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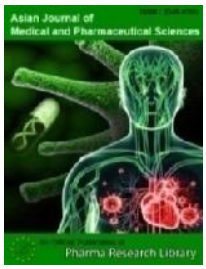

R E V I E W A R T I C L E

A Review on Serotonin Syndromep

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A B S T R A C T

Serotonin syndrome is a potentially dangerous syndrome that is accumulation of serotonin levels will be observed by the use of serotonergic drugs and hyperactivity of both the peripheral and central postsynaptic 5HT-1A and, most probably, 5HT-2A receptors. A combination of mental status changes, neuromuscular hyperactivity, and autonomic hyperactivity will be observed in this syndrome. Mostly the serotonin syndrome occurs due to the therapeutic use of serotonergic drugs alone, an overdose of serotonergic drugs, or most commonly due to the drug interaction between two serotonergic drugs that work by different mechanisms. A multitude of drug combinations can result in serotonin syndrome. This review describes the presentation and treatment of serotonin syndrome and discusses the drugs and interactions that can precipitate this syndrome.

Key words: Serotonin syndrome, neuromuscular hyperactivity, serotonergic drugs.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

What is Serotonin?[1]

Serotonin or 5-hydroxytryptamine is a monoamine neurotransmitter. Serotonin is a biochemical conversion process that combines tryptophan, a component of proteins, with tryptophan hydroxylase, a chemical reactor and furtherly this combination forms 5-hydroxytryptamine (5-

HT), or serotonin. It is primarily found in the gastrointestinal tract, blood platelets and in the central nervous system. As it occurs widely throughout the body, it is believed to influence a variety of body and psychological function.

Functions:[1]

It acts as a neurotransmitter, serotonin send signals between nerve cells nd neuron and regulating their intensity. It is believed to help and regulate the mood and social behavior, appetite and digestion, sleep, memory, sexual desire and function. It also plays an important role in functioning of nerve and brain cells and has an impact on mood.

Introduction:[2]

Serotonin was first detected in 1948 in blood serum when too much serotonin builds up in your body or your brain; this is known as serotonin syndrome. Serotonin syndrome, also known as serotonin toxicity, may occur due to the use of serotonergic medications or drugs. It is a potentially serious negative drug reaction associated with increased serotonergic activity in the central nervous system (CNS). It is seen with therapeutic medication use, drug interactions, and intentional self-poisoning Serotonin syndrome can occur when you increase the dose of such a drug or add a new drug to your regimen. Serotonin syndrome is also associated with some illegal drugs and food.

Serotonin is a chemical your body produces that's needed for your nerve cells and brain to function. But too much serotonin causes symptoms that can range from mild (shivering and diarrhea) to severe (muscle rigidity, fever and seizures). If this syndrome is not treated this will be severe and fatal. [3]

Milder forms of serotonin syndrome may go away within a day of stopping the medications that cause symptoms and sometimes taking drugs that block serotonin. Serotonin syndrome can be severe if you don't receive proper treatment.

Definition[4]**:** Serotonin syndrome is characterized by the triad of altered mental status, autonomic dysfunction and neuromuscular abnormalities. It is predictable consequences of excess serotonergic antagonism of the central nervous system and peripheral serotonergic receptors that produce this spectrum of clinical findings from barely perceptible to lethal.

2. Epidemiology and Demographics

It was first described in 1955; in the central nervous system. Increase in use of serotonergic agonists is increasing day by day in recent cases. Serotonin syndrome is roughly calculated to occur in approximately 14% to 16% of patients who were on overdose with the use of selective serotonin reuptake inhibitors (SSRIs).

It occurs within 5 to 6 weeks after discontinuing fluoxetine, sertraline, paroxetine, or monoamine oxidase inhibitors (MAOIs) and or after starting a serotonergic agent.

- ✓ 2002 Toxic Exposure Surveillance System:
- ✓ 99,860 incidences of exposures to antidepressant
- ✓ 46,244 incidences of exposures to SSRIs
- ✓ 7349 (16%) with moderate to major toxic effects
- ✓ 93 (0.2%) deaths

Serotonin syndrome was not clearly listed as an outcome

- ➢ From newborns to elderly it was occurred in all ages.
- ➢ Between ages of 22 and 50 years: Majority (75.6%)
- ➢ Between ages of 0 to 21 years: 14.6%
- ➢ Male to female ratio of 1:1.7

It has been described after a single 60 mg dose of fluoxetine (Prozac) was administered in a child.

Serotonin Syndrome Symptoms[6]

After administering a new medication it affects increasing serotonin levels within few hours or it affects by increasing the dose of medication excessively. Symptoms may include:

- ✓ Confusion
- ✓ Agitation or restlessness
- ✓ Dilated pupils
- ✓ Headache
- ✓ Changes in blood pressure and/or temperature
- ✓ Nausea and/or vomiting
- ✓ Diarrhea
- ✓ Rapid heart rate
- ✓ Tremor
- ✓ Loss of muscle coordination or twitching muscles
- ✓ Shivering and goose bumps
- ✓ Heavy sweating

In severe cases, serotonin syndrome can be life threatening disorder which leads to death. If any of these symptoms were experienced by you, then you or someone with you should look for medical attention immediately:

- ✓ High fever
- ✓ Seizures
- ✓ Irregular heartbeat
- ✓ Unconsciousness

3. Pathophysiology

Serotonin a neurotransmitter synthesized from the dietary amino acid known as L-tryptophan. Serotonin is produced both peripherally and centrally from this amino acid whereas from intestinal chromaffin cells it was produced peripherally and centrally by nuclei found in the lower pons and upper brain stem cells [8].

Serotonin biosynthesis and metabolism:

Serotonin a neurotransmitter used by the nervous system to send the signals from one cell to the other cell down the axon.[9] L-tryptophan is converted to 5-hydroxytryptophan and then to 5-hydroxytryptamine an end product when it is taken up by the presynaptic neuron.[10] After the conversion of amino acid the serotonin is produced by the presynaptic vesicles and stored until the neuron is stimulated.[9] The serotonin then stimulates the 5-HT receptors and is taken up by postsynaptic neuron[10] The remaining unused serotonin in the synaptic cleft is taken up by the presynaptic neuron receptors and is stored in vesicles until the next axonal stimulation occurs.[9]

Mechanism:[11]

The different mechanisms of causing serotonin syndrome are:

- ♦ Stimulation if post synaptic 5-HT1A and 5-HT2A receptors

- Increasing serotonergic neurotransmission.
- Increase in serotonin synthesis
- Decrease in serotonin metabolism
- Increase in serotonin release
- Inhibition of serotonin uptake

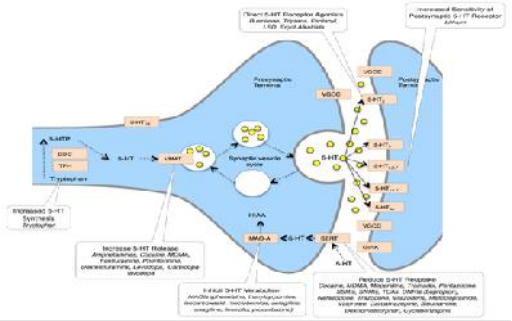

Figure 1

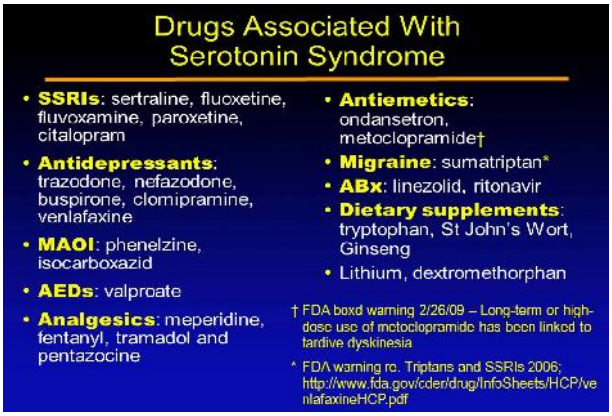

Figure 2

Table 2

Combinations That May Result in Serotonin Syndrome

All SSRIs in combination
Venlafaxine & lithium
Venlafaxine & moclobemide
Venlafaxine & fluoxetine
Venlafaxine & mirtazapine
Fluoxetine & sertraline
Fluoxetine & tramadol
Trazodone & buspirone
Clomipramine & MAOI
Clomipramine & trazodone
Clomipramine & moclobemide
Dextromethorphan & paroxetine
Dextromethorphan & moclobemide
Linezolid & citalopram
SSRI & St. John's wort
SSRI & MAOI
Meperidine & MAOI

SSRI: selective serotonin reuptake inhibitor; MAOI: monoamine oxidase inhibitor.
Source: References 2, 6, 9.

Figure 3

4. Diagnostic Criteria

Serotonin syndrome is diagnosed on the basis of clinical findings. We suggest diagnosing serotonin syndrome using the Hunter Toxicity Criteria Decision Rules [14]. A patient must have taken a serotonergic agent and meet one of the following condition to fulfill the Hunter Criteria:

- Spontaneous clonus
- Inducible clonus PLUS agitation or diaphoresis
- Ocular clonus PLUS agitation or diaphoresis
- Tremor PLUS hyper reflexia
- Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus

To define serotonin syndrome, several sets of diagnostic criteria have been developed, of which the Hunter Criteria are most accurate (when compared with gold standard of diagnosis by medical toxicologist it was 84 percent sensitive and 97 percent specific).the hunter criteria performed with greater accuracy and were less likely to miss early, mild, or sub-acute forms of serotonin syndrome when compared with the original sternbach.

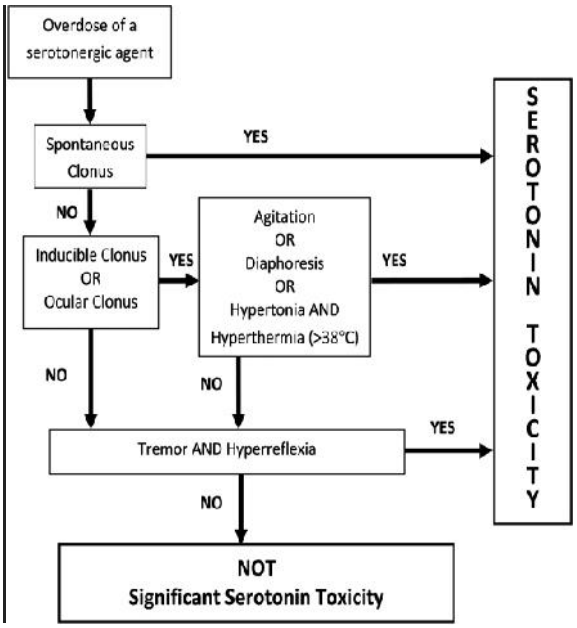

Figure 4

Diagnostic tests may include: [14]

- ✓ Blood cultures
- ✓ Complete blood count
- ✓ CT-Scan of the brain
- ✓ Drug and alcohol screen
- ✓ Electrolyte levels
- ✓ Electrocardiogram
- ✓ Kidney and liver function test
- ✓ Thyroid function test.

5. Treatment

We suggest the medication based on severity of the serotonin syndrome.

- If your symptoms are seen to be minor, consult the doctor and stop the use of this medication which causes the syndrome.
- If you recognize any symptoms then concern with your doctor, and make sure that whether these symptoms gone severe or not by staying in the hospital for several hours.
- If you have severe serotonin syndrome, patient should take intensive treatment in a hospital without any complications.
- Depending on your symptoms, you may receive the following treatments:

- Muscle relaxants. Benzodiazepines, such as diazepam (Valium) or lorazepam (Ativan), can help control agitation, seizures and muscle stiffness.
- Serotonin-production blocking agents. If any other medication is not working, then medication like cyprohepatadine can help by blocking serotonin production.
- Breathing oxygen through a mask helps to maintain normal oxygen levels in your blood and intravenous fluids are used to treat dehydration and fever.
- Drugs include esmolol (brevibloc) or nitroprusside (nitropress), are used to reduce a high heart rate or high blood pressure. Your doctor may prescribe phenylephrine (neo – synephrine) or epinephrine (adrenalin, epipen) when your blood pressure is too low.
- A breathing tube and machine and medication to paralyze your muscles. If you have a high fever you may need a breathing tube and medication to paralyze your muscles.
- Milder forms of serotonin syndrome usually go away within 24 to 72 hours of stopping medications that increase serotonin, and by taking medications to block the effects of serotonin already in your system if they're needed.
- Hence, symptoms of this syndrome caused by some antidepressants could take several weeks to go away completely.

6. Conclusion

Many commonly used medications have proven to be the culprits of serotonin syndrome. Promoting appropriate treatment may prevent significant morbidity and mortality and will improve the accuracy of diagnosis by providing proper education and awareness about serotonin syndrome.

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