SEROTONIN SYNDROME

INTRODUCTION

Serotonin syndrome is defined as a group of signs and symptoms caused by excessive stimulation of the serotonin receptors. Serotonin syndrome is caused by therapeutic doses, drug interactions, or overdoses of medications that directly or indirectly affect the serotonergic system. The first case of diagnosed serotonin syndrome occurred in the mid 1950s, but case reports of unrecognized serotonin syndrome predate that by at least 20 years.

The clinical presentation of serotonin syndrome can be intense and dramatic, but can it can also be mild and subtle. Serotonin syndrome can also be mistaken for an infectious or metabolic disorder or for the clinical syndromes caused by anticholinergic or sympathomimetic poisoning, or for the neuroleptic malignant syndrome or malignant hyperthermia. Although it is unusual for the serotonin syndrome to cause a fatality, a severe case of serotonin syndrome is a medical emergency that can rapidly cause multi-system organ failure.

Nurses must be aware of the serotonin syndrome because drugs that can cause the serotonin syndrome are in common use, intentional overdoses with drugs that can cause the serotonin syndrome are being seen with increasing frequency, and serotonin syndrome can be difficult to detect and easily mistaken for other pathologies.

OBJECTIVES

When the student has finished with this module, he/she will be able to:

1. Correctly identify the definition of serotonin syndrome.
2. Correctly identify the basic cause of serotonin syndrome.
3. Name a class of drugs that inhibits the reuptake of serotonin.
4. Name two drugs that can cause excessive release of serotonin.
5. List three illicit drugs that may cause serotonin syndrome.
6. List the three categories of signs/symptoms that are diagnostic of serotonin syndrome.
7. Identify the diagnostic sign that is most reliably noted in cases of serotonin syndrome.
8. Identify autonomic, cognitive, and neuromuscular changes seen in serotonin syndrome.
9. Identify the name of the criteria that are used to diagnose serotonin syndrome.
10. List three clinical conditions that may be mistaken for malignant hyperthermia.
11. Identify the usual time of onset of the signs and symptoms of serotonin syndrome.
12. Identify three serious complications of serotonin syndrome.
13. Identify the best therapy for serotonin syndrome and three specific treatments.
14. Identify three drugs that may be helpful in treating serotonin syndrome.
15. List four drugs that should not be used to treat serotonin syndrome.

SEROTONERGIC SYSTEM

Serotonin (also called 5-hydroxytryptamine) is a monoamine neurotransmitter that acts centrally and peripherally. It is synthesized in the central nervous system and in
enterochromaffin cells in the gastrointestinal tract. Serotonin has many complex functions, and the full range and activity of these is not known. It inhibits gastric secretion, acts as a smooth muscle stimulant, affects vascular tone, and is a central and peripheral neurotransmitter. In the brain, serotonin is involved in mood, personality, affect, appetite, motor function, temperature regulation, sexual activity, pain perception, and sleep induction.

Serotonin is stored in vesicles in presynaptic neurons. It is released into the synaptic cleft and binds to a serotonin receptor on the postsynaptic neuron. There are seven families of serotonin receptors (5-HT\(_1\) to 5HT\(_7\)) and several of these have different subtypes, e.g., 5-HT\(_{1A}\). Serotonin binding to a 5-HT receptor initiates a wide variety of effects on the post-synaptic neuron (decreasing or increasing intracellular cAMP levels, causing Na\(^+\) and Ca\(^{2+}\) influx and depolarization, etc.) but the basic effect of serotonin is excitatory. After binding to the receptor, serotonin is transported back to the presynaptic neuron where it reenters the vesicles or is broken down by monoamine oxidase.

**Learning Break:** Neurotransmitters such as serotonin, dopamine, glycine, etc. function by binding to receptors on the membranes of post-synaptic neurons. These receptors are ligand-gated ion channels or G protein receptors. When a neurotransmitter binds to a ligand-gated ion channel, the channel opens and ions enter or leave the cell: depending on which ions enter or leave, the effect of the neurotransmitter can be excitatory (causing cell depolarization) or inhibitory (preventing cell depolarization). When a neurotransmitter binds to a G protein, the same effects occur. Example: When serotonin bind to G proteins of the 5-HT\(_1\) receptors, potassium ions channels open, potassium leaves the cell – increasing membrane potential and inhibiting depolarization – and cAMP concentrations are decreased, and the effect is inhibitory. It is important to remember that the terms inhibition and excitation refer to how the neurotransmitter affects the cell. The physiological action produced by excitation may be a decrease in a particular function (e.g., decreased peristalsis) and the physiological action produced by inhibition may be an increase in a particular function, e.g., muscle tremor or hyperreflexia.

**SEROTONIN SYNDROME: EPIDEMIOLOGY**

The exact incidence of serotonin syndrome is not known. Many physicians do not know about the serotonin syndrome and mild cases may be overlooked or misdiagnosed. There is no way to confirm serotonin syndrome using laboratory tests, there are other clinical syndromes that may be mistaken for serotonin syndrome, and there is some dispute about the best diagnostic parameters. One author noted that 14% – 16% percent of all patients who took an overdose of a selective serotonin reuptake inhibitor (SSRI) had signs and symptoms of serotonin syndrome. Fatality rates have been reported to be between 2% -12%, but death from serotonin syndrome is considered to be an unusual event.

**SEROTONIN SYNDROME: CLINICAL PRESENTATION**
Serotonin syndrome is caused by excess stimulation of the serotonergic receptors. The stimulation is excitatory and causes the tachycardia, hypertension, agitation, and excessive muscular activity and other signs and symptoms of the syndrome. The excess stimulation occurs by one of these five mechanisms:\(^9,10\)

- **Direct stimulation of the serotonergic receptors:** Buspirone, carbamazapine, lithium, LSD.
- **Excessive release of serotonin:** Amphetamines, cocaine, dextromethorphan, ecstasy/MDMA, levodopa, monoamine oxidase inhibitors (MAOIs), reserpine.
- **Decreased breakdown of serotonin:** Monoamine oxidase inhibitors, St. John’s wort.
- **Increase in serotonin precursors:** Tryptophan
- **Decreased serotonin reuptake:** Selective serotonin-reuptake inhibitors (e.g. fluoxetine, paroxetine), dextromethorphan, MAOIs, methadone, trazadone.

It is not known exactly which families and which subtype of serotonin receptors are involved in the serotonin syndrome, and that could be one of the factors accounting for the variability of the clinical presentation of this pathology.\(^11\) However, although there is a wide range of signs and symptoms that are possible, the serotonin syndrome is definitely characterized and diagnosed by abnormal **autonomic**, **cognitive**, and **neuromuscular changes.**\(^12\)

- **Autonomic:** Autonomic changes include hyperthermia, hypertension, tachycardia, diaphoresis, flushing, increased bowel sounds, diarrhea, and mydriasis. The hyperthermia can be very severe with a body temperature = 38.5° C.
- **Cognitive:** There are many cognitive changes associated with serotonin syndrome such as agitation, drowsiness, coma, hypomania, anxiety, confusion, hallucinations, and delirium.
- **Neuromuscular:** Akathisia, anxiety, agitation, clonus, hyperreflexia, myoclonus, rigidity, shivering, and tremor.

**Learning Break:** Clonus – inducible, ocular, or spontaneous – is the most reliable finding when diagnosing serotonin syndrome. Clonus is defined as alternate muscular contraction and relaxation in rapid succession.

These are the signs and symptoms that may possibly be seen: not all will be seen in all patients and their severity varies, as well. Serotonin syndrome is like many other medical conditions: there are mild cases and cases which are severe and life-threatening. Patients with a mild case of serotonin syndrome may feel restless and anxious, they may have a low-grade fever, and mild, intermittent tremors. A **severe case of serotonin syndrome** is
a medical emergency. Patients with a severe case of serotonin syndrome may have a body temperature > 41° C. Coma, metabolic acidosis, renal failure, rhabdomyolysis, and disseminated intravascular coagulation (DIC) may occur and all of this can develop very rapidly. The onset of the signs and symptoms can be within minutes of ingestion and they usually occur within six to eight hours after exposure to a drug.13,14

Learning Break: Severe cases of serotonin syndrome appear to be more common if multiple drugs are taken than when a single serotonergic drug is taken in overdose or therapeutically. Monoamine oxidase inhibitors are particularly dangerous when combined with selective serotonin-reuptake inhibitors (SSRIs), ecstasy, dextromethorphan, or meperidine.

DRUGS THAT CAUSE SEROTONIN SYNDROME

It would be impossible to list all the drugs that have caused or could cause serotonin syndrome. Certain classes of medications have been definitely identified as drugs that can cause serotonin syndrome, and this makes sense because their therapeutic effect is based on their action on the serotonergic system. The SSRIs such as fluoxetine and sertraline and MAOIs such as phenelzine and moclobemide are common examples of these drugs.

Other drugs may cause serotonin syndrome, but the connection between the syndrome and the drug is not as obvious because many drugs affect uptake or metabolism of multiple neurotransmitters and this does not translate to a measurable or observable clinical effect. Two examples are bromocriptine and tramadol. Both drugs do have an in vivo effect on the serotonergic system. However, the therapeutic effect of bromocriptine is caused by dopamine receptor agonist activity, and the therapeutic effect of tramadol is caused by agonism of the mu opioid receptors, yet both drugs can cause serotonin syndrome.

Commonly used drugs that have been identified as causing serotonin syndrome or are strongly suspected of doing so include:15,16

- MAOIs
- SSRIs
- Tricyclic antidepressants (TCAs)
- Illicit drugs such as amphetamine, cocaine, ecstasy/MDMA, and LSD
- Antidepressants such as bupropion, buspirone, clomipramine, nefazodone, trazodone, and venlafaxine.
- Analgesics such as fentanyl, meperidine, and tramadol
- Antiemetics such as metoclopramide and ondansetron
- Dietary supplements/herbal products such as ginseng, St. John’s wort, and tryptophan
- Miscellaneous drugs such as carbamazapine, carisoprodol, dextromethorphan, levodopa, lithium, methylene blue, phentermine, reserpine, and sumatriptan

Serotonin syndrome occurs after overdose, it can also happen after ingestion of a single dose but this is unusual.17,18,19 It is far more common for serotonin syndrome to be caused by a combination of drugs that act at different 5-HT receptor sites.20 Drug interactions
can also be a cause of serotonin syndrome, even if one of the drugs does not affect the serotonergic system. If a patient who is taking an SSRI is prescribed a medication that inhibits the cytochrome P450 enzyme that metabolizes the SSRI, serotonin syndrome is possible.\textsuperscript{21} Discontinued medications can cause serotonin syndrome, as well. Norfluoxetine is a metabolite of fluoxetine that has a very long half-life. Five weeks after therapy with fluoxetine was stopped, a patient was given paroxetine and developed serotonin syndrome.\textsuperscript{22} Drug combinations that have been reported to, or may result in serotonin syndrome are:\textsuperscript{24}

- SSRIs with other SSRIs
- SSRIS with St. John’s wort
- SSRIs with MAOIs
- Amphetamines and MAOIs
- Venlafaxine with fluoxetine or other SSRIs, lithium, or moclobemide
- Fluoxetine, sertraline and other SSRIs with tramadol
- Trazodone and buspirone
- Paroxetine and buspirone
- Clomipramine with MAOIs, moclobemide, or trazodone
- Dextromethorphan with moclobemide or paroxetine
- Linezolid and citalopram
- Meperidine and MAOIs
DIAGNOSING SEROTONIN SYNDROME

Serotonin syndrome is diagnosed by a) a physical exam of the patient, b) taking a careful health history, and c) looking for evidence of other clinical syndromes that resemble the serotonin syndrome. There are no laboratory tests that can confirm a diagnosis of serotonin syndrome.

Physical Exam

Traditionally, serotonin syndrome had been diagnosed using Sternbach’s criteria. This is a list of 10 clinical findings such as agitation, diarrhea, myoclonus, etc., and it was thought that if three or more of these were present, a diagnosis of serotonin syndrome could be made. Sternbach’s criteria have been criticized as being inaccurate and non-specific and they should not be used. The Hunter Serotonin Toxicity Criteria are more sensitive and specific.

Ingestion of a serotonergic drug within 5 weeks or overdose of a serotonergic drug?

Spontaneous clonus? Yes? Serotonin syndrome

No

Inducible clonus ocular clonus? Yes? Agitation,
diaphoresis,

No

Tremor? Yes? Hyperreflexia? Serotonin syndrome

No

Not Serotonin Syndrome

Health History

Taking an accurate health history is very important. It is very important to determine what medications the patient is taking and has been taking. Remember: some drugs can cause serotonin syndrome even when the patient has not been taking them for many weeks. Ask if doses have recently been changed, ask if the patient has been taking any dietary or herbal supplements.

Clinical Conditions That Resemble Serotonin Syndrome

Make sure that client does not have a metabolic or infectious condition that could cause his/her signs and symptoms. The clinical conditions that can resemble serotonin syndrome include.
• **Neuroleptic malignant syndrome:** Neuroleptic malignant syndrome (NMS) is an idiosyncratic drug reaction to treatment with, or withdrawal from drugs such as levodopa and antipsychotics that act as dopamine antagonists. Important differences between serotonin syndrome and NMS are: a) the causative agents, b) the slow development over several days of signs and symptoms, c) normal, not mydriatic pupils, d) normal bowel sounds, e) very rigid, “lead-pipe like” muscle tone, e) bradyreflexia, and f) it is not caused by overdose.

• **Anticholinergic syndrome:** The anticholinergic toxidrome is caused by overdose of drugs such as antihistamines that act as antagonists of acetylcholine at peripheral and central muscarinic receptors. Important differences between serotonin syndrome and the anticholinergic syndrome are: a) the causative agent, b) temperature is usually 38.8°C or less, c) dry mucous membranes, d) hot, dry skin, e) decreased or absent bowel sounds, and f) normal muscular tone and reflexes, and g) urinary retention.

• **Malignant hyperthermia:** Malignant hyperthermia is an idiosyncratic response to inhalational anesthesia. Important differences between the serotonin syndrome and malignant hyperthermia are: a) causative agent, b) temperature can be as high as 46°C, and c) hyporeflexia.

Other clinical conditions that could be mistaken for serotonin syndrome include the sympathomimetic syndrome (caused by a large dose or an overdose of sympathomimetic drugs), acute baclofen withdrawal, encephalitis, meningitis, non-convulsive seizures, metabolite-mediated opioid toxicity caused by high opioid doses or opioids in patients with renal failure, sepsis, thyroid storm, dystonic reactions, and tetanus.28,29,30

There are many clinical conditions that can be mistaken or serotonin syndrome, and trying to remember them all and their distinguishing features is difficult. However, by far the most commonly occurring are NMS and the anticholinergic syndrome. To distinguish between NMS and the anticholinergic syndrome and serotonin syndrome, pay special attention to:

- The drug ingested.
- Body temperature.
- Onset and development of the signs and symptoms.
- Bowel sounds.
- Presence or absence of hyperreflexia.
- Presence or absence of clonus.

**SEROTONIN DISCONTINUATION SYNDROME**

When checking for the presence of the serotonin syndrome, it is important to know what medications the patient has been taking; this was previously discussed. However, if a symptomatic patient had been taking an SSRI or another drug that affects the serotonergic system, this can confuse the issue of assessment because if these drugs are
not tapered correctly, the patient may develop serotonin discontinuation syndrome. The syndrome occurs in approximately 20%-25% of all patients who stop taking a serotonergic drug. The signs and symptoms of serotonin discontinuation syndrome usually start within several days of decreasing the dose or discontinuing the drug and they last approximately two weeks. Signs and symptoms include dizziness, unsteady gait, manic behavior, mood changes, and mood instability, diarrhea, myalgia, and others.

TREATMENT

Most cases of serotonin syndrome will improve dramatically or resolve with 24 hours but if the patient has taken a drug with a long half-life, a drug with pharmacologically active metabolites, or an extended release form of a drug, the signs and symptoms can last for weeks. Mild cases can be observed for six hours, but moderate and severe cases should be admitted, and patients who have ingested an extended release preparation should be admitted or observed for longer than six hours.

Death from serotonin syndrome is unusual, but severe cases do occur and the condition of these patients deteriorates very quickly. The use of the drugs suspected of causing the serotonin syndrome must be immediately stopped: in mild cases this may be enough to allow the patient to recover. In order to avoid serious harm and to successfully treat serotonin syndrome, it is critical to be able to a) quickly identify serotonin syndrome, and b) aggressively provide supportive care. The basics of care for a patient with serotonin syndrome include:

**Basic Care**

- Aggressive cooling: Aggressive cooling should be used for patients who are hyperthermic. Acetaminophen will not help because hyperthermia in serotonin syndrome is caused by excessive muscular activity, not by a change in central thermoregulation.

- Intubation and neuromuscular paralysis: This will treat the hyperthermia and also treat the basic cause of hyperthermia. Do not use the neuromuscular blocker succinylcholine during the intubation process. Use a nondepolarizing drug such as vecuronium. Patients who are hyperthermic often have rhabdomyolysis. Rhabdomyolysis increases serum potassium and increases the risk of arrhythmias, and succinylcholine can cause hyperkalemia.

- Benzodiazepines: Benzodiazepines decrease muscular rigidity and their use alone may be all that is needed for a mild to moderate case of serotonin syndrome.

- Direct-acting sympathomimetics: If the patient is hypotensive, use the direct-acting sympathomimetics epinephrine, norepinephrine, or phenylephrine. Dopamine acts indirectly. It must be metabolized to epinephrine and norepinephrine before it can work and in cases of serotonin syndrome the metabolizing enzyme (monoamine oxidase) may be inhibited.
• Nitroprusside: Nitroprusside is a good drug to use for treating hypertension caused by serotonin syndrome because its effects are very short-acting: the half-life of nitroprusside is two to three minutes. The autonomic instability in severe cases of serotonin syndrome means that blood pressure can be very unstable and unpredictable so using a drug that can tightly controlled is a big advantage.

• Fluids: Hydration is obviously a very important treatment for serotonin syndrome.

• Monitor for complications: The complications of serotonin syndrome are coma, DIC, metabolic acidosis, renal failure, and rhabomyolysis.

**Special Therapies**

There is no antidote for serotonin syndrome that has been proven to be effective and safe. Bromocriptine, chlorpromazine, cyproheptadine, dantrolene, olanzapine, and propranolol have been used. However, the evidence that supports or does not support use of these drugs can be categorized as Level II (case control studies, epidemiologic studies, etc.) There are no controlled studies that compare these drugs or truly determine how effective they are. There are case reports that suggest that chlorpromazine, cyproheptadine, and olanzapine helped control and shorten the duration of the signs and symptoms of serotonin syndrome, but it may simply be that these cases represented a natural process of recovery and the drugs had no effect.

• Chlorpromazine: Chlorpromazine (commonly known as Thorazine®) is an antipsychotic. The therapeutic effect of chlorpromazine is due to its action as a centrally acting dopamine antagonist. But chlorpromazine also blocks serotonin binding to 5-HT$_{2A}$ receptors and there are several case reports of chlorpromazine being an effective drug for treating serotonin syndrome. Chlorpromazine can cause hypotension and it may aggravate hyperthermia, so it should be used cautiously when treating serotonin syndrome. Chlorpromazine is contraindicated for treating NMS because it is a dopamine antagonist.

• Cyproheptadine: Cyproheptadine (Periactin®) is an antihistamine that acts as a 5-HT$_{2A}$ antagonist and it has been successfully used to treat cases of serotonin syndrome. The drug is given orally. The dose is 12 mg followed by 2 mg doses every two hours if the symptoms persist. The maintenance dose is 8 mg every six hours.

• Olanzapine: Olanzapine (Zyprexa®) is an atypical antipsychotic. One of its actions is 5-HT$_2$ receptor antagonism, and sublingual olanzapine has been used successfully to treat cases of serotonin syndrome. Although most of the patients in these studies had a very quick and complete resolution of the signs and symptoms, the clinical experience with using olanzapine to treat these cases so far consists of eight patients.
• Bromocriptine: Bromocriptine has been used to treat serotonin syndrome. However, it has serotonergic effects and its use has caused one fatality.\textsuperscript{43,44} The drug should \textit{not} be used to treat serotonin syndrome.

• Dantrolene: Dantrolene is a skeletal muscle relaxant that is used to treat malignant hyperthermia. It should \textit{not} be used to treat serotonin syndrome. There is no clinical evidence that it is effective, animal studies showed that it not effective, it may actually cause serotonin syndrome, and its use in a suspected case of serotonin syndrome was associated with a fatality.\textsuperscript{45,46,47}

• Propranolol: Propranolol acts as a 5-HT\textsubscript{1A} antagonist but it can cause hypotension. It decreases heart rate, making it difficult to assess the patient’s condition. It should \textit{not} be used to treat serotonin syndrome.
SUMMARY

- Serotonin syndrome is defined as a group of signs and symptoms caused by excessive stimulation of serotonin receptors. Serotonin syndrome is caused by therapeutic doses, overdoses, or drug interactions between medications that directly or indirectly affect the serotonergic system.
- Serotonin syndrome is caused by direct stimulation of serotonin receptors, decreased breakdown of serotonin, increased inhibition of serotonin reuptake, an increase in serotonin precursors, or an excessive release of serotonin.
- Medications that can cause serotonin syndrome include SSRIs, MAOIs, illicit drugs such as cocaine and amphetamines, atypical antipsychotics, analgesics such as fentanyl, meperidine, and tramadol, and dextromethorphan.
- The incidence and severity of serotonin syndrome are greatest when multiple drugs have been ingested. A particularly dangerous drug combination is the MAOIs combined with SSRIs, dextromethorphan, ecstasy, or meperidine.
- The syndrome is characterized by autonomic, cognitive, and neuromuscular derangements. Agitation, tachycardia, hypertension, hyperthermia, muscle rigidity, clonus, hyperreflexia, diaphoresis, diarrhea are commonly seen. Signs and symptoms usually start within six to eight hours and typically last 24 hours.
- Clonus, inducible, spontaneous or ocular, is the most reliable clinical finding. Hyperreflexia is also diagnostic.
- Other clinical conditions resemble serotonin syndrome. To distinguish serotonin syndrome, determine what drug was ingested, determine when the signs and symptom started, look for clonus and hyperreflexia, and check body temperature and bowel sounds. The findings will be specific for serotonin syndrome.
- A severe case of serotonin syndrome is a medical emergency. The patient’s condition can deteriorate rapidly and dramatically.
- The complications of serotonin syndrome are coma, DIC, metabolic acidosis, renal failure, and rhabdomyolysis.
- The best treatment is supportive care. Consider using activated charcoal if the patient arrives within an hour of the ingestion. Aggressive cooling, neuromuscular paralysis and intubation, benzodiazepines, and IV hydration are the most important and effective therapies.
- Use epinephrine, norepinephrine, or phenylephrine to treat hypertension. Use nitroprusside to control hypertension.
- Chlorpromazine, cyproheptadine, and olanzapine may be effective, but there is no proof that these drugs are useful therapies for treating serotonin syndrome.
- Bromocriptine, dantrolene, propranolol, and succinylcholine should not be used to treat serotonin syndrome.
REFERENCES

32. Shelton RC. The nature of the discontinuation syndrome associated with antidepressant