Long-Term Care Updates

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Causes, Risks, and Prevention of Serotonin Syndrome

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Introduction:

Serotonin syndrome, or toxicity, is a consequence of excessive serotonergic activity in the central nervous system (CNS) that can occur with prescription doses of serotonergic agents, herbal supplements, illicit drugs, and intentional overdoses.[1,2] Serotonin is a monoamine neurotransmitter responsible for multifaceted regulatory processes, including thermoregulation, behavior, attention, vasoconstriction, bronchoconstriction, and gastric motility.[2] In the context of serotonin syndrome, symptoms will vary depending on severity but will reflect dysregulation in the function of serotonin. This can include (but is not limited to) hyperthermia, hypertension, tachycardia, altered mental status, and hyperreflexia.[1,2] Serotonin syndrome is rare, but it is important to reduce unnecessary risks and be vigilant when prescribing agents with the potential to augment serotonergic activity.

The overall incidence of serotonin syndrome is reportedly uncommon and hard to measure, but in 2016 the Toxic Exposure Surveillance System received 54,000 reports of toxicity from selective serotonin reuptake inhibitor (SSRI) exposure with 102 deaths.[2] The recognition and diagnosis of serotonin syndrome is probably under representative of its true incidence.[1] Mild symptoms are often overlooked or not suspected as serotonin syndrome, co-ingestion of stimulant drugs can cause a mixed presentation rather than one consistent with pure serotonergic dysregulation, and symptoms can be masked in some patients.[1-3] Geriatric patients, especially those with baseline cognitive deficits and/or polypharmacy, may be suffering from serotonin toxicity that is not recognized due to their comorbidities.[3] Altered mental status and confusion can easily be ascribed to other causes. Here, the potential risks and considerations for serotonin syndrome are reviewed to encourage provider vigilance and recognition of avoidable adverse drug events.

Novel Drug Approvals (April 2025)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Imaavy	Nipocalimab-aahu	Generalized myasthenia gravis	Neonatal Fc receptor blocker	Intravenous injection
Vanrafia	Atrasentan hydrocholoride	Primary immunoglobulin A nephropathy in adults (to reduce proteinuria)	Endothelin receptor antagonist	Oral tablets

Risks for Serotonin Syndrome:

While any serotonergic substance may be able to precipitate serotonin syndrome, there are some particularly culpable drug classes and circumstances that are often present.[1] One common, and often avoidable, risk factor is polypharmacy.[1] This becomes increasingly difficult to avoid in polymorbid and geriatric patients. When presented with a patient with depression, agitation/psychosis, and insomnia, it is conceivable to see SSRIs, atypical antipsychotics, and tricyclic antidepressants (TCAs) all prescribed to the same patient. Younger patients starting this regimen may tolerate, and even thrive, on such therapy, but it should be recognized as a perilous precipice being navigated for the clinician and pharmacist as patients age and as circumstances evolve. With multiple serotonergic (or serotonin funneling, as in atypical antipsychotics) drugs now exerting their effects, there is an increased risk of a single insult precipitating a serotonin toxidrome. A broken bone may lead to a serotonergic opioid like tramadol, or an infection could be treated with linezolid, which is capable of inhibiting monoamine oxidase (MAO), the enzyme responsible for the breakdown of serotonin. Should this patient develop neuropathy, it is possible a serotonin norepinephrine reuptake inhibitor (SNRI) be added to manage it. As patients age and become part of the geriatric population, there are known changes in pharmacokinetic and pharmacodynamic factors than can influence how patients tolerate therapy, even if they had been stable previously.[3-5]

A study in geriatric patients found that in a enrolled population taking serotonergic antidepressants 25.2% met the Hunter Serotonin Toxicity Criteria for serotonin syndrome. There was a significant association between having serotonin syndrome and taking a combination of serotonergic antidepressants, with 51.7% of patients with serotonin syndrome taking multiple contributing agents versus 41.1% of patients in the control group taking combination regimens. The association between serotonin syndrome and any combination therapy had an odds ratio of 1.94 (95% CI 1.04-3.61). These did not represent classical therapeutic duplications, which could be a prescribing error, but rather accepted therapy combinations taking advantage of multiple mechanisms of action, with one patient (who was reported with serotonin syndrome) taking an SSRI, SNRI, and mirtazapine.[5] There is an additional concern should a patient enter a long-term care facility where their drug administrations are monitored and invariably compliant, as this may represent a dose increase if they were previously poorly compliant with their medications. Realistically, it cannot be ascertained how close a patient is to serotonin syndrome until symptoms start to manifest, but an abundance of caution should be used when managing these medications. At every possible juncture, a reassessment of medication regimens consisting multiple serotonergic agents for their necessity, as well as a patient evaluation for possible serotonin toxicity, should be made.

Another potentially avoidable risk relates to the types of serotonergic drugs being used. Given a diagnosis like depression, multiple drug classes may be used depending on provider preference and patient history. Current practice favors the use of SSRIs when considering initiations of therapy, but some providers may favor older classes they have more experience with, and some older patients whose therapy was started before the popularization of SSRIs may be on a drug that would now be considered antiquated. It is important to understand how all of these medications work and their potential for adverse effects. TCAs, SSRIs, and SNRIs will all cause serotonin to linger in the synaptic cleft to exert its effects longer by inhibiting reuptake and have been implicated in serotonin syndrome, with SSRIs being the most common due to its prevalence.[1] MAO inhibitors, which are no longer common in practice, cause serotonin to persist by inhibiting its degradation. Above all other classes, MAO inhibitors are implicated in severe instances of serotonin syndrome.[1] The addition of serotonergic agents to a patient using an MAO inhibitor is generally contraindicated due to risk. Other potentially causative or contributory agents are those that block the 5-HT2A serotonin receptor, like some antipsychotics, which is theorized to shuttle serotonin effects towards other receptors, like 5-HT1, which subsequently increases serotonergic activity in the CNS.[2] Some drugs directly modulate serotonin receptors as full or partial agonists, like triptans, certain antipsychotics, and some antidepressants. While sometimes present in cases of serotonin toxicity, they are rarely present as monotherapy or as the causative agent in severe cases.[1]

A critical risk factor every clinician and pharmacist should be cognizant of when prescribing or dispensing serotonergic agents is patient intention. Of all scenarios that may lead to serotonin toxicity, those caused by intentional overdose are often the most serious and difficult to manage.[1] Suicidal ideation, especially in younger patients, is a known serious adverse effect when initiating antidepressant therapies. Warnings regarding this risk need to be explicit, and patients should be asked clearly what their intent and ideation is. Resources for help should a patient find themselves contemplating ending their own life should be freely offered without being prompted. The conversation may be uncomfortable and emotionally burdensome for providers, but it enforces care to those for whom care or lack thereof may be of grave consequence.

Conclusion:

Serotonin syndrome can be a trojan horse, approaching the gates unsuspected until symptoms reveal themselves. The usefulness of serotonergic agents in multiple clinical scenarios, and the fact they are often well-tolerated, can lead to an accumulation of serotonergic drugs being prescribed to a single patient. Many patients will be on such regimens for extended periods of time, and variations in how they metabolize, eliminate, and tolerate medications can lead to the development of serotonin syndrome in a previously stable and well-managed patient. Acute insults, like infections or acute pain, can lead to the addition of serotonergic agents capable of breaking the proverbial camel's back. Vigilance regarding patient risk factors and appropriate symptom surveillance should be encouraged. Awareness of opportunities for deprescribing and non-serotonergic or less serotonergic substitutions represent a potent strategy for risk reduction and should be implemented in the evaluation of patients suffering from polypharmacy, particularly with multiple serotonergic agents.

References:

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