravascular coagulation.14 Laboratory investigations aimed at monitoring the above, including urea and electrolytes, coagulation, creatine kinase and arterial blood gases, can help guide management of the acutely ill patients. Given that serotonin toxicity may emerge secondary to overdose, clinicians should

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**Table 2. Summary of serotonin syndrome signs and symptoms**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>Agitation</td>
<td>Confusion</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Hypervigilance</td>
<td>Agitated delirium</td>
</tr>
<tr>
<td>Tremor</td>
<td>Ocular clonus</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Inducible clonus</td>
<td>Sustained clonus</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Hyper-reflexia</td>
<td>Myoclonus</td>
<td>Coma</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Fever</td>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Diaphoresis</td>
<td>Shock</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Skin flushing</td>
<td></td>
</tr>
<tr>
<td>Hyperactive bowel sounds</td>
<td>Mydriasis</td>
<td></td>
</tr>
</tbody>
</table>

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Adapted with permission from Buckley et al, 2014
also consider paracetamol and salicylate levels along with ECG monitoring in any patient who may have ingested an overdose of mixed composition.

Management in primary care

GP's will initiate, titrate and review serotonergic agents frequently in their day-to-day practice. Familiarity with the serotonergic effects and mechanisms of action of these medications will minimise risk of serotonin toxicity, and allow for more confident decision making when considering the likelihood of serotonin toxicity. Detailed medication history, including any recent changes or discontinuation of medicines, as well as overdose history (accidental or intentional), will be vital in assessing the potentially toxic patient. Also consider recreational drugs and OTC or herbal medicines.

Prescribers should observe washout periods as indicated when cross titrating medications. The Maudsley prescribing guidelines provide a detailed summary table of recommended cross titration practice for all commonly prescribed antidepressants.22

Neurological examination and recording of autonomic parameters will help in establishing whether or not the Hunter criteria are met with particular attention to clonus, hyperreflexia, hyperthermia and diaphoresis. Assessing mental state for signs of anxiety, agitation or confusion is also necessary.

Wherever possible, prescribers should avoid co-prescribing more than one serotonergic agent, bearing in mind the serotonergic effects of non-psychiatric medications. If absolutely necessary, patients taking more than one serotonergic agent will require monitoring and review, and both patients and family members or carers should be educated as to the signs and symptoms of serotonin toxicity and how to access help should it develop. Patients should also be advised about the risks of using OTC preparations such as St John's Wort if already on a serotonergic medication for any reason.23 Patients should not be prescribed a MAOI in conjunction with any other potent serotonergic agent in combination.24

If in doubt, prescribers should discuss with local pharmacy or medicines information teams to advise further on medication concerns.

References


Declarations of interest

None to declare.

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