Editor's key points

- Serotonin syndrome, more aptly named *serotonin toxicity,* is a potentially fatal drug-induced condition caused by too much serotonin in synapses in the brain. Patients present with a combination of neuromuscular, autonomic, and mental status symptoms.
- Most cases involve 2 drugs that increase serotonin in different ways or an overdose of 1 serotonin drug. Monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors are the most common culprits. The use of 2 high-dose serotonin drugs at the same time should be avoided.
- Prevention of serotonin toxicity is key. Education of prescribers and patients is important to avoid and detect serotonin toxicity.

Demystifying serotonin syndrome (or *serotonin toxicity*)

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Abstract

Objective To review the symptoms of serotonin toxicity (commonly referred to as *serotonin syndrome*) and the causative drugs and their mechanisms of action, and to equip primary care providers with practical strategies to prevent and identify serotonin toxicity.

Quality of evidence PubMed and Google Scholar were searched for relevant articles on serotonin toxicity, the causes, and the differential diagnosis using search terms related to serotonin toxicity (*serotonin syndrome, serotonin toxicity, serotonin overdose*), causes (individual names of drug classes, individual drug names), and diagnosis (*differential diagnosis, neuroleptic malignant syndrome, anticholinergic toxicity, discontinuation syndrome, malignant hyperthermia, serotonin symptoms*). Experts in psychiatric medicine, psychiatric pharmacy, clinical pharmacology, and medical toxicology were consulted. Evidence is level II and III.

Main message Serotonin toxicity is a drug-induced condition caused by too much serotonin in synapses in the brain. Cases requiring hospitalization are rare, and mild cases caused by serotonin-mediated side effects are unlikely to be fatal. Patients present with a combination of neuromuscular, autonomic, and mental status symptoms. Serotonin-elevating drugs include monoamine oxidase inhibitors, serotonin reuptake inhibitors, and serotonin releasers. Most cases involve 2 drugs that increase serotonin in different ways; the most concerning combination is a monoamine oxidase inhibitor with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor.

Conclusion Family physicians play a key role in identifying and preventing serotonin syndrome by teaching patients to recognize symptoms and monitoring patients throughout therapy.

Serotonin toxicity (commonly referred to as *serotonin syndrome*) is a potentially life-threatening drug-induced condition caused by too much serotonin in the synapses of the brain.[1-3] Patients present with a combination of neuromuscular, autonomic, and mental status symptoms. Most cases involve 2 drugs that increase serotonin in different ways or an overdose of 1 serotonin-elevating drug.[1-3] While the most common culprits are monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs), the list of potential contributors is long and includes often-overlooked substances such as herbals and illicit drugs.[1-3]

Cases of serotonin syndrome resulting in hospitalization or death are rare. Most cases do not require medication intervention, but can be managed by stopping the drug or decreasing the dose. Mild toxicity appears to be rare but is likely under-reported, unrecognized, or confused with other syndromes.[2] The lack of agreed-upon diagnostic criteria, inconsistencies in clinical symptoms, and clinicians who are not trained to identify it mean that case reports are published even when patients do not experience serotonin toxicity, which complicates the literature.[1,2,4] With the ever increasing use of antidepressants

for mood and other conditions such as anxiety, pain, sleep, and menopausal hot flashes, clarity is needed to help health care professionals prevent, identify, and manage serotonin toxicity.[5,6]

The objective of this update is to review the symptoms of serotonin toxicity and the causative drugs and their mechanisms of action, and to equip primary care providers with practical strategies to prevent and identify serotonin toxicity.

Quality of evidence

We searched PubMed and Google Scholar for relevant articles on serotonin toxicity, the causes, and the differential diagnoses. A selection of search terms related to serotonin toxicity (*serotonin syndrome, serotonin toxicity, serotonin overdose*), causes (individual names of drug classes, individual drug names), and diagnosis (*differential diagnosis, neuroleptic malignant syndrome, anticholinergic toxicity, discontinuation syndrome, malignant hyperthermia, serotonin symptoms*) was used. We consulted with experts in psychiatric medicine, psychiatric pharmacy, clinical pharmacology, and medical toxicology. Recommendations were based on the criteria outlined by *Canadian Family Physician,* where level I evidence includes at least 1 properly conducted randomized controlled trial, systematic review, or meta-analysis; level II includes other comparison trials and non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than 1 study; and level III includes expert opinion or consensus statements. Recommendations are based on level II and III evidence.

Main message

We developed the infographic in **Figure 1** based on the best available evidence (**Table 1**).[1-4,7-12] The infographic and an English-only patient handout are available at **CFPlus**.*

Assess the patient. The best available information on the symptoms of serotonin toxicity is from a retrospective analysis of prospective data collected by the Hunter Area Toxicology Service in Australia (level II evidence).[1] Patients present with a triad of neuromuscular, autonomic, and mental status changes that start within hours to 1 day of increasing a dose or adding a serotonergic drug (**Table 2**).[1,2,12,13] If untreated, serotonin toxicity escalates quickly and can be fatal.[2] Because toxicity presents on a spectrum rather than as a defined set of signs and symptoms (ie, a syndrome), *serotonin toxicity* is more accurate than *serotonin syndrome*.[1]

Mild symptoms, which include nervousness, insomnia, nausea, diarrhea, tremor, and dilated pupils, can progress to moderate symptoms such as hyperreflexia (increased reflexes), sweating, agitation, restlessness, clonus (rhythmic muscle spasms), and ocular clonus (side-to-side eye movements). Patients with severe symptoms should be referred to the hospital immediately; severe symptoms include temperature greater than 38.5°C (101.3°F), confusion, delirium, sustained clonus or rigidity, and rhabdomyolysis.

Cases of serotonin toxicity that require hospitalization are straightforward to diagnose, as severe symptoms (such as bilateral, symmetric clonus in the legs more than in the arms) are not common in other conditions. The combination of nonspecific autonomic manifestations, a range of possible signs and symptoms, and a lack of definitive laboratory tests makes milder cases less straightforward to diagnose, although such cases are unlikely to be fatal.

Assess the drug. Because serotonin toxicity is a drug-induced condition, an accurate drug history is necessary for diagnosis, especially when a patient has recently used an MAOI or another serotonin-elevating drug. Serotonin toxicity most often happens when 2 or more serotonin-elevating drugs are used together, especially if they increase serotonin in different ways.[1,2,12,13] An MAOI with an SSRI, an SNRI, or another MAOI is the riskiest combination, but other combinations can also result in toxicity. Some experts report that therapeutic doses of a single drug can cause toxicity, but the risk is low, as it is a dose-related drug toxicity.[1,2,14]

Serotonin is formed from dietary tryptophan and stored in the presynaptic terminal.[15] It is released into the synapse where it acts on the presynaptic and postsynaptic terminals, and is taken back up into the presynaptic terminal to be degraded by monoamine oxidase (**Figure 2**).[15] Drugs that increase synaptic concentrations of serotonin include MAOIs, serotonin reuptake inhibitors, and serotonin releasers.[4]

Monoamine oxidase inhibitors: Monoamine oxidase inhibitors slow the breakdown of serotonin by blocking monoamine oxidase.[15] This class of drugs is most concerning, specifically MAOIs that bind irreversibly and non-selectively to both types of monoamine oxidase (MAO-A and MAO-B); MAO-A inhibitors are more likely to cause toxicity because MAO-A plays a larger role in the breakdown of serotonin.[1,15] Combination of 2 MAOIs or an MAOI and another serotonergic drug carries the greatest risk of serotonin toxicity. Although not common anymore, the most recognizable MAOIs are those used to treat depression, such as phenelzine, isocarboxazid, tranylcypromine, and moclobemide. Other agents less frequently recognized as MAOIs include the antibiotics isoniazid (irreversible, non-selective) and linezolid (reversible, non-selective).[3,16]

*The **infographic** (**Figure 1**) and an English-only **patient handout** are available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Figure 1

Target Serotonin Syndrome

def. Toxicity caused by excessive serotonin levels that results from a drug overdose or interaction

Assess the patient

Symptoms start within hours to 1 day of increasing a dose or adding a drug

Mild	Moderate	Severe
Nervousness	Hyperreflexia	Fever >38.5°C/101.3°F
Insomnia	Sweating	Confusion/delirium
Nausea/diarrhea	Agitation/restlessness	Sustained clonus/rigidity
Tremor	Inducible clonus	Rhabdomyolysis
Big pupils	Side-to-side eye movements	Death

Assess all drugs

Most cases involve 2 drugs that increase serotonin in different ways – full list on back

Prescription drugs

OTC and natural drugs

Illicit drugs

Rule out

Serotonin syndrome can look like other things; diagnosis requires an accurate drug history

Similar-looking conditions:
- Antidepressant Discontinuation
- Anticholinergic Toxicity
- Malignant Hyperthermia
- Neuroleptic Malignant Syndrome
- Meningitis/Encephalitis
- Drug Overdose
- Alcohol/Benzo Withdrawal

Remind all patients: Non-toxic increases in serotonin can cause anxiety, restlessness and irritability for 1-2 weeks

If you suspect serotonin syndrome

Don't wait, take action – it progresses rapidly

Stop the drug(s)

Refer patient to hospital

once symptoms are gone

Try other drugs or restart low doses slowly

Prevent serotonin syndrome

Stay alert – most cases can be prevented

- ✓ Use lowest effective dose
- ✓ Ask about illicit drug use
- ✓ Check drug monographs for tapering and wash-out periods
- ✓ Follow up 1-2 days after upping a dose or starting a new drug
- ✓ Reassess the need for a serotonin drug yearly
- ✓ Teach patients to recognize serotonin syndrome

AVOID: Group A with Group A or Group A with Group B

CAUTION: TWO or more Group B drugs especially when ONE is used at a high dose

MONITOR: If a patient uses a Group B drug and a second Group B drug is added, start low, increase the dose cautiously, and watch for symptoms for 24-48h after every change

Group A

Non-selective and irreversible MAOi A and B
Isocarboxazid
Isoniazid
Phenelzine
Tranylcypromine

Non-selective and reversible MAOi A and B
Linezolid

Selective and irreversible MAOi B
Selegiline (non-selective at higher doses)
Rasagiline

Selective and reversible MAOi A
Moclobemide
Methylene blue (non-selective at higher doses)

Group B

Antidepressants
Selective Serotonin Reuptake Inhibitors (SSRI): Paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, fluoxetine

Serotonin Norepinephrine Inhibitors (SNRI): Venlafaxine, desvenlafaxine, duloxetine

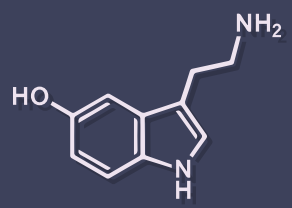
Tricyclic Antidepressants: Clomipramine, imipramine

Opioids and other pain medications
Tramadol, meperidine, methadone, fentanyl (unlikely with morphine, codeine, oxycodone, buprenorphine)

Cough, cold and allergy
Dextromethorphan ("DM"), chlorpheniramine

Natural health products
St. John's wort, L-tryptophan, diet pills

Illicit drugs
Ecstasy (MDMA), amphetamine, cocaine



Commonly listed but unlikely to cause serotonin syndrome
Triptans (e.g., sumatriptan)

Antidepressants: amitriptyline, mirtazapine, trazodone

Antiemetics: 5HT3 receptor antagonists (e.g., ondansetron), metoclopramide

Buspirone, lithium

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Table 1. Evidence supporting the key considerations for practice

CLINICAL CONSIDERATIONS	EVIDENCE RATING	REFERENCES
The best available evidence for the clinical presentation of toxicity is from the Hunter Area Toxicology Service in Australia	Level II*	1
Serotonin toxicity most often happens when 2 serotonin-elevating drugs are used together. The use of an MAOI with an SSRI, an SNRI, or another MAOI is the most concerning drug combination	Level III†	1,3
Some drugs thought to cause serotonin toxicity do not (eg, triptans, ondansetron)	Level III†	1,4,7-11
Prevention of serotonin toxicity through good prescribing practices and monitoring is important	Level III†	2,12

MAOI—monoamine oxidase inhibitor, SNRI—serotonin-norepinephrine reuptake inhibitor, SSRI—selective serotonin reuptake inhibitor.
*Level II: Comparison trials other than randomized controlled trials, systematic reviews, or meta-analyses; non-randomized, cohort, case-control, or epidemiologic studies; and preferably more than 1 study.
†Level III: Expert opinion or consensus statements.

Table 2. Signs and symptoms of serotonin toxicity

CATEGORY	SIGNS AND SYMPTOMS
Neuromuscular	• Tremor • Hyperreflexia (increased reflexes)* • Clonus (rhythmic muscle spasms that can be spontaneous, inducible, or ocular)*
Autonomic	• Mydriasis (dilated pupils) • Diaphoresis (sweating) • Tachycardia (increased heart rate) • Tachypnea (increased breathing rate)
Mental status	• Agitation • Excitement • Restlessness • Confusion • Delirium

Data from Dunkley et al,[1] Boyer and Shannon,[2] Ables and Nagubilli,[12] and Isbister et al.[13]
*Hyperreflexia and clonus are often worse in the legs than in the arms.

Serotonin reuptake inhibitors: Serotonin reuptake inhibitors prevent the transport of serotonin from the synapse back into the presynaptic terminal to be degraded, keeping it at the site of action.[15] Drugs that prevent the reuptake of serotonin include SNRIs, SSRIs, tramadol, certain tricyclic antidepressants (TCAs), certain opioids, dextromethorphan, the antihistamines chlorpheniramine and brompheniramine, and herbals such as St John's wort.[7,13]

After MAOIs, SNRIs and SSRIs are the most concerning serotonergic drugs, as their main mechanism is to increase serotonin.[1,2] The SNRI venlafaxine causes toxicity more often than SSRIs do, possibly because it has another serotonergic mechanism other than a reuptake inhibitor.[3]

Certain synthetic opioids such as tramadol, methadone, meperidine, fentanyl, and dextromethorphan are weak serotonin reuptake inhibitors and can cause toxicity, but opioids with a structure similar to morphine are not reuptake inhibitors, meaning that morphine, codeine, oxycodone, and buprenorphine do not cause toxicity.[7] Because of the risk of dextromethorphan and the antihistamines chlorpheniramine and brompheniramine, remind patients who take serotonin drugs to talk to a physician or pharmacist before taking a cough and cold medication.

Tricyclic antidepressants are also serotonin reuptake inhibitors, with clomipramine and imipramine being the most potent and likely the only TCAs to be involved in serotonin toxicity; other TCAs such as amitriptyline are weaker inhibitors and are thus unlikely to cause toxicity.[3,7]

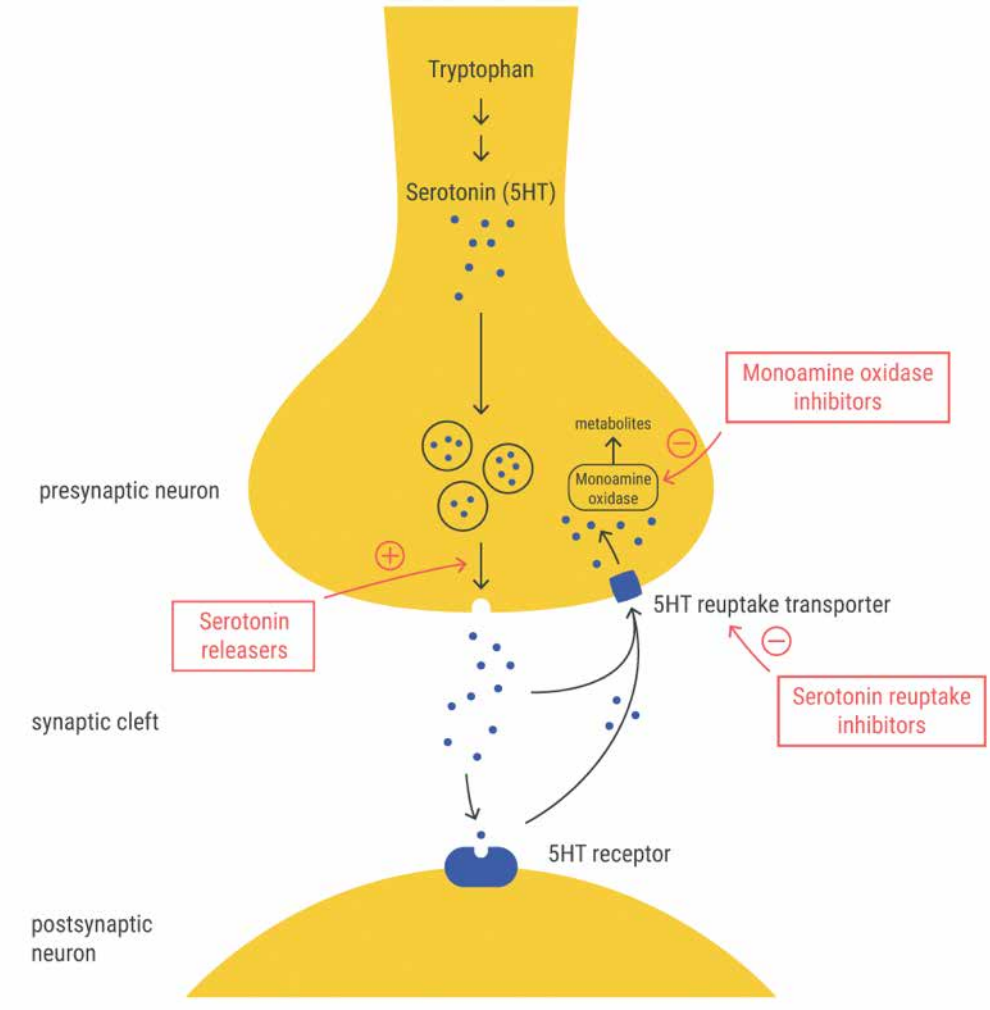
Serotonin releasers: Serotonin releasers cause more serotonin to be released from the presynaptic terminal into the synapse. Serotonin releasers include amphetamine, but not methylphenidate, and the illicit drug ecstasy (3,4-methylenedioxymethamphetamine).[3,7,12]

L-Tryptophan: A drug that does not fit into any of these 3 categories is L-tryptophan, which can be used for various mood disorders.[3] L-Tryptophan can increase serotonin levels because serotonin is made from tryptophan; however, the risk is low.

Controversies. Experts disagree on the list of implicated drugs. The lists of serotonin drugs published by the US Food and Drug Administration (FDA) and Health Canada include drugs that are unlikely to cause toxicity based on their mechanisms of action—either they work on different receptors than the ones involved in serotonin toxicity or they block rather than activate the receptors.[8,9] Examples include triptans (used for migraines), antiemetics such as ondansetron, olanzapine, mirtazapine, cyclobenzaprine, bupropion, trazodone, buspirone, lithium, and amitriptyline.[1,4,7-11] That these are unlikely to cause serotonin toxicity is supported by the lack of case reports implicating these drugs, through case series, by reviewing the evidence for case reports, and by understanding the pharmacology of these drugs.

In 2016, an FDA warning[8] stated that opioids interact with migraine medications (triptans), a warning partly based on poor-quality case reports that did not use validated criteria (eg, the Hunter Serotonin Toxicity Criteria) to diagnose serotonin toxcity.[4] Similarly, the FDA, Health Canada, and the World Health Organization issued warnings about 5-HT_3 antagonists (eg, antiemetics such as ondansetron and granisetron) despite a lack of high-quality evidence of this drug class causing toxicity.[8-10,17,18]

Figure 2. Serotonin physiology: *Serotonin is formed in the presynaptic terminal from tryptophan. Once packaged into vesicles, it is released into the synaptic cleft where it can bind to serotonin receptors on the postsynaptic neuron to exert its action. Serotonin is transported through a transporter to the presynaptic terminal where it is broken down by monoamine oxidase.[15] The 3 classes of drugs that increase serotonin in synapses are highlighted in red.*



5HT—5-hydroxytryptamine.

Based on these controversial data, there is a risk that inaccurate information has been incorporated into drug interaction–checking software used in pharmacies and physicians' offices. In Canada, RxVigilance and First Databank maintain updated databases that are used in electronic decision support tools for health care providers, such as the drug information needed for an interaction checker.[19,20] Although these companies recognize that the FDA and Health Canada have published information based on weak evidence, their interaction checkers still flag combinations of drugs that are unlikely to cause serotonin toxicity. As a result, prescribers might avoid prescribing a medication that might otherwise prove to be useful for a patient.

What to rule out. Other conditions look similar to serotonin toxicity.

Antidepressant discontinuation: Symptoms start within days of stopping or tapering a drug and are usually self-limited, lasting 1 week.[21] Symptoms include flu-like symptoms, nausea, imbalance, sensory disturbances, hyperarousal, and changes in mood, sleep, and appetite.[21]

Anticholinergic toxicity: Anticholinergic toxicity results from an overdose of anticholinergic medications. Symptoms include dry mouth, dry and flushed skin, urinary retention, decreased bowel sounds, dilated pupils, blurry vision, fever, agitation, delirium, and hallucinations.[22] A distinguishing feature is that muscle tone and reflexes are normal in anticholinergic toxicity.[22]

Malignant hyperthermia: Malignant hyperthermia is triggered by specific volatile anesthetics during or shortly after surgery. Telltale signs include hyperthermia (>39°C), tachycardia, tachypnea, acidosis, muscle rigidity, and rhabdomyolysis.[23] Family history is a factor.

Neuroleptic malignant syndrome: Unlike serotonin toxicity, neuroleptic malignant syndrome is not dose-related but is an idiosyncratic reaction to neuroleptic drugs. Onset is slower, taking place over days, and it is differentiated from serotonin toxicity by the presence of bradykinesia and lead-pipe or cogwheel rigidity.[23]

Other conditions: Other similar-looking conditions include meningitis or encephalitis, drug overdose, and alcohol or benzodiazepine withdrawal.[12,13] Notably, it is normal for nontoxic increases in serotonin to cause anxiety, restlessness, and irritability for 1 to 2 weeks after starting a drug or increasing a dose.[24]

If you suspect serotonin toxicity. If you suspect serotonin toxicity, stop the serotonin drugs. Refer patients with severe symptoms or patients who have ingested an MAOI and a serotonin reuptake inhibitor to the hospital, as their condition can worsen quickly.[13] Teach patients to recognize serotonin toxicity and tell them to call their primary practitioner if they suspect toxicity. Once signs and symptoms have resolved, try other drugs or restart low doses slowly, and rule out other contributing drugs such as over-the-counter medications or illicit drugs. For most patients who experience serotonin-mediated side effects, these changes to their medications will manage symptoms and prevent toxicity, and a hospital referral will not be required.

Preventing serotonin toxicity. Serotonin toxicity remains a confusing area for practitioners and can be a scary, potentially fatal experience for patients. As most cases are avoidable, learning to identify and prevent it is key.

Before prescribing a serotonin drug and at check-ups: Ask patients about over-the-counter drug, herbal, and illicit drug use. Remind patients to check with their prescribers or pharmacists before starting a new drug.

When prescribing: Make sure you use the lowest effective dose and avoid the use of 2 high-dose serotonin drugs at the same time.

If stopping or switching drugs: Check drug monographs for tapering and wash-out periods, and stress careful adherence to the crossover schedule.

After prescribing: Follow up with patients a few days after increasing the dose or starting a new drug, and check yearly if the patient still needs to be taking the drug.

Conclusion

Serotonin toxicity is an important topic for primary care providers. Education of both practitioners and patients is the only way to prevent serotonin toxicity.

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Contributors

Dr Grindrod conceived of the project. All authors were involved in drafting the infographic and the manuscript and approving the final draft.

Competing interests

None declared

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