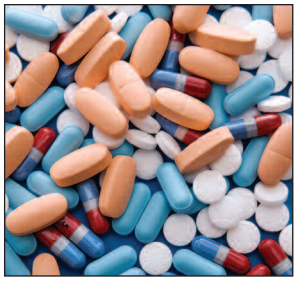

Central Serotonin Syndrome: Part I—Causative Agents, Presentation, and Differential Diagnosis

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This is the first part of a two-part series that examines central serotonin syndrome in the elderly. Part I reviews the history and prevalence of the disorder, causative agents, presentation and diagnostic criteria, and ways to distinguish the condition from other similar states, such as neuroleptic malignant syndrome. Part II will focus on the pathophysiology, opiate and psychiatric drug-drug interactions, and treatment approaches for central serotonin syndrome in the elderly.

INTRODUCTION

The term *serotonin syndrome* was first used in a case report in 1982, but study of this condition dates back to the 1950s and 1960s. At that time, unusual drug interactions involving monoamine oxidase inhibitors (MAOIs) were observed in research animals.[1-5] When rats were exposed to elevated central serotonergic levels, they displayed a condition that became known as *serotonin behavioral syndrome*. The pathophysiology of central serotonin syndrome evolved from a study of these animals. In 1991, Sternbach[6] published the first diagnostic criteria for serotonin syndrome in humans based on his review of the 38 cases then published. Since that early definition, serotonin syndrome has become more clinically prominent due to the increasing number of available drugs that intentionally affect the level of central nervous system serotonin, and the dramatically increased number of prescriptions for these drugs (eg, selective serotonin reuptake inhibitors [SSRIs]).[2,3,7] The additional prominence is also related to the growing exposure to other prescribed medications (eg, linezolid), over-the-counter remedies (eg, cold medications), pain medications (eg, meperidine), and street drugs (eg, ecstasy) with unintended serotonergic properties.

Patients and physicians are often unaware of the additive serotonergic effects of various medications and the resulting increased risk for developing serotonin syndrome. A 1999 study of general practitioners showed that 85.4% were not familiar with serotonin syndrome.[8] This finding raises concern since primary care physicians write more prescriptions for SSRIs than psychiatrists.[8,9] Compounding physicians' general lack of knowledge about the syndrome is a lack of clear, definitive diagnostic criteria, which is in part due to serotonin syndrome's various presentations. It is hoped that this article will educate physicians about the condition, its most common presentations, and the drugs that most frequently cause it.

RATE AND CAUSATIVE AGENTS

Serotonin syndrome is not considered to be an idiosyncratic drug reaction since there is a clear correlation between the level of serotonin-enhancing effect of vari-

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TABLE I

List of Reported or Suspected Drugs That Alone or in Combination Have Been Associated with Serotonin Syndrome by Category

Analgesics
Fentanyl
Meperidine
Methadone
Oxycodone
Pentazocine
Propoxyphene
Remifentanil
Tramadol

Antibiotics
Clarithromycin
Furazolidone
Iproniazid
Isoniazid
Linezolid
Ritonavir

Antiemetics
Ondansetron
Granisetron
Metoclopramide

Antiparkinsonian Agents
Bromocriptine
Carbidopa
Levodopa
Selegiline

Antipsychotics
Ziprasidone

Apathy or Weight Loss Agents
Dextroamphetamine
Methamphetamine
Fenfluramine
Phentermine
Sibutramine

Herbals
5-hydroxytryptophan
Ginseng
Hypericum perforatum (St. John's Wort)
L-tryptophan
S-adenosylmethionine
Soya extracts

MAOIs
Clorgyline
Isocarboxazid
Phenelzine
Tranylcypromine
Selegiline patch
Iproniazid

Migraine Medications
Almotriptan
Dihydroergotamine and other ergot alkaloids
Eletriptan
Naratriptan
Rizatriptan
Sumatriptan
Zolmitriptan

Miscellaneous
Benztropine
Buspirone
Diphenoxylate and atropine
Procarbazine
Reserpine

Mood Stabilizers
Carbamazepine
Lithium
Valproate

Over-the-Counter Drugs
Brompheniramine
Chlorpheniramine
"Cold medications"
Dextromethorphan
Loperamide
Pseudoephedrine

Recreational Drugs
Amphetamines
Cannabis
Cocaine
LSD
MDMA or "Ecstasy"
Nicotine

SNRI and Other Antidepressants
Bupropion
Duloxetine
Mirtazapine
Nefazodone
Trazodone
Venlafaxine

SSRIs
Paroxetine
Sertraline
Fluoxetine
Fluvoxamine
Citalopram

Tricyclic Antidepressants
Clomipramine
Imipramine
Amitriptyline
Doxepin
Desipramine

MAOIs = monoamine oxidase inhibitors; LSD = lysergic acid diethylamide; MDMA = 3,4-methylenedioxymethamphetamine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors.

ous medications, either alone or in combination, and the risk for developing the condition[10] (Table I). The rate of occurrence and the mortality caused by serotonin syndrome is difficult to estimate due to the multiple drug combinations that can cause it, its varying presentations (eg, after drug overdose vs following normally prescribed doses of medication or medications in combination), individual differences in ability to metabolize drugs (eg, 7% of population being slow metabolizers of SSRIs), and the milder forms of the condition, which often go undiagnosed.[5,11,12] Severe cases of serotonin syndrome carry a mortality of between 0.1% and 12%.[11,13,14] In a study of 58 consecutive patients admitted to a European emergency room with agitation, two were later diagnosed with serotonin syndrome, indicating that frequency of occurrence might be higher than most physicians expect.[15]

The risk of developing serotonin syndrome is greater when medicines are given in combination, particularly when one of the medications is some form of serotonin reuptake inhibitor.[2,10,16-18] During 2004, the Toxic Exposure Surveillance System

TABLE II

Symptoms Produced in Humans and Animals with Elevated Levels of Serotonin with Reported Frequency of Occurrences

Symptoms in Humans

Mental/CNS
Agitation (32-45%)
Akathisia
Altered consciousness (38-54%)
Anxiety (16-20%)
Coma
Confusion (38-54%)
Death (0.1-12%)
Easily startled
Hallucination (1-10%)
Hyperactivity (32-45%)
Hypervigilance
Hypomania (9-24%)
Insomnia (10-11%)
Irritability
Lethargy (15-20%)
Pressured speech
Seizures (11-14%)
Unresponsiveness (16-28%)

Gastrointestinal
Abdominal cramping (1-5%)
Diarrhea (12-13%)
Hyperactive bowel sounds

Neuromuscular
Ataxia (9-38%)
Clonus (34-57%)
Hyperkinesia
Hyperreflexia (29-55%)
Hypertonia (22-50%)
Myoclonus (34-57%)
Nystagmus(13%)
Pyramidal rigidity (22-50%)
Shivering (25-26%)
Tremor (26-50%)
Trismus (6%)

Autonomic
Diaphoresis (26-46%)
Flushed skin (3-14%)
Hyperpyrexia (19-46%)
Hypertension (33-60%)
Hypotension (14%)
Mydriasis (8-26%)
Tachycardia (17-41%)
Tachypnea (16-28%)
Unreactive pupils (26%)

Symptoms in Rats

Flat body posture
Gnawing
Head-weaving
Hind limb abduction
Hyperactivity
Hyperthermia
Piloerection
Random circling
Reciprocal forepaw treading
Salivation
Straub tail

CNS = central nervous system.

reported more than 31,000 hospital-treated cases of toxicity related to SSRI use (as a single agent or in combination), with approximately 8000 cases being moderate to severe and 103 resulting in death.[19]

If one of the agents involved blocks the central degradation of serotonin (eg, MAOI), the risk of developing serotonin syndrome is greatly elevated.[20] Approximately 50% of patients who overdose on a combination of an SSRI and MAOI will develop the syndrome, usually in a more severe form.[21] Even at normal therapeutic doses, 4% of patients treated with an SSRI or venlafaxine, who are later started on linezolid (weak MAOI properties), develop serotonin syndrome.[22]

Serotonin syndrome can also occur from the administration of a single agent.[2,16-18] A study in England reported a rate of occurrence of 0.4 (19 out of 11,834 patients by Sternbach criteria) cases per thousand patient-months for the drug nefazodone (now rarely used in the United States due to liver toxicity).[8] Multiple studies report that 14-16% of patients will develop some degree of serotonin syndrome following intentional overdose with SSRIs.[23] This low rate of serotonin syndrome following, at times, massive overdoses of SSRIs has led some researchers to postulate that SSRIs may have a ceiling effect on the central serotonin levels they produce, which prevents most users from reaching a toxic state from just their action alone.[24]

Factors that affect drug concentration, and therefore an individual's risk of developing serotonin syndrome, include drug metabolism (eg, ability of liver and kidneys to clear active compounds), individual tolerance, age of the patient, and level of dehydration.[10-12,25-27] A specific example of compromised drug metabolism potentially causing serotonin syndrome is the interaction of medications that block the CYP 2D6 pathway when given with paroxetine and/or venlafaxine, both of which are also metabolized by this pathway.[12,17,25,27,28] In addition, many antidepressants, such as fluoxetine, paroxetine, and bupropion, can inhibit the CYP 2D6 pathway, resulting in toxic

TABLE III

Varying Diagnostic Criteria for Serotonin Syndrome

Sternbach (1991)[6]	Radomski et al (2000)[5]	Dunkley et al (2003)[41]
1. Requires serotonergic agent started or increased 2. At least 3 of the following clinical features are present: - Agitation - Diaphoresis - Diarrhea - Fever - Hyperreflexia - Incoordination - Mental state changes (confusion, hypomania) - Myoclonus - Shivering - Tremor 3. Other causes ruled out 4. A neuroleptic had not been started or increased in dosage	1. Requires serotonergic agent started or increased 2. Presence of 4 of the following major symptoms or 3 major and 2 of the following minor symptoms: *Major symptoms* - Diaphoresis - Elevated mood - Fever - Hyperreflexia - Impaired consciousness - Myoclonus - Rigidity - Semicoma/coma - Shivering - Tremor *Minor symptoms* - Akathisia - Diarrhea - Dilated pupils - Hypertension or hypotension - Incoordination - Insomnia - Restlessness - Tachycardia - Tachypnea or dyspnea 3. Symptoms not related to preexisting psychiatric disorder or better explained by another process (eg, infection, change in neuroleptic medication)	Presence of one of the following conditions suggests serotonin syndrome: - Spontaneous clonus - Inducible clonus and agitation or diaphoresis - Ocular clonus and agitation or diaphoresis - Tremor and hyperreflexia - Hypertonic and temp 38°C and ocular clonus or inducible clonus

elevations of other medications, especially the tricyclic antidepressants.[11,12,17,28] Another P450 enzyme pathway that has been associated with serotonin syndrome is the CYP 3A4 system.[14,27] There are case reports of serotonin syndrome occuring in individuals who have genetic variances in the CYP 3A4 pathway. These individuals develop supratherapeutic blood levels on "normal doses" of several medications.[25,26] There are also case reports of elderly patients developing serotonin syndrome while being treated with therapeutic doses of an SSRI.[26,29] In these particular cases, pharmacokinetic changes related to the age of the patient were felt to contribute to the onset of the condition.[26,29]

PRESENTATION

The symptoms of serotonin syndrome traditionally fall into three main categories: mental status changes, neuromuscular abnormalities, and autonomic dysfunction.[8,12,14,16,25,30,31] Symptoms usually appear within two hours of taking serotonergic compounds; however, under certain circumstances they may take up to 24 hours to present.[2,4,12,25,32,33] The inclusion of a fourth symptom category, gastrointestinal (GI) disturbances, can also be helpful in distinguishing this syndrome from other conditions (Table II). Both the frequency and severity of symptoms reported in the literature varies widely. The mental changes reported include confusion, hyperactivity/agitation, anxiety, hypomania, unresponsiveness, lethargy, seizures, insomnia, and hallucinations, which are most often visual.[1,5,28,32,34-37] Neuromuscular changes, as a class of symptoms, occur most frequently and include hyperreflexia, shivering, clonus (inducible, spontaneous, ocular), myoclonus (usually bilateral with lower extremities occurring

first), hypertonia/pyramidal rigidity, ataxia, nystagmus, trismus, and tremor.[1,4,5,28,32,35-37] Autonomic changes involve hyperpyrexia (38-41°C), hypertension, hypotension, diaphoresis, mydriasis (pupillary dilation), unreactive pupils, flushed skin, tachypnea, and tachycardia.[1,4,5,10,14,28,31,32,35-37] Gastrointestinal changes include diarrhea, abdominal cramps, and hyperactive bowel sounds.[37,38] Individuals with serotonin syndrome do not necessarily demonstrate symptoms from all four categories simultaneously. They may also show a disproportionate number of symptoms from one category.[12,14,37]

There are multiple diagnostic criteria proposed for the identification of serotonin syndrome, each with varying sensitivities and specificities[5,6,14,32,39-41] (Table III). Due to the potential for any of the current diagnostic categories missing the diagnosis of serotonin syndrome, no one set of criteria should be considered definitive or absolute when trying to make the diagnosis.[32] Radomski et al[5] have further proposed a graded classification system of sertonergic symptoms using categories such as *mild*, *full-blown*, and *toxic*. Individuals with mild cases need to be frequently reassessed since it is possible for serotonin syndrome to progress from mild to severe over the course of one to two hours (termed *evolving toxicity*).[10] Generally, once the condition is identified and the medications responsible for its production are stopped, mild to moderate cases resolve within 24-72 hours.[2,16,23,25,38] Severe cases can persist for one to two weeks.[2]

Reviews of case reports associated with the use of linezolid (an oxazolidinone antibiotic with weak, reversible, competitive, and nonspecific MAOI properties) report a pattern of presentation different than that seen with traditional serotonin syndrome.[13] In a case review series (n = 11) by Morales-Molina et al,[13] most patients studied were taking a combination of linezolid and an SSRI for an average of 9.5 days (range, 0.5-21 days) before symptoms began. The older the patient, the longer the time on medications before symptoms of serotonin syndrome were identified. For patients over the age of 70 (n = 3), the average length of time from onset of medication therapy to symptom onset was 21 days.[13] This finding was slightly at odds with a similar case review (n = 11) done by Taylor et al,[22] who found the average onset of symptoms was approximately six days after the initiation of medications, while for patients older than age 80 (n = 3), symptoms averaged 10 days to onset. These studies show that serotonergic symptoms may be delayed in onset or unrecognized for days after beginning treatment with the causative agents, especially in the elderly. Often, the initiation of treatment with linezolid for infection cannot be delayed. It is recommended that linezolid be started in patients taking SSRIs only if it is the sole effective antibiotic. When this is the case, the physician should decrease the dose of other serotonergic compounds by half, and then taper them over four to seven days to prevent a serotonin discontinuation syndrome.[13,22,42]

There are no confirmatory diagnostic tests for serotonin syndrome.[7,12,43,44] To date, there are no clinically significant studies that relate peripheral serotonin blood levels, platelet serotonin levels, or cerebrospinal fluid values with the clinical severity of central serotonin syndrome.[1,12,44,45] Twenty-four hour urinalysis for serotonin and its metabolites (5-HIAA) usually takes too long to be clinically useful.[12] In 80-90% of cases where drug levels have been drawn while patients are symptomatic, the levels return at therapeutic to below therapeutic levels.[1] Nonspecific laboratory abnormalities that may occur with serotonin syndrome include mild elevations of liver enzymes, decreased bicarbonate levels, elevated creatine kinase levels, mild to moderate leukocytosis (10,000-20,000/µL [10-20 X 10^9/L]), or leukopenia.[1,2,7,12,18,34,38,43]

TABLE IV

Differential Diagnoses

Agitated depression	Lithium toxicity
Alcohol withdrawal	Malignant hyperthermia
Anticholinergic delirium	Neuroleptic malignant-like syndrome (aka, Parkinsonism–hyperpyrexia syndrome)
Anticholinergic toxicity	Neuroleptic malignant syndrome
Benzodiazepine withdrawal	Salicylate toxicity
Carcinoid syndrome	Sepsis
Delirium	Serotonin discontinuation syndrome
Drug toxicity (cocaine, ecstasy)	Stiff-man syndrome
Dystonic reactions	Strychnine toxicity
Encephalitis	Tetanus
Heat stroke	Thyroid storm
Hepatic encephalopathy	
Lethal catatonia	

DIFFERENTIAL DIAGNOSIS AND SECONDARY DISEASE COMPLICATIONS

The symptoms of serotonin syndrome can initially mimic an agitated delirium, alcohol withdrawal, or neuroleptic malignant syndrome (NMS), which often makes early diagnosis difficult (Table IV). The diagnosis is further complicated by the varying severities of presentation from mild to moderate to severe.[10] Often, mild cases have such minimal and/or ambiguous symptoms that the condition is difficult to diagnose. Mild serotonin syndrome usually resolves with supportive treatment (cool environment/cooling blanket, gentle-to-moderate hydration, stopping of initiating pharmacologic agent), but moderate to severe serotonin syndrome requires pharmacological treatment (eg, cyproheptadine or chlorpromazine) to prevent the possibility of permanent brain damage or death from occurring.[10,23,30,43] Although hyperthermia is associated with the syndrome, it is often absent from mild to moderate cases.[14] Fatal complications, which can occur in severe cases of serotonin syndrome, include rhabdomyolysis, multiorgan failure (eg, renal, hepatic, respiratory, cardiac), hyperkalemia, severe metabolic acidosis, adult respiratory distress syndrome/hypoxia related to muscle rigidity, stroke, and disseminated intravascular coagulation.[12,16,18,25,30,32,43]

Although serotonin syndrome can have a presentation similar to NMS (eg, delirium, hyperthermia, rhabdomyolysis, tachycardia, diaphoresis, rigidity, elevated blood pressure), there are several specific characteristics that help differentiate the two conditions.[44,46-48] The quick onset from minutes to hours after taking a serotonergic medication may help to differentiate serotonin syndrome from NMS, which often takes up to a day or longer to present.[4,14,18,46,47] Serotonin syndrome symptoms start within two hours of medication ingestion in approximately 50% of cases. Sixty percent of patients with central serotonin syndrome present to a physician within six hours of ingesting medicine, with 75% of individuals displaying symptoms within 24 hours.[12,14] Mild cases, on the other hand, can present chronically with low-level symptoms. Cases associated with delayed metabolism of serotonergic drugs secondary to hepatic damage can present several days after starting a new medication.[14,32] Another way to differentiate central serotonin syndrome from NMS is that serotonin syndrome more commonly presents with myoclonus, ankle clonus, hyperreflexia, and seizures than NMS.[4,7,18,24,36,38,44] The characteristic GI dysfunction that occurs with central serotonin syndrome is typically not seen with NMS.[7,38]

Another medication-induced state that may be difficult to distinguish from serotonin syndrome is anticholinergic delirium. Both serotonin syndrome and anticholinergic delirium can present with altered

mental status, tachycardia, and fever.[4] Serotonin syndrome often presents with diaphoresis, clonus, and increased GI activity, which help distinguish it from anticholinergic delirium, where patients have dry mucous membranes and skin, widened pulse pressure, and decreased GI activity.[4]

A third commonly encountered state, with a presentation similar to serotonin syndrome, is alcohol or benzodiazepine withdrawal.[4] Both of these conditions can present with hyperreflexia, clonus, altered mental status, hallucinations, tremor, tachycardia, seizures, and elevated blood pressure.[4] A good history of the patient's medications, symptom onset, and alcohol and/or drug intake is helpful to differentiate these conditions. Urine and blood toxicology may also be helpful.

CONCLUSION

It is important that geriatricians are aware of serotonin syndrome since it occurs with regularity in older adults, has varying degrees of severity, often presents in association with other conditions (eg, large differential diagnosis of diseases commonly seen in elderly patients), and is caused by a plethora of medications and combinations of medications that are not often thought to have specific serotonin effects. This condition is readily treated when identified early and the offending medications are discontinued, but physicians have to know to look for it. When unrecognized, the results can be fatal.

The authors report no relevant financial relationships.

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