

The scoop on serotonin syndrome

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Introduction

When filling prescriptions, drug interaction alerts about serotonin syndrome are common but often misunderstood, leaving pharmacists unsure of how to proceed. This uncertainty likely results from confusion about the drugs that cause serotonin toxicity and a lack of education about the underlying physiological and pharmacological mechanisms.^{1,2} Here is what pharmacists need to know to prevent and identify serotonin syndrome.

Clarifying serotonin toxicity

Although commonly called *serotonin syndrome*, *serotonin toxicity* is a more accurate term, since toxicity presents on a spectrum rather than as a defined set of symptoms (i.e., a syndrome).^{1,3} Serotonin toxicity is a drug-induced condition caused by too much serotonin in synapses in the brain.¹⁻³ It begins within hours to 1 day of starting a new serotonin-elevating drug or increasing a dose of a serotonin-elevating agent and can be quickly fatal if untreated. Therapeutic doses of a single drug are unlikely to cause toxicity—serotonin toxicity is dose related and most often happens when 2 drugs that increase serotonin in the brain are used together, especially if they increase serotonin in different ways.^{1,3} Most cases do not require active medical intervention but can be managed by stopping the drug and reducing the dose. Cases that result in hospitalization are rare and occur almost exclusively when a monoamine oxidase inhibitor (MAOI) is used with a selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI) or another MAOI.³

Assess the patient

Patients who have serotonin toxicity are likely to present with 1 or more symptoms of a triad of neuromuscular, autonomic and mental status

TABLE 1 Signs and symptoms of serotonin toxicity^{1,2,6,7}

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

*Hyperreflexia and clonus are often worse in the legs than the arms.

changes (Table 1).¹⁻⁵ Mild symptoms include nervousness, insomnia, nausea, diarrhea, tremor and dilated pupils. These can progress to moderate symptoms such as hyperreflexia (increased reflexes), sweating, agitation, clonus (rhythmic muscle spasms) and ocular clonus (side-to-side eye movements). Severe symptoms include temperature greater than 38.5°C (101.3°F), sustained clonus or rigidity, confusion, delirium and rhabdomyolysis. Patients with severe symptoms should be referred to the hospital immediately, as toxicity escalates quickly and is fatal.

Serotonin toxicity that warrants hospitalization is straightforward to diagnose: classic symptoms such as bilateral, symmetric clonus in the legs more than in the arms are not seen in other

TABLE 2 Drugs that increase serotonin classified by mechanism of action

Monoamine oxidase inhibitors
Isocarboxazid
Isoniazid
Phenelzine
Tranylcypromine
Linezolid
Selegiline
Rasagiline
Moclobemide
Methylene blue
Metaxalone
Serotonin reuptake inhibitors
Selective serotonin reuptake inhibitors: citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, fluoxetine
Serotonin norepinephrine reuptake inhibitors: venlafaxine, desvenlafaxine, duloxetine
Tricyclic antidepressants: clomipramine, imipramine
Narcotics and pain medications: tramadol, meperidine, methadone, fentanyl
Dextromethorphan
Chlorpheniramine, brompheniramine
St. John's wort
Serotonin releasers
Ecstasy (MDMA)
Amphetamine
Serotonin precursor
L-tryptophan

conditions. Other key symptoms are clonus, hyperreflexia, tremor and agitation.¹⁻³ However, milder serotonin elevations result in a range of symptoms that, combined with nonspecific autonomic symptoms and a lack of definitive laboratory tests, makes diagnosis difficult.¹

Drugs that cause serotonin toxicity

In the brain, serotonin is formed from tryptophan, stored in the presynaptic terminal of a neuron and released into the synapse where it acts on serotonin receptors on the postsynaptic terminal. It is degraded by monoamine oxidase in the presynaptic terminal (see practice tool on next page).⁶ Following this pathway, there are 3 types of drugs that can increase serotonin in the brain.³ Common serotonin-elevating drugs are classified by mechanism of action in Table 2. Since serotonin toxicity is drug induced and dose related, an accurate drug history is necessary for diagnosis.

MAOis block the MAO enzyme that breaks down serotonin.⁶ These serotonergic drugs—particularly those that bind to the MAO enzyme irreversibly and those that nonselectively inhibit both the MAO type A and type B enzymes—are most likely to cause toxicity.^{1,6} MAO-A preferentially breaks down serotonin, making MAOI-A drugs more toxic than MAOI-B. Any combination of an MAOI with another serotonin drug is risky, but never combine an MAOI with another MAOI, an SSRI or an SNRI.³ Commonly recognized MAOis are antidepressants phenelzine, isocarboxazid and moclobemide, but watch out for uncommonly dispensed MAOis such as isoniazid (irreversible, nonselective) for tuberculosis and the antibiotic linezolid (reversible, nonselective).⁶⁻⁸ Metaxalone, a weak MAOI, is a skeletal muscle relaxant found in the United States that can cause serotonin toxicity when used with a serotonin reuptake inhibitor.⁹

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

Nervousness
Insomnia
Nausea/diarrhea
Tremor
Big pupils

Moderate

Hyperreflexia
Sweating
Agitation/restlessness
Inducible clonus
Side-to-side eye movements

Severe

Fever >38.5°C/101.3°F
Confusion/delirium
Sustained clonus/rigidity
Rhabdomyolysis
Death

Assess all drugs

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



Prescription drugs



OTC and natural drugs



Illicit drugs

Rule out

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

Antidepressant Discontinuation
Anticholinergic Toxicity
Malignant Hyperthermia
Neuroleptic Malignant Syndrome
Meningitis/Encephalitis
Drug Overdose
Alcohol/Benzo Withdrawal

} Similar-looking conditions

Remind all patients:

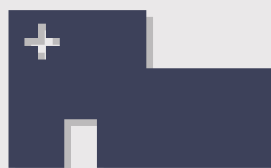
Non-toxic increases in serotonin can cause anxiety, restlessness and irritability for 1-2 weeks

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

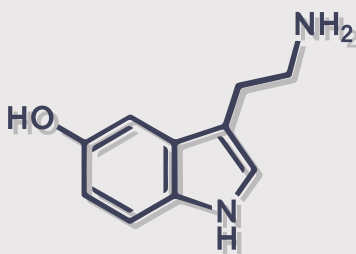
Dextromethorphan ("DM"), chlorpheniramine

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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Serotonin reuptake inhibitors stop serotonin from being transported back to the presynaptic terminal to be degraded.⁶ Aside from MAOis, SNRIs and SSRIs are the most toxic serotonin-elevating drugs.^{1,2} Interestingly, the SNRI venlafaxine is more concerning than SSRIs; experts suspect that it increases serotonin by an additional, unknown mechanism.³

Certain pain medications are reuptake inhibitors. Tramadol, methadone, meperidine and fentanyl cause serotonin toxicity, but morphine analogues such as morphine, codeine, oxycodone and buprenorphine do not, as they are weaker inhibitors of the serotonin transporter.^{3,10}

The potent tricyclic antidepressants (TCAs) cause toxicity—clomipramine and imipramine do, but amitriptyline and other TCAs do not since they are weaker inhibitors of the serotonin transporter.^{3,10} The herbal medication St. John's wort is a reuptake inhibitor, as are the antihistamines chlorpheniramine and brompheniramine.^{5,10} Since dextromethorphan is also a reuptake inhibitor, be cautious with cough and cold preparations that combine dextromethorphan and chlorpheniramine.¹⁰

Serotonin releasers cause more serotonin to be released from the presynaptic terminal into the synapse.⁶ They include the often-overlooked illicit drug ecstasy (MDMA).^{4,10} Amphetamine is also a releaser, but methylphenidate is not.³

A drug that does not fit into these 3 categories is L-tryptophan, which can be used in various mood disorders.³ L-tryptophan can increase serotonin levels because serotonin is made from tryptophan, but the risk is low.

Drugs that do not cause serotonin toxicity

Publication of serotonin toxicity case reports in which further evaluation indicates that toxicity did not actually occur has resulted in confusion in the health care field about the implicated drugs.^{11,12} Adding to the confusion, the World Health Organization, Food and Drug Administration and Health Canada have stated that 5-HT₃ antagonists (e.g., the antiemetic ondansetron) and triptans that are used for migraines can cause serotonin toxicity, although their pharmacological actions do not support the warnings.¹¹⁻¹⁷ Serotonin toxicity is caused by activation of specific serotonin receptors, but these drugs either block the serotonin receptors or work on different receptors. Triptans activate serotonin receptors that are not involved in the

mechanism of serotonin toxicity, while the 5HT₃ antagonists used as antiemetics block a type of serotonin receptor that is also not involved in toxicity.^{4,11,14} Other drugs that are incorrectly thought to cause toxicity are olanzapine, mirtazapine, cyclobenzaprine, bupropion, trazodone, buspirone and lithium.^{1,3,4,11-14}

In Canada, RxVigilance and First Databank are the main companies that house an updated database of drug information that is used in decision support tools for health care professionals, such as electronic medical records in physician offices and in pharmacy management systems. For example, the drug interaction checking software in Kroll, Ubik and Healthwatch use information from RxVigilance, and PharmaClik through McKesson uses First Databank (McKesson Canada Pharmacy Technology Solutions, phone call, August 14, 2017).^{18,19} Although RxVigilance and First Databank recognize the controversy surrounding certain implicated drugs, drug interaction checkers still flag combinations of drugs that are unlikely to cause serotonin syndrome, meaning that primary care providers and pharmacists might avoid prescribing or dispensing a medication that could be beneficial for a patient.

Rule out

The most important differential diagnoses for pharmacists are the symptoms that result from stopping or starting an antidepressant. After stopping an antidepressant, flu-like symptoms, nausea, imbalance, sensory disturbances, hyperarousal and changes in mood, sleep and appetite are common.²⁰ These symptoms start later than serotonin toxicity—within days of stopping or tapering a drug—and usually last 1 week. When starting an antidepressant or increasing a dose, anxiety, restlessness and irritability for 1 to 2 weeks is normal.²¹ Follow up with patients about side effects to differentiate normal jitteriness or discontinuation symptoms from serotonin toxicity. The time of symptom onset and the severity of symptoms in relation to the initiation or dose increase of a serotonergic drug will help differentiate these symptoms from those of serotonin toxicity.

Practice tips

Prevention of serotonin syndrome is key. Here are some points to remember:

- Teach patients and their families/caregivers to recognize serotonin toxicity (symptoms,

onset and progression) and tell them to call their prescriber or go to the hospital if they experience symptoms. If you suspect toxicity, refer them immediately since they can worsen quickly.

- After recovery, recommend different drugs or lower doses. Follow up with prescribers and patients to ensure that this happens.
- Ask patients about over-the-counter, herbal and illicit drug use. Remind patients to check with their prescriber or pharmacist before starting a new drug.
- At annual medication reviews, check if a patient still needs a serotonin drug.
- Recommend the lowest effective dose and avoid using 2 high-dose serotonin drugs at the same time.
- Encourage patients to adhere carefully to taper schedules and wash-out periods. Note that drugs with long half-lives such as the SSRI fluoxetine can precipitate toxicity for 5 weeks after administration.
- Follow up with patients a few days after starting a drug or increasing a dose. ■

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