Serotonin Syndrome

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Selective serotonin reuptake inhibitors (SSRIs) are replacing tricyclic antidepressants (TCAs) with increasing frequency in the United States. Although SSRI poisoning tends to be less serious than TCA poisoning, the incidence of adverse side effects and drug interactions may be greater. The serotonin syndrome is a potentially severe adverse drug interaction characterized by the triad of altered mental status, autonomic dysfunction, and neuromuscular abnormalities. The serotonin syndrome is similar to the neuroleptic malignant syndrome, leading to misdiagnosis. Although serotonin syndrome may result in death, most patients recover completely with supportive care alone. The main pathophysiologic mechanism appears to be excessive 5-hydroxytryptophan stimulation; this finding is supported by reports of beneficial effects with serotonin-antagonist treatment. The incidence of the serotonin syndrome may increase as SSRIs continue to replace TCAs. Morbidity and costly diagnostic procedures may be avoided if prompt diagnosis and appropriate treatment are provided.

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INTRODUCTION

A new class of antidepressants named selective serotonin reuptake inhibitors (SSRIs) has gained wide acceptance in the United States. Sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), and fluvoxamine (Luvox) are US Food and Drug Administration (FDA)–approved SSRIs. Several others are being developed. Clomipramine (Anafranil), venlafaxine (Effexor), and nefazodone (Serazone) are antidepressants with nonselective serotonin reuptake–inhibitor properties. SSRI agents have many uses (Figure 1).

Fortunately, SSRI poisoning is usually less severe than poisoning with tricyclic antidepressants (TCAs).[1] On the other hand, adverse effects and adverse drug interactions associated with SSRIs are common and sometimes life

threatening. The serotonin syndrome, usually the result of an adverse drug interaction, may result in serious toxicity including death. Data from the 1994 National Prescription Audit suggest that SSRIs are replacing first-generation TCAs to a dramatic extent (Table)[2], suggesting that the frequency of TCA poisoning will decrease but also that the frequency of the serotonin syndrome will increase. The purpose of this article is to review the pathophysiology, clinical manifestations, and proposed treatments of the serotonin syndrome.

SEROTONIN SYNDROME

The serotonin syndrome, initially called the "serotonin behavioral" or "hyperactivity syndrome," was described in animal experiments[3-5] before it was described[6-8] and later diagnosed[9] in human beings. In animals, the serotonin syndrome is characterized by a stereotypical behavioral response (hyperactivity and reactivity, forepaw-treading, head-weaving, hind-limb abduction, and the Straub or arched tail) and the usual physiologic response (tremor, rigidity, salivation, flushing, myoclonus, and seizures).

Manifestations of the serotonin syndrome were first reported in patients treated with monoamine oxidase inhibitors (MAOIs) in the early 1950s and 1960s.[6,10] Some of the patients were also taking tryptophan.[6] Tryptophan is hydroxylated, then decarboxylated, to form serotonin (5-HT). Oates demonstrated a dose-response relationship between tryptophan and the clinical manifestations. With tryptophan doses of 20 mg/kg, the most striking effect was altered mental status with a state mimicking inebriation. With doses of tryptophan 30 mg/kg, hyperreflexia and clonus were also noted. At doses of 50 mg/kg or greater, diaphoresis and myoclonus were also noted. Smith[7] also described a dose-dependent relationship, with typical symptoms observed in patients given 70 to 90 mg/kg L-tryptophan alone without an MAOI.

In human beings, the serotonin syndrome is characterized by the classic triad of altered mental status, autonomic dysfunction, and neuromuscular abnormalities (Figure 2).[11-14] The characteristic manifestations of this syndrome in human beings include agitation, delirium, coma, mydriasis, diaphoresis, hyperthermia, tachycardia, fluctuating blood pressure, mutism, tremor, rigidity, and myoclonus and seizures. Tachypnea may be a result of the autonomic dysfunction or of agitation or the hypermetabolic state and increased CO_2 production yielded by increased muscle activity. Laboratory findings may include increased total WBC count and creatine phosphokinase levels and a decreased serum bicarbonate level. Mild to moderately severe cases of the serotonin syndrome usually resolve completely within 24 to 72 hours. In several cases, mild to moderate symptoms persisted for weeks without progression, then ended on discontinuation of the precipitating drugs.[15,16] Severe cases of the serotonin syndrome are uncommon but may be complicated by rhabdomyolysis, myoglobinuria, kidney or liver failure, disseminated intravascular coagulation, or adult respiratory distress syndrome.[13,17,18]

Diagnosis of serotonin syndrome is based on finding the characteristic clinical manifestations in association with a typical drug history and the exclusion of other medical conditions. No diagnostic test for the serotonin syndrome exists.

PATHOPHYSIOLOGY OF THE SEROTONIN SYNDROME

The pathophysiology of the serotonin syndrome is not completely understood. The most widely accepted cause

Figure 1.
Clinical uses of SSRIs.

Appetite reduction
Bulimia*
Depression*†‡
Diabetic neuropathy
Headache
Myoclonus
Narcolepsy
Obesity
Obsessive-compulsive disorder*§
Pain
Panic disorders

FDA-approved indication: *fluoxetine, †sertraline, ‡paroxetine, §fluvoxamine.

Table.
1994 Ranking of antidepressants, new and refill prescriptions.

Drug	Rank
Fluoxetine (Prozac):	9
Sertraline (Zoloft):	20
Paroxetine (Paxil):	53
Amitriptyline:	72
Nortriptyline:	111

From ranking of top 200 drugs in the United States, from data from the National Prescription Audit, conducted by IMS America, Limited. Desipramine, doxepine, imipramine, and other antidepressants were also ranked in the top 200.Appetite reduction.

is excess stimulation of the 5-HT_{1A} receptors.[19] Yamada showed that a 5-HT_{1A} agonist could reproduce the syndrome in mice. The effect was blocked by 5-HT_{1A} antagonists but not by a 5-HT_2 antagonist.[20] However, other agents may be involved—such as 5-HT_2 agonists[21,22], catecholamines, dopamine, and tryptamine[23]—may be involved. Reserpinized rats failed to demonstrate the behavioral syndrome, suggesting a role for catecholamines.[24] Dopamine antagonists such as haloperidol have been used effectively to treat this syndrome in animal models, supporting a role for dopaminergic agents in the cause of the syndrome.[25-28] Some authors have suggested that the ratio of reuptake inhibition of serotonin to dopamine is a critical factor.[25-28]

Marsden suggested an important role for tryptamine by showing a greater increase of tryptamine than 5-HT with the syndrome and the effectiveness of decreased tryptamine synthesis on preventing the syndrome.[29,30] Neither Sleight nor Green observed the typical behavioral syndrome when clorgyline-treated rats were administered L-tryptophan.[23,31] Both authors hypothesized that both types of MAO must be inhibited to demonstrate the behavioral syndrome and that increased 5-HT level alone is not sufficient. One possible reason for these disparate results is the dependence in animal studies on typical behavioral endpoints rather than on physiologic criteria. Another is that certain drugs alleviate some but not all manifestations of the serotonin syndrome. Despite these alternate or additional mechanisms, most investigators believe that excess 5-HT_{1A}–receptor stimulation is the primary mechanism.

Figure 2.
Clinical manifestations of serotonin syndrome.

Altered mental status
- Agitation
- Coma
- Confusion
- Delirium
- Hallucinations
- Mania
- Mutism

Autonomic dysfunction
- Blood pressure fluctuation
- Diaphoresis
- Diarrhea
- Hyperthermia
- Lacrimation
- Mydriasis
- Shivering
- Tachycardia

Neuromuscular abnormalities
- Akathisia (restlessness), clonus, hyperreflexia, incoordination, myoclonus, nystagmus (horizontal or vertical), ocular oscillation, oculogyric crisis, opisthonos, rhabdomyolysis, rigidity, seizures, tremor

PRECIPITANTS OF THE SEROTONIN SYNDROME

Precipitating events involve excessive 5-HT_{1A}–receptor stimulation, including the administration of excess amounts of serotonin precursors or agonists (eg, L-tryptophan[32], LSD[27], lithium[15,16,33], L-dopa[34], and buspirone[35]), agents that enhance the release of serotonin such as methylenedioxy-methamphetamine (MDMA or "ecstasy")[36,37], excess levels of or unusual sensitivity to SSRI agents[38,39], and certain drug combinations. Precipitating drug combinations include any two or more of the following: serotonin precursors or agonists, serotonin-release stimulators[40], SSRI agents, nonselective serotonin-reuptake inhibitors (eg, clomipramine[41], imipramine[42], dextromethorphan[5,43,44], meperidine[45,46], pentazocine[47], trazodone[35]), and nonspecific inhibitors of 5-HT metabolism (cocaine[48,49], MAOIs[50]). Sporer[13] and Bodner[14] have produced tables of published case reports of drug combinations thought to have precipitated the serotonin syndrome. Because of the long half-life of fluoxetine (up to 1 week) and its active metabolite norfluoxetine (up to 2.5 weeks), as well as the duration of effect of the "irreversible" MAOIs, the serotonin syndrome may occur when a precipitating drug is introduced, even as long as 5 or 6 weeks after discontinuation of fluoxetine, sertraline, paroxetine, or an irreversible MAOI.[51,52]

There are two main types of MAO enzymes: A and B.[53,54] Dopamine, tyramine, octamine, and tryptamine are deaminated by both types of MAO. MAO-A preferentially deaminates 5-HT, metanephrine, epinephrine, and norepinephrine and is found mainly in the intestine and liver. It is the primary defense against the systemic effects of ingested tyramine and other exogenous amines because of its enteric location. MAO-B preferentially deaminates phenylethylamines, phenylethanolamines, and O-tyramine. It is responsible for all MAO activity in platelets and 80% of MAO activity in the brain. Inhibition of MAO-B is considered essential for antidepressant effects. Except for pargyline (MAO-B), the first-generation MAO inhibitors (MAOIs) are nonselective, possessing both MAO-A and MAO-B activity.[54] First-generation MAOIs include phenelzine (Nardil), isocarboxazid (Marplan), pargyline (Eutonyl), procarbazine (Matulane), and tranylcypromine (Parnate). Newer MAOI agents such as selegiline (MAOI-B) (Eldepryl) and other agents not yet approved by the FDA,

moclobemide (MAOI-A) and clorgyline (MAOI-A), are relatively selective MAOIs.

Because MAO-A preferentially deaminates 5-HT, nonselective and MAOI-A agents are more likely to produce the serotonin syndrome.[8,9,55] Theoretically, MAOI-B agents could be effective antidepressants without causing serotonin syndrome or tyramine (cheese) reaction.[56,57] In support of this theory, several severe cases of serotonin syndrome have been reported with moclobemide (MAO-A)[41,42,58] and clorgyline[8], whereas selegiline (MAO-B) combined with L-tryptophan did not induce serotonin syndrome.[59] Like other selective MAOIs, the selectivity of selegiline (MAO-B) is relative to dose[60] and is seen only at subtherapeutic doses.[61] At therapeutic or higher doses, selegiline loses its selectivity and may be capable of inducing serotonin syndrome.[62] The loss of selectivity at therapeutic doses is consistent with case reports of two mild and one severe serotonin-like syndrome associated with selegiline (MAO-B) therapy.[46,63] The manufacturer of Eldepryl, a trade brand of selegiline, recently revised its labeling " . . . to warn prescribers of the potential for serious CNS toxicities associated with the combined use of Eldepryl . . . ."[64] This warning apparently stemmed from reports of serotonin syndrome–like reactions in 16 patients taking selegiline (MAO-B) and TCAs and 15 patients taking selegiline and SSRIs.[64] These case reports suggest that all available MAOIs can induce serotonin syndrome.

Serious and sometimes fatal adverse drug interactions have been reported between MAOIs and TCAs, meperidine, dextromethorphan, pentazocine, and indirect-acting sympathomimetics such as pseudoephedrine and phenylpropanolamine.[54,61,65] Whether these interactions are entirely due to serotonin syndrome is still uncertain. Emergency physicians should avoid the use of known precipitating agents in patients currently being treated or recently treated with an MAOI.

DIFFERENTIAL DIAGNOSIS

Suggested differential diagnoses of the serotonin syndrome encompass other diseases, including the stiff-man syndrome[66] and poisonings[67] (Figure 3). Neuroleptic malignant syndrome and serotonin syndrome are very similar and may have a common pathophysiology.[68,69] Heyland[69] even suggested a new label: "drug- induced central hyperthermic syndrome." Many believe that dopamine deficiency plays a central role in neuroleptic malignant syndrome. However, serotonin may play a role in neuroleptic malignant syndrome[70] and dopamine may play a role in serotonin syndrome.[25-28] At variance with the hypothesis of a common mechanism are the observations that bromocriptine is a proposed treatment for neuroleptic malignant syndrome[71,72] and a precipitant of serotonin syndrome.[34] Halman[70] suggested that an increased level of 5-HT induces a relative hypodopaminergic state leading to extrapyramidal symptoms or neuroleptic malignant syndrome.

The distinguishing features of neuroleptic malignant syndrome are the history (prolonged exposure to neuroleptic agents or withdrawal of dopamine agonists), lead-pipe rigidity (rather than clonus, myoclonus, or hyperreflexia), and absence of mydriasis.[73] Because of the similarity of the two syndromes and general unfamiliarity with serotonin syndrome, some cases attributed to neuroleptic malignant syndrome may actually represent serotonin syndrome.[69,70,74-76] Unfortunately, laboratory tests do not distinguish between the two syndromes.

MANAGEMENT OF SEROTONIN SYNDROME

Removal of the precipitating agents and supportive care are often sufficient in the treatment of serotonin syndrome, but deaths have been reported.[17,58,74,75,77,78] The patients in five fatal cases described by Neuvonen[56] were all taking moclobemide (MAOI-A) in excessive quantities. In the reports by Kline and Brennan of two fatal cases, each of

Figure 3.
Differential diagnosis of serotonin syndrome.

Diseases
- Catatonia
- Dystonic reaction, severe
- Encephalitis
- Hyperthyroidism
- Malignant hyperthermia
- Meningitis
- Neuroleptic malignant syndrome
- Septicemia
- Stiff-man syndrome
- Tetanus

Poisonings
- Anticholinergics
- Amphetamines
- Cocaine
- 2,4-Dichlorophenoxyacetic acid
- Dinitrophenol
- Lithium
- LSD
- MAOIs
- Pentachlorophenol
- PCP (phencyclidine)
- Salicylates
- Strychnine
- Water hemlock

the patients was taking three medications known to precipitate the serotonin syndrome.[74,75] The death of Libby Zion led to nationwide regulations limiting consecutive working hours for house staff. It has been speculated that her death was due to a severe adverse drug interaction between phenelzine (MAOI) and meperidine, perhaps another fatal case of serotonin syndrome.[79]

Most cases resolve within 24 to 36 hours with supportive care and conventional symptomatic therapy. Appropriate supportive care may require external cooling, sedatives, paralytics, mechanical ventilation, anticonvulsants, and antihypertensives. Aggressive use of cooling measures and paralytics may substantially reduce the complications of extreme hyperthermia and excessive muscle activity[80,81]; however, it is difficult to judge the adequacy of supportive care alone from case reports.

In severe cases, more specific therapy may be necessary to minimize morbidity and mortality. Case reports and the findings of animal studies suggest that serotonin antagonists are effective therapy for serotonin syndrome. In fact, 5-HT_{1A} antagonists have been shown to be more effective than 5-HT_2 antagonists.[82] Results of some animal studies suggest that nonspecific 5-HT antagonists such as chlorpromazine[26], cyproheptadine[83], methysergide[27,84,85], and propranolol[85-87] may be effective treatments for serotonin syndrome. Not all studies support the efficacy of serotonin-antagonist therapy. The authors of one animal study did not find propranolol or chlorpromazine effective.[84] Beneficial effects have been reported in three patients treated with propranolol[88-90], yet one patient who died was reported to have been taking propranolol when the syndrome developed.[75] Myoclonus and other symptoms thought to be due to serotonin syndrome were successfully treated with cyproheptadine 4 mg/hour.[35,91] Methysergide 2 mg twice a day was reported to be effective within hours in one case.[34]

Other, less specific therapies that have been recommended include benzodiazepines, dopamine antagonists, and dantrolene. Several authors have reported that benzodiazepines may be effective therapy for serotonin syndrome[92,93], but failure to respond has also been reported.[91] Benzodiazepines are said to relieve muscle hyperactivity and to reduce excessive sympathetic outflow.[44]

Haloperidol, a D_2-receptor antagonist, has been effective in the treatment of serotonin syndrome in animal studies.[25-28] Despite these reports, the use of D_2 antagonists is not recommended until further studies demonstrate efficacy and safety.

Bromocriptine is a recommended treatment for neuroleptic malignant syndrome. However, it increases brain serotonin levels in rats[94-96] and has been reported as a possible cause of the serotonin syndrome.[34] Until further studies have demonstrated the safety and efficacy of bromocriptine in atypical cases of neuroleptic malignant syndrome (which may actually be serotonin syndrome), it may be wise to avoid the use of bromocriptine.

Dantrolene inhibits the influx of calcium into skeletal muscle cytoplasm from the sarcoplasmic reticulum. It has been recommended for the treatment of hyperthermia when associated with hyperrigidity as in malignant hyperthermia, the neuroleptic malignant syndrome and many poisonings.[97,98] Dantrolene appeared effective but did not prevent death in two cases of serotonin syndrome.[74,75,99] Optimal doses of dantrolene (up to 10 mg/kg) were not administered in the fatal cases.[74,75] Recent observations suggest that dantrolene treatment of neuroleptic malignant syndrome may enhance central serotonin metabolism, presumably increasing availability of serotonin.[100]

In summary, serotonin syndrome is unfamiliar to many emergency physicians but may be more commonly encountered as SSRIs replace first-generation TCAs. Typical manifestations involve altered level of consciousness, autonomic dysfunction, and neuromuscular abnormalities. The pathophysiology is unclear, but most believe the syndrome is due mainly to excessive 5-HT_{1A} stimulation. One of the most common precipitating events is the combination of an MAOI and an SSRI drug. Because of the prolonged half-lives and duration of action of some of these drugs, this syndrome can result from the addition of one drug weeks after the discontinuation of another. The differential diagnosis includes many critical conditions that must be ruled out clinically, sometimes with the help of the laboratory. For most cases, careful supportive care suffices. For severe cases, specific and nonspecific therapeutic agents have been recommended, but none has been shown to be clearly effective.

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