Central Serotonin Syndrome: Part II—Pathophysiology, Drug Interactions, and Treatment

Ryan C.W. Hall, MD, Richard C.W. Hall, MD, and Marcia J. Chapman

This is the second part of a two-part series on central serotonin syndrome in the elderly that reviews the incidence, how central serotonin syndrome presents in the elderly, which psychiatric and nonpsychiatric medications interact to exacerbate or cause the syndrome, the pathophysiology of the disorder, and its treatment. Part I discussed the history and prevalence of the disorder, causative agents, presentations and diagnostic criteria, and ways to distinguish the condition from other conditions with which it might be initially confused, such as neuroleptic malignant syndrome. Part II focuses on its pathophysiology, opiate and psychiatric drug interactions, and the treatment of central serotonin syndrome in the elderly.

Pathophysiology

Serotonin is a biogenic amine synthesized from tryptophan and found in the periphery of the body (eg, gastrointestinal system, platelets) and the central nervous system (brain, spinal cord, with particularly high levels in the hypothalamus and basal ganglion) (Table I).[1-4] Serotonin is not able to cross the blood-brain barrier, and is therefore synthesized both in the periphery and centrally.[5,6] The central effects of serotonin are thought to include modulation of mood, the sleep-wake cycle, hormone secretion, nociception (pain), motor tone, sexual behavior, thermoregulation, and nausea.[1,2,4,6-8] Serotonin syndrome is believed to be caused by increased 5-hydroxytryptamine at the intrasynaptic cleft as the result of the pharmacological effect of a drug or a combination of drugs (usually having two different mechanisms of action affecting serotonin levels or cell response).[1,2,9] This increase in intrasynaptic serotonin has both a direct and an indirect effect on noradrenergic pathways, dopaminergic pathways, and the GABA adrenergic inhibitory pathways, which are also responsible for some of the symptoms that occur. These pathways are also involved in the genesis of symptoms by indirectly increasing central serotonin levels.[6,10,11-13]

Currently, there are at least seven types of identified serotonin receptors, each with several subclassifications.[1,5,14] Although multiple neurotransmitters, feedback mechanisms, and receptor types are involved in producing serotonergic syndrome, the predominant receptors are thought to be 5HT1A (overstimulation may cause hyperactivity, hyperreflexia, and anxiety)[1,2,8,15] and 5HT2A (associated with hyperthermia, incoordination, and neuromuscular excitement).[1,6-8,16-20] 5HT1A receptors are distributed heterogeneously in human brains, with increased concentrations in the hippocampus, frontal cortex, amygdala, and raphe nuclei.[6,21] Overstimulation of 5HT1A receptors in the central gray nuclei and the medulla are thought to be primarily responsible for the major symptoms of serotonin syndrome.[6,8] There is a clear association between the overstimulation of 5HT1A receptors and the serotonin behavioral syndrome that occurs in animals.[16,20,21] Although there are several similarities between serotonin behavioral syndrome and human serotonin syndrome, some neuroscientists suggest caution in generalizing the findings from one condition to the other.[16,20] 5HT1A receptors have a higher affinity for serotonin than the 5HT2A receptors, causing them to become sat-

TABLE I

Locations of Serotonin and Serotonin Receptors in the Body

Brain (in general)
- Amygdala
- Basal ganglion (region of specific intensity)
- Central gray nuclei
- Frontal cortex
- Hippocampus
- Hypothalamus (region of specific intensity)
- Medulla
- Raphe nuclei

Gastrointestinal tract

Platelets

Spinal cord

Dr. Ryan Hall is from the Department of Psychiatry and Behavioral Sciences, John Hopkins Hospital, Baltimore, MD; Dr. Richard Hall is Courtesy Clinical Professor of Psychiatry, University of Florida, Lake Mary; and Ms. Chapman is Research Assistant to Dr. Richard Hall.

urated when lower concentrations of serotonin exist at the synaptic cleft.[16] This may explain why hyperthermia and muscle rigidity are seen more commonly in severe forms of the disease. The 5HT2A receptor becomes overstimulated once the 5HT1A receptor is saturated.[16] Animal studies, where the animal subjects were pretreated with a 5HT2A antagonist, showed prevention of both hyperthermia and death, whereas pretreatment with benzodiazepines and chlormethiazole reduced the degree of hyperthermia but not death.[16] Stimulation of the 5HT3 receptors is thought to explain the gastrointestinal side effects of diarrhea, nausea, and abdominal pain.[6,17,20]

The concentration of 5HT2A receptors decreases by approximately 18% per decade in human brains up until age 50.[18,22] Theoretically, this puts the elderly at a higher risk of developing serotonin syndrome because less serotonin is required to saturate the existing receptors. Case reports of elderly patients developing serotonin syndrome while taking normal therapeutic doses of serotonergic medications support the notion that the elderly are at greater risk of developing the syndrome under conditions where younger patients do not.[18,23,24] However, aging also reduces neurotransmitter synthesis and postsynaptic receptor sensitivity. The decreasing level of neurotransmitters, receptors, and receptor sensitivity may actually decrease the risk of the elderly developing serotonin syndrome.[18] Small case number studies with linezolid in which the elderly were delayed in showing serotonin symptoms as compared to younger patients indicate that the elderly are at a decreased risk for developing this condition.[18] Additional research is needed to clarify this issue since age may be neither directly protective nor a liability. The reported changes in the elderly may be caused by some other factor, such as their ability to metabolize medications.

Central norepinephrine levels are also increased in persons with serotonin syndrome. This elevation is caused by the elevated serotonergic concentrations causing increased catecholamine release. The increased release of norepinephrine may be responsible for some of the symptoms seen in serotonin syndrome, such as the heightened levels of general arousal and anxiety.[9,18]

There are six proven mechanisms by which drugs produce the serotonin syndrome: (1) increase synthesis (L-tryptophan); (2) stimulate the release of serotonin (eg, cocaine, levodopa); (3) act as a serotonin agonist (eg, LSD, carbamazepine); (4) prevent serotonin reuptake (eg, selective serotonin reuptake inhibitors [SSRIs]); (5) increase postsynaptic responses (lithium); and (6) prevent breakdown of serotonin (monoamine oxidase inhibitor [MAOI], linezolid).[6,8,25,26] A seventh potential mechanism may exist: drug-induced changes in the relative ratio of neurotransmitters may produce changes in other non-serotonin neurotransmitters, such as dopamine, resulting in increased serotonin release and/or receptor sensitivity[6] (Table II).

An important drug-drug interaction involves phenylpiperidine opiates (eg, fentanyl, sufentanil, alfentanil, meperidine, loperamide) and their analogues (Table III). Many physicians are not aware that this class of opiates significantly elevates central serotonin levels. There is debate by which mechanism these elevations occur (eg, direct serotonin release, weak reuptake inhibition, indirect pathways, or a combination).[3,6,14,27-29] It appears that opiates such as morphine, codeine, buprenorphine, and other morphine analogues do not significantly affect serotonin levels and do not contribute to serotonin syndrome.[14] It is important to remember this since the general comorbidity between depression and pain is 50%, with a higher frequency occurring in the elderly.[6,27,30,31] This high comorbidity leads to a higher likelihood that elderly patients will eventually end up on a combination of an antidepressant and a pain medication.[6]

Due to the fact that serotonin syndrome does not occur without a pharmacologic agent present, this condition is iatrogenic in nature.[2] Its incidence and severity increase with the number of serotonin-enhancing medications

TABLE II

Ways in Which Medications Can Cause Serotonin Syndrome

1. Increases synthesis of serotonin
2. Stimulates release of serotonin
3. Acts as a serotonin agonist
4. Prevents serotonin reuptake
5. Increases postsynaptic responses to serotonin
6. Prevents breakdown of serotonin intracellularly
7. Changes the relative ratio of neurotransmitters, resulting in increased serotonin release and/or indirectly increased receptor sensitivity

TABLE III

Opiates and Serotonergic Syndrome

Opiates Associated with Serotonergic Syndrome	*Opiates Not Associated with Serotonergic Syndrome*
Alfentanil	Buprenorphine
Fentanyl	Codeine
Loperamide	Morphine
Meperidine	Extended-release morphine
Methadone	Other morphine analogues
Oxycodone	
Pentazocine	
Propoxyphene	
Remifentanil	
Sufentanil	

TABLE IV

Commonly Proposed Treatment Options

- *Supportive care*—Discontinuation of offending agents with supportive care, including aspiration precautions, hydration, fever reduction, and intubation if required.
- *Cyproheptadine* (primarily histamine antagonist)—Mechanism of action: serotonin receptor antagonism; dosing initially 4-8 mg with a repeat dose administered within 2 hours, with a maximum of 32 mg per day (8 mg QID).
- *Chlorpromazine* (neuroleptic)—Mechanism of action: serotonin receptor antagonism; can be given orally, intravenously, or as an intramuscular preparation in doses of 50-100 mg.
- *Benzodiazepines* (eg, lorazepam, oxazepam)—Treatment of hyperadrenergic symptoms; recommended to use low-dose, short-acting agents, with minimal hepatic metabolism.
- *Nitroprusside* (peripheral vasodilator)—Mechanism of action: blood pressure control and treatment of hyperthermia by producing dilation of peripheral blood vessels.
- *Propranolol and pindolol* (beta blockers)—Mechanism of action: exhibit 5HT1A receptor antagonism, and possibly some 5HT2A antagonism; also decrease the neuromuscular effects and autonomic complications associated with the syndrome; suggested dose of propranolol is 40-60 mg per day.

prescribed. Because of this and the dose-related nature of the disorder, some researchers are calling for the term *serotonin syndrome* to be changed to *serotonin toxicity syndrome.*[16,32,33]

Treatment

Generally, treatment for serotonin syndrome is supportive care with discontinuation of any medication that may cause the condition.[34] Approximately 70% of cases resolve within 24 hours after stopping causative medicines.[6] In moderate to severe cases, additional interventions may be required to treat symptoms and prevent death. Most treatment recommendations are based on theoretical concerns, anecdotal reports, and small case series (Table IV). No large-scale, prospective treatment studies for serotonin syndrome have yet been completed.[10,19]

The two most common medications used to reduce the duration and severity of serotonergic syndrome in case reports (no controlled studies) are cyproheptadine and chlorpromazine, both of which exert a serotonin receptor antagonism.[7,8,26] Cyproheptadine is a histamine receptor antagonist with nonspecific muscarinic, anticholinergic, and antiserotonergic properties.[7,8,35,36] The usual starting dose for cyproheptadine for the treatment of serotonin syndrome is 4-8 mg with a repeat dose administered within 2 hours.[1,35,37] When improvement is seen, a maximum of 32 mg per day (8 mg QID) can be given.[1,35] Cyproheptadine has an 85-95% receptor binding affinity when given at doses of 12-32 mg per day.[6,7]

Chlorpromazine, an aliphatic phenothiazine neuroleptic with 5HT1A and 5HT2A receptor antagonist properties, can be given orally, intravenously, or as an intramuscular preparation in doses of 50-100 mg.[6,14] Patients should be well hydrated prior to administrating chlorpromazine to reduce or prevent the postural hypotension caused by chlorpromazine's alpha-2 adrenergic receptor antagonism.[14] The intravenous or intramuscular preparation may be beneficial in severe cases where individuals are not able to take oral medication due to confusion or difficulty swallowing secondary to muscular rigidity.[7,8,35]

There have been suggestions in the literature that certain atypical neuroleptics can also be used because of their serotonin antagonism at the 5HT1A and 5HT2A receptors.[7,36] Animal data shows that risperidone can help prevent or decrease the severity of serotonergic toxicity in animals.[20,36] Currently, however, we do not recommend the use of typical (with the possible exception for chlorpromazine) or atypical neuroleptics as first-line therapeutics for serotonin syndrome due to the potential difficulties in differentiating neuroleptic malignant syndrome (NMS) from serotonin syndrome. If the diagnosis is incorrect, the administration of neuroleptics could lead to a worsening of the condition if the patient has NMS. Also, some of the atypical neuroleptics that have been suggested in the literature, such as ziprasidone, actually have serotonin agonist properties and may worsen serotonin syndrome.[8,38]

Benzodiazepines are often used to treat the hyperadrenergic symptoms of serotonin syndrome.[7] Benzodiazepines can help with muscle rigidity/hyperactivity, myoclonus, seizures, and agitation.[1,6,19,26,39] It needs to be remembered—especially in the elderly—that benzodiazepines can also worsen delirium, result in hypotension, and may take longer to be metabolized by the liver and kidneys than in younger patients.[40,41] Initial low-dose use of short-acting agents, such as lorazepam or oxazepam, which undergo minimal hepatic metabolism, is recommended.

Bromocriptine, a dopamine agonist, which has been suggested as a possible treatment for NMS, is not recommended for treatment of serotonin syndrome.[14] There is no overt theoretical benefit for using a dopamine agonist, and there is at least one case report of a patient whose

symptoms worsened after being treated with a bromocriptine and dantrolene combination.[7]

In severe cases of serotonin syndrome, patients may develop rigidity of the respiratory muscles and bronchospasm leading to a state of profound sudden hypoxia.[14,27] In cases of extreme rigidity, intubation and drug-induced paralysis may be required to protect the patient's airway and cause muscle relaxation.[9,14,39] Some case series have reported that as many as 25% of patients with severe serotonin syndrome require ventilation.[5,6]

Debate over the usefulness of dantrolene exists in the literature. It is commonly used to treat malignant hyperthermia and the rigidity and fever of NMS. In vitro muscle studies suggest that dantrolene treats rigidity and hyperthermia by inducing muscle relaxation by inhibiting calcium release from the muscle's sarcoplasmic reticulum.[10,16,40,41] To date, there are limited and conflicting case reports concerning the benefit of dantrolene in the treatment of patients with serotonin syndrome. Animal data suggest no survival benefit from dantrolene treatment.[16,7]

Additional symptomatic treatments include nitroprusside and the short-acting beta blockers, such as esmolol, for blood pressure control.[4] These agents show benefit over longer-acting measures, which may result in hypotension due to autonomic instability. Nitroprusside has the additional benefit of treating the patient's hyperthermia by producing dilation of peripheral blood vessels, which results in a reduction of core body temperature.[40,41]

Elevated serotonin levels inhibit nitric oxide synthesis, which then leads to a further increase in serotonin levels.[42] Some case reports have found that treatment with nitroglycerin and other compounds, which are converted to nitric oxide in the body, are useful in treating serotonin syndrome.[42]

Other beta blockers that have been suggested to help treat serotonin syndrome include propranolol or pindolol. These agents exhibit 5HT1A receptor antagonism and possibly some 5HT2A antagonism.[1,5,8,10,36,39] In case reports and animal studies, these medications are credited with decreasing the neuromuscular effects and autonomic complications, such as tachycardia and hypertension, associated with the syndrome.[5,6] The dose of propranolol recommended for treatment, based on animal studies and case reports, is 40-60 mg per day.[10]

Once the serotonin syndrome has resolved, some of the causative medications can be carefully restarted within 1-2 weeks.[17] Medications need to be restarted individually at lower doses and slowly titrated for efficacy.[17] Most of the SSRIs have a half-life of 12-36 hours and require approximately a 1-2–week washout period before restarting agents that may affect serotonin levels. The one notable exception to this is fluoxetine, which has active metabolites with a 5-7–day half-life, thereby requiring a 5-week washout.[7] In cases where an MAOI was involved in the syndrome, sertonergic agents should not be started for at least 2 weeks after the discontinuation of the MAOI to allow for synthesis of new MAO protein.[6,7,25,43]

An agent being considered for future treatment of serotonin syndrome is the gastric pentadecapeptide BPC 157. This peptide was initially investigated as a drug to control inflammatory bowel disease due to its interactions with serotonin in the gastrointestinal tract.[44] Currently, there is indication that this peptide also has effects on central serotonin levels as well. Animal data suggest that BPC 157, through suspected antagonistic effects at the 5HT2A receptor, can prevent symptoms of serotonin syndrome in rats given pargyline (irreversible monoamine oxidase inhibition)/L-tryptophan.[44] Additional study is still needed before this agent can be recommended as a treatment.

Conclusion

Serotonin syndrome usually results from the coadministration of multiple medications, some of which are rarely thought to have direct serotonergic effects. Early identification and discontinuation of the precipitating medication can prevent the syndrome from progressing to its severe stages, where more drastic interventions, such as intubation, are required. Although the elderly may be at a physiologically lower risk for developing the condition due to their decrease in receptor numbers and activity, their overall risk is high due to their reduced ability to metabolize medications and their use of multiple medications, particularly the combination of antidepressants and analgesics. The diagnosis of serotonin syndrome needs to be considered in the differential diagnosis for older adults with changes in mental status. ■

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