

Serotonin syndrome: a brief review

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Case 1

A 50-year-old man was admitted to hospital with hyperhidrosis, nausea, vomiting and diarrhea. He had been taking fluoxetine (120 mg/d), meprobamate (400 mg/d) and aceprometazine (13.55 mg/d). The dose of fluoxetine had just been increased. The patient was agitated and had insomnia and hyperreflexia, but there were no focal neurological findings. His blood pressure was 155/80 mm Hg, his heart rate, 96 beats/min, his respiratory rate, 20 breaths/min and his temperature, 37.2°C. The findings of the complete blood count, blood potassium, blood glucose, liver function and kidney function tests, and the erythrocyte sedimentation rate were normal. A blood alcohol test was negative. ECG, chest radiograph, blood gas measurements and a brain CT scan showed no anomaly.

Case 2

A 50-year-old depressed woman was admitted to hospital for agitation, insomnia and tremors. She had been taking citalopram (20 mg/d), prazepam (10 mg/d), meprobamate (400 mg/d) and aceprometazine (13.55 mg/d). The patient's blood pressure was 135/70 mm Hg, her heart rate, 130 beats/min, her respiratory rate, 32 breaths/min and body temperature, 37°C. The patient was confused and had hyperhidrosis, hyperreflexia and myoclonus, but there were no focal neurological findings. Her blood electrolytes were normal, her leukocyte count was $13.3 \times 10^9/L$ and her total creatine kinase was 494 U/L (MB isoenzyme fraction < 6%). The aldolase level, liver function tests, and blood creatinine, hemoglobin, platelet and fibrinogen levels were normal. Qualitative plasma tests for alcohol, carbamates, salicylates, paracetamol, barbituates, benzodiazepines and tricyclic antidepressants were negative. ECG indicated sinus tachycardia. The findings of a brain CT scan were normal.

Serotonin (5-HT) is a neurotransmitter with neurons located in the raphe nuclei. Serotonin neurons play a part in sleep-wakefulness cycles, mood, emotional and food behaviours, and thermoregulation.¹ Serotonin syndrome is the result of overstimulation of 5-HT_{1A} receptors (Fig. 1) by selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI) or other serotonergic agents.²⁻⁵ The use of SSRIs is related to the frequency of the syndrome.^{2,3} Regardless of age or sex, onset is observed within 24 hours following the administration or overdose of a serotonergic agent.^{2,4} Serotonin syndrome is characterized by a triad of mental, autonomic and neurological disorders.^{2-4,6-8} Serotonin syndrome is confirmed by the presence

of 4 major symptoms or 3 major symptoms plus 2 minor ones.^{3,9} Serotonin syndrome can be fatal, but in most cases there is a good prognosis when medication is discontinued.^{2,4} Improvement following the administration of cyproheptadine or chlorpromazine has been reported.³ Further studies of the therapeutic effects of propranolol and ziprasidone, which block 5-HT_{1A} receptors, would be justified.

Physiopathology

Serotonin syndrome is the result of overstimulation of 5-HT_{1A} receptors in central grey nuclei and the medulla and, perhaps, of overstimulation of 5-HT₂ receptors.^{2-4,10} Few cases have been reported in association with citalopram.^{2,11} In the case of fluoxetine, a high dose increases the risk of serotonin syndrome.^{4,7,9} Drug combinations may also have been involved. Meprobamate, which is metabolized in the liver through hydroxylation and glucuronide conjugation, might slow down the metabolism of a SSRI through competitive inhibition. Promethazine, a competitive inhibitor of 5-HT₂ receptors,¹² might cause hyperactivation of 5-HT_{1A} receptors in the presence of SSRIs.

Several situations indicate an overstimulation of 5-HT_{1A} receptors: excess precursors of serotonin or its agonists and higher release, lower recapture or metabolic slowdown of serotonin (Table 1).^{2,3,8} Cases of mild serotonin syndrome have been reported in patients who have taken *Hypericum perforatum* (St. John's wort), an in-vitro 5-HT reuptake inhibitor, in conjunction with SSRIs.¹³

Diagnosis

In order to reach a diagnosis of serotonin syndrome, a history of use of a serotonergic agent, recognized signs and symptoms, and the exclusion of other conditions are required.^{2,8,9} Serotonin syndrome involves mental, autonomic and neurological disorders of sudden onset less than 24 hours after the beginning of treatment or an overdose.^{2-4,6-9} The diagnosis of serotonin syndrome is guided by the Sternbach criteria¹⁴ but is still difficult in cases of benign symptoms or normal neurological test results.^{3,9,15} Radomski and colleagues⁹ have revised these criteria and classified serotonin syndrome as a mild state of serotonin-related symptoms, or serotonin syndrome (full-blown form) (4 major symptoms or 3 major ones plus 2 minor ones) (Box 1) or toxic (coma, generalized tonic-clonic seizures, fever that might exceed 40°C).^{3,9}

There is no specific test for serotonin syndrome. An elevation of the total creatine kinase and leukocyte count and

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elevated transaminase levels or lower bicarbonate levels have been reported.^{2,3,8} Disseminated intravascular coagulation, kidney failure, acidosis or acute respiratory distress syndrome are secondary complications.^{2,9}

The principal differential diagnosis is neuroleptic malignant syndrome (NMS) (Box 2).^{2-4,7,8,10,16} Common criteria are alteration of consciousness, diaphoresis, autonomic instability, hyperthermia and elevated creatine kinase levels. NMS is observed most often following a rapid increase in dosage of a neuroleptic drug.^{2,10,17} These symptoms appear within 7 days in 66% of cases.¹⁷ Certain risk factors (dehydration, agitation, organic cerebral disorders) are associated with development of the syndrome following a brief expo-

sure.¹⁸ Our patients were taking a phenothiazine (aceprometazine), one of the antipsychotic drugs associated with NMS, but the absence of hyperthermia and muscular rigidity and the presence of diarrhea and myoclonus were indicators of serotonin syndrome.^{19,20} The most frequent differences between serotonin syndrome and NMS are indicated in Table 2.

Treatment

Serotonergic agents must be discontinued.^{2,3,9} Monitored intravenous (IV) electrolyte solution is administered in a hospital environment in order to maintain diuresis above

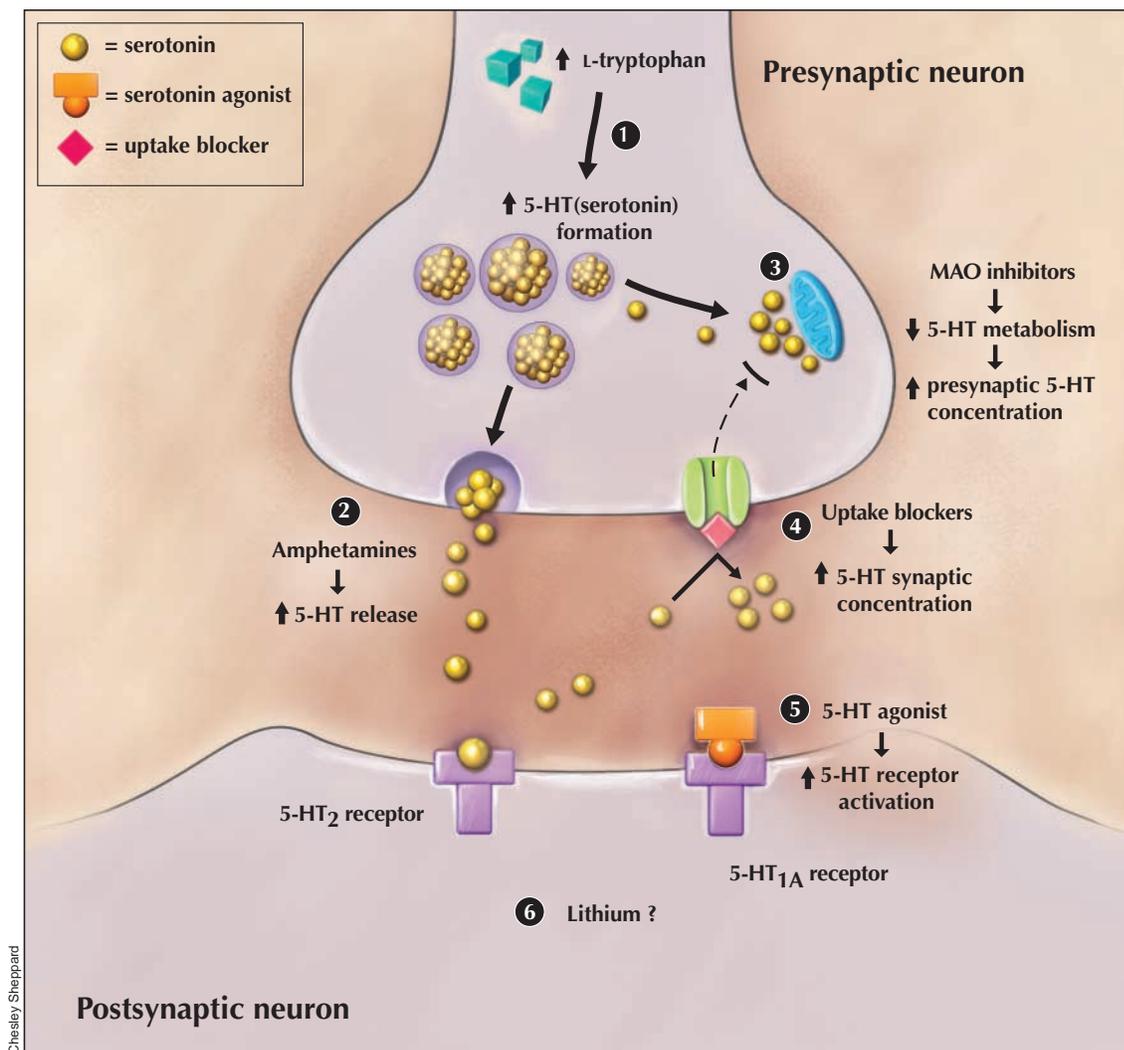


Fig. 1: Mechanisms of serotonin syndrome. (1) Increased doses of L-tryptophan will proportionally increase 5-hydroxytryptamine (5-HT or serotonin) formation. (2) Amphetamines and other drugs increase the release of stored serotonin. (3) Inhibition of serotonin metabolism by monoamine oxidase (MAO) inhibitors will increase presynaptic 5-HT concentration. (4) Impairment of 5-HT transport into the presynaptic neuron by uptake blockers (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants) increases synaptic 5-HT concentration. (5) Direct serotonin agonists can stimulate postsynaptic 5-HT receptors. (6) Lithium increases postsynaptic receptor responses. Adapted with permission from Elsevier Science (*Critical Care Clinics* 1997;13[4]:763-83).

50–100 mL/h and to avoid the risk of myoglobinuria.³ Benzodiazepines may be prescribed to reduce anxiety. One case of partial improvement has been reported during treatment with propranolol.²¹ The benefits of β -blockers, which block 5-HT_{1A} receptors, may be supported by other studies.¹⁶ Resuscitation (cooling off, mechanical ventilation, anticonvulsing agents, antihypertensive agents) may be required for serious cases.^{2,3,22,23}

Although their effectiveness has not been demonstrated scientifically, cyproheptadine and chlorpromazine have been described as possible therapy for serotonin syndrome.^{2,3} Cyproheptadine is a histamine-1 receptor antagonist with anticholinergic and antiserotonergic characteristics and can cause drowsiness.^{22,24} Chlorpromazine is a 5-HT_{1A} and 5-HT₂ receptor antagonist neuroleptic that can have anticholinergic effects and cause hypotension, dystonias or NMS.^{3,22,25} Cyproheptadine, which is taken orally, has lesser adverse effects.³ Among newer antipsychotic drugs, ziprasidone is the most powerful for blocking 5-HT_{1A} receptors.²⁶ Further study might outline its possible benefits; it has moderate extrapyramidal effects.

Course

Most patients improve completely within 24 hours after being admitted. This is the case for individuals who have been taking cyproheptadine or chlorpromazine.² For 40% of patients, some symptoms persist longer. The more powerful the serotonergic agent and the higher the dose, the more serious these symptoms. Duration seems related to the half-life of the drug.^{4,27} Prescribing the antiemetic metoclopramide may increase the long half-life of fluoxetine (4–6 days).²⁸

Cases revisited

Case 1

A diagnosis of full-blown serotonin syndrome was reached taking into account the sudden increase in dosage

Table 1: Situations that cause overstimulation of serotonin (5-HT_{1A}) receptors^{2,3,8}

Situation	Associated drugs
Excess of precursors of serotonin or its agonists	Buspirone, L-dopa, lithium, LSD, L-tryptophan, trazodone
Increased release of serotonin	Amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, reserpine
Reduced reuptake of serotonin	SSRI, TCA, trazodone, venlafaxine, meperidine
Slowing down of serotonin metabolism	MAOI, e.g., isocarboxazid, selegiline

Note: LSD = lysergic acid diethylamide, MDMA = methylenedioxy-methamphetamine, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors.

of fluoxetine and the presence of 3 major symptoms (elevated mood, hyperhidrosis, hyperreflexia) and 2 minor ones (insomnia, diarrhea). The patient's medication was discontinued. He was administered 3 L of electrolytic solution every 24 hours, 10 mg of IV metoclopramide dihydrochloride every 8 hours and 20 mg of dipotassium clorazepate orally every 12 hours. Nausea, vomiting, diaphoresis and diarrhea disappeared within 72 hours. The patient's anxiety subsided more slowly, and he was discharged 5 days later.

Case 2

A diagnosis of full-blown serotonin syndrome was reached because the patient was taking citalopram, there was probable voluntary overdose and 5 major symptoms (confusion, myoclonus, tremors, hyperreflexia, hyperhidrosis) were present. The medication was discontinued. The patient was administered 3 L of electrolytic solution every 24 hours. The patient's condition improved sufficiently regarding her confusion and the autonomic and neurological symptoms for her to be discharged 24 hours later.

Box 1: Revised diagnostic criteria for serotonin syndrome^{3,9*}

1. Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms plus 2 minor ones

Mental (cognitive and behavioural) symptoms

Major symptoms: confusion, elevated mood, coma or semicoma

Minor symptoms: agitation and nervousness, insomnia

Autonomic symptoms

Major symptoms: fever, hyperhidrosis

Minor symptoms: tachycardia, tachypnea and dyspnea, diarrhea, low or high blood pressure

Neurological symptoms

Major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia

Minor symptoms: impaired co-ordination, mydriasis, akathisia

2. These symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotonergic agent.

3. Infectious, metabolic, endocrine or toxic causes must be excluded.

4. A neuroleptic treatment must not have been introduced, nor its dose increased, before the symptoms appeared.

*Adapted from Radomski et al⁹

Box 2: Major differential diagnoses^{2,3}

- Malignant neuroleptic syndrome
- Infectious causes
- Herpetic encephalopathy
- Heat stroke
- Myocardial necrosis
- Delirium tremens
- Intoxication by adrenergic or anticholinergic agents

Table 2: Most frequent distinctions between serotonin syndrome and neuroleptic malignant syndrome^{2,3,8-10,17-20}

Characteristic	Serotonin syndrome	NMS
Onset	Sudden, within 24 h following introduction of a serotonergic agent	Slower, within 7 d following introduction of a neuroleptic agent
Symptoms	Agitation, diarrhea	Dysphagia, hypersalivation, incontinence
Signs	Dilated pupils, myoclonus, hyperreflexia	Hyperthermia (> 38°C), akinesia, extrapyramidal "lead pipe" rigidity, rhabdomyolysis
Mortality	23 deaths reported until 1999*	15%–20%

Note: NMS = neuroleptic malignant syndrome.

*No percentage is reported in the literature, because there are too few cases.

Comment

The diagnosis of serotonin syndrome was straightforward in these 2 patients who presented with the classic triad of mental, neurological and autonomic signs and symptoms. This is one of the first instances in which 2 cases of serotonin syndrome are reported based on the revised Radomski criteria. This classification aids diagnosis by allowing for a quick evaluation of the seriousness of the situation. Discontinuation of causal agents and treatment of symptoms is effective. This syndrome must be prevented by educating patients to avoid self-medication, by limiting drug combinations and by improving compliance with "drug holidays."

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