The Perfect Storm

How to prevent, recognize and manage **serotonin syndrome**

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Serotonin syndrome, also known as serotonin storm, is a preventable, serious and potentially life-threatening adverse drug reaction that is due to excess serotonergic activity in the nervous system. This condition can affect a person of any race, sex or age.[1,2] The risk of developing serotonin syndrome varies across a life span, due to changes in enzyme levels, health status, age and/or medications. The causes are multifaceted and include therapeutic drug use, intentional or unintentional self-poisoning, and inadvertent drug-drug, drug-food or drug-herbal/natural product interactions.[A number of factors can exacerbate the severity of the serotonin storm. This paper addresses the root causes of serotonin syndrome, potential contributing factors, differential diagnosis and what pharmacists can offer to prevent or alter the vector of the storm.

Incidence

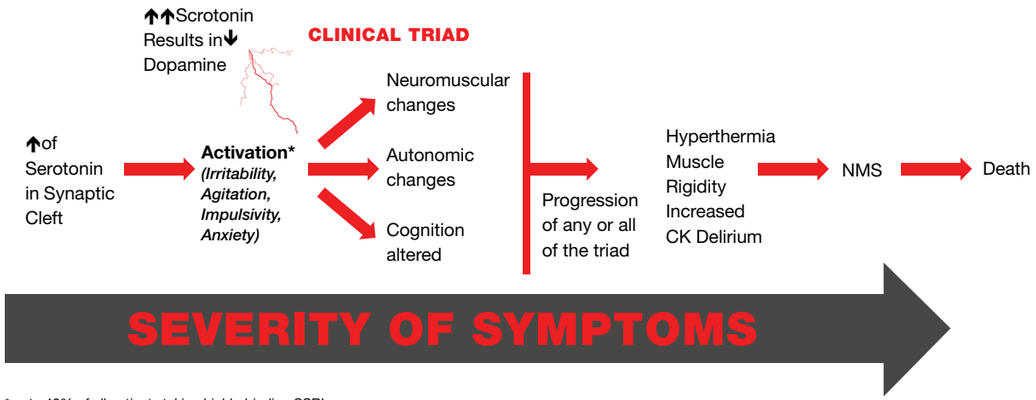
According to U.S. Toxic Exposure Network data from 2004, 8,187 significant toxic events resulted from ingestion of immediate-release selective serotonin reuptake inhibitors (SSRIs). These events included 103 deaths (i.e., a 1.26% mortality rate).[3] This number is significant given the fact that serotonin syndrome is often underdiagnosed and, as such, under-reported.[4,5] Under-reporting may occur secondary to lack of education and awareness, as it is estimated that more than 85% of physicians are unaware of the pathophysiology of serotonin syndrome, how it clinically manifests, what criteria must be met for a diagnosis, and how to appropriately manage these patients.[6,7]

Pathophysiology

Serotonin syndrome should ***not*** be thought of as an idiopathic drug reaction.[1,7] Instead, it is a predictable result of increased levels of serotonin at neuronal synapses and, therefore, an excess of agonistic effects at the serotonin receptors in the central and peripheral nervous systems.[1]

Serotonin is produced by the decarboxylation and hydroxylation of L-tryptophan. Serotonin receptors are divided into seven 5-hydroxytryptamine families (5-HT_1 to 5-HT_7), several of which have multiple subcategories (e.g., 5-HT_{1A}).[1,7] Evidence to date suggests that agonistic effects at

Figure 1
Serotonin syndrome as a spectrum of symptoms and severity[1,7,10,38-42]



*up to 40% of all patients taking highly-binding SSRIs
- Increases in norepinephrine seconary to effects of accelerated breakdown of dopamine via -hydroxylase (hypothesized)

CK = Creafine Kinase
NMS = Neuroleptic Malignant Syndrome
SSRI = Selective serotonin reuptake inhibitor

5-HT_{2A} receptors contribute substantially to the development of serotonin syndrome.[1,3,5,7] Noradrenergic central nervous system (CNS) activity and hyperactivity may play a critical role as well. Moreover, the degree to which CNS norepinephrine concentrations are increased in serotonin syndrome may correlate with the clinical outcome, such that higher norepinephrine levels may enhance the patient's autonomic symptoms. N-methyl-D-aspartate (NMDA) receptor antagonists and gamma-aminobutyric acid (GABA) may also be involved in the development of this syndrome, although their role is less clear. Dopaminergic receptors have also been implicated, given the movement disorders seen in serotonin syndrome. Pharmacokinetic, pharmacodynamic and direct interactions between serotonin and the dopamine receptor interface may also be involved.[1]

Etiology
The development of serotonin syndrome usually requires the patient to be receiving at least two medications with serotonergic properties. As a clinical rule of thumb, when three or more medications (at therapeutic doses) that have serotonergic properties are on board, or two medications (at therapeutic doses) plus one other confounder (e.g., genetic polymorphism), the incidence and risk of serotonin syndrome markedly increase.[1] Serotonin syndrome rarely occurs with only one medication possessing serotonergic properties.[1] Exceptions include patients that have overdosed, those on dialysis, or those with serotonergic increases secondary to genetic polymorphisms, metabolic

Table 1 Common medication classes with serotonergic properties[1,30,36,37]

- Antidepressants
  - ~ Serotonin selective reuptake inhibitors (SSRIs; e.g., sertraline, fluoxetine)
  - ~ Serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, duloxetine)
  - ~ Norepinephrine-dopamine reuptake inhibitors (NDRIs; e.g., bupropion)
  - ~ Norepinephrine and specific serotoninergic antidepressants (NaSSAs; e.g., mirtazapine)
  - ~ Tricyclic antidepressants (e.g., imipramine, clomipramine)
  - ~Monoamine oxidase inhibitors (e.g., phenelzine)
  - ~ Other antidepressants (e.g., trazodone)
- Antiemetics (e.g., ondansetron, granisetron, metoclopramide)
- Anti-infectives (e.g., linezolid)
- Anxiolytics (e.g., buspirone)
- Atypical antipsychotics (e.g., olanzapine, risperidone, aripiprazole)
- Herbals (e.g., Panax ginseng, tryptophan, St. John's wort)
- Illicit drugs, such as LSD (lysergic acid diethylamide), MDMA (3,4-methylenedioxymethamphetamine, also known as "ecstasy"), DMT (N,N-dimethyltryptamine)
- Intravenous dyes (e.g., methylene blue)
- Migraine agents (e.g., sumatriptan)
- Mood stabilizers
  - ~ Lithium
  - ~ Anticonvulsants (e.g., valproate, divalproex)
- OTC drugs (e.g., dextromethorphan)
- Opioids (e.g., morphine, codeine, fentanyl, methadone, meperidine, tramadol)

factors, or disease states such as multiple sclerosis (in clinical observation). Table 1 lists common medications with serotonergic properties.

Signs and Symptoms
Serotonin syndrome presents as a triad of clinical changes (Figure 1), which manifest in the cognitive, neuromuscular and autonomic domains.[1,3,5,7,8] Cognitive effects may include agitation and hypervigilance. Autonomic changes include fever, tachycardia, hypertension, shivering, diaphoresis and mydriasis. Neuromuscular effects include tremor, myoclonus, eyelid spasms (blepharospasm), hyperreflexia (predominantly in the lower extremities), muscular rigidity and hypertonicity.[1,7,9]

It is important to be aware that the full triad of changes may not always be present and that symptoms may exist on a spectrum of severity.[1,7,10] The patient may present with symptoms of activation, such as tremor, increased gastrointestinal complaints (e.g., diarrhea), headache, irritability and anxiety on the mild end of the spectrum, through to life-threatening neuroleptic malignant syndrome (NMS) with symptoms of delirium, neuromuscular rigidity and hyperthermia. Activation may occur 40% of the time with tightly-binding serotonergic agents and, in itself, should not be thought of as serotonin syndrome.[11]

The most common presentations after activation include cognitive changes, followed by neuromuscular or tremor/myoclonic changes and autonomic instability. The early signs of serotonin syndrome (e.g., changes in cognition) may be barely perceptible and may be easily overlooked by clinicians and patients. This, in turn, may lead to an inadvertent increase in the dose of the causative agent, or the addition of another medication with serotonergic properties. Rapid clinical deterioration may thus ensue, although this does not hold true for all patients.[1]

When assessing any patient receiving a serotonergic drug(s), it is essential to determine whether the patient is experiencing agitation or activation, as activation is often a signal that the patient may be at increased risk of serotonin syndrome.

Mild neuromuscular symptoms of serotonin syndrome may start with akathisia or tremor and progress to an altered mental status with inducible clonus. Such clonic reactions may be subtle in nature and present as a spasm of the eyelid (blepharospasm). As the patient progresses along the spectrum, he/she may develop sustained clonus, muscular hypertonicity and hyperthermia. At this point, the patient is considered to be experiencing life-threatening toxicity.[10]

In addition to clinical signs and symptoms, patients may present with other markers of serotonin syndrome, including elevated creatine kinase (CK) levels (rhabdomyolysis), metabolic acidosis, elevated aminotransferases, elevated creatinine (acute renal failure) and disseminated intravascular coagulopathy (DIC).[1,7,8]

Diagnosis
The diagnosis of serotonin syndrome requires a comprehensive patient history and examination.[1,7,8] This includes an evaluation of symptom evolution and rate of change experienced by the patient.[1]

Clonus (inducible, spontaneous or ocular) is the most important finding in establishing a diagnosis.[1] A diagnosis can be made using the traditional diagnostic Hunter criteria.[7] A simpler diagnostic method presented by Boyer can be used by pharmacists as a screening tool.[1] It suggests that if serotonin syndrome is suspected, the pharmacist should determine whether a serotonergic agent has been started in the past five weeks.[1] If the answer is no, then the patient is not considered to have serotonin syndrome. If yes, then the pharmacist should inquire about the presence of any symptoms that are typically observed in serotonin syndrome (e.g., tremor, hyperreflexia, clonus, muscular rigidity, fever, diaphoresis). If none of these symptoms are present, then serotonin syndrome can be ruled out. If the patient exhibits any or a collection of these symptoms, then the physician should be contacted promptly, as the patient requires further diagnostic evaluation for serotonin syndrome, either in the physician's office or in an emergency room setting.[1]

When considering a diagnosis of sero-

Table 2
TAIDCC Therapeutic Thought Process[14]

T	Therapeutic. Is it the right drug?
A	Allergies/Accurate. Is the drug safe for the patient? Is the dose correct?
I	Interactions. Are there complications with current pharmacotherapy?
D	Duplication of therapy. Is the patient already receiving therapy?
C	Compliance. What can be done to enhance adherence with pharmacotherapy?
C	Cost/Coverage by Rx plan. Can the patient afford (economics and adverse effects) to use the medication?

tonin syndrome, the clinician needs to consider all agents that act on serotonin pathways (Table 1). A thorough medication history should be completed in order to obtain a list of all prescription and OTC medications, herbal products, natural products and dietary supplements that the patient may be taking, as well as social and illicit substance use.[1] The patient and family members' medication histories (e.g., anesthetic agents, unusual reactions to 2D6 substrates) should also be considered in order to rule out other potential diagnoses (e.g., malignant hyperthermia, anticholinergic syndrome).

Serotonin syndrome often has a rapid onset, typically presenting with hours of increased synaptic serotonin levels. Although symptoms may occur within minutes, 60% of serotonin syndrome cases have presented after six hours of an increase in serotonin level at the synapse.[1,3,7]

Management

To manage serotonin syndrome, it is essential to immediately remove the precipitant serotonergic drugs. Symptoms usually resolve within 24 hours of discontinuing the contributing medications. However, symptoms may persist if the precipitant drugs have long half-lives, active metabolites or have been used at high doses. Supportive care (e.g., intravenous [IV] fluids, correction of vital signs) is also essential. Physical restraints are ill advised as they may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis, elevated CK and hyperthermia.[1,7] Overall, the types of management will depend on the severity of the patient's symptoms.[1,3,7]

In **mild cases**, after removal of precipitant medications, supportive care and treatment of agitation may also be required.[1] Benzodiazepines are the drugs of choice for treatment of agitation (e.g., lorazepam 1 mg Q4H is used in clinical practice in the absence of any contraindications).[1] The route of administration will depend on the patient's mental status. For dangerous agitation in the intensive care setting, midazolam 5 mg IV is often used in clinical practice. Intramuscular injections are not optimal as they may further elevate CK via muscle damage inherent with the injection.[1,12]

In **moderate** and **severe cases,** all of the above types of management should be employed, in addition to aggressive correction of abnormal cardiorespiratory and thermal regulation. Administration of 5–HT_{2A} antagonists, such as cyproheptadine 16–32 mg/day (an initial dose of 12 mg, and then 2 mg Q2H if symptoms continue, followed by a maintenance dosage of 8 mg Q6H) may also be indicated.[1,7] They may also be used preemptively to prevent serotonin syndrome in perioperative patients in situations where use of serotonergic agents cannot be avoided. However, at this point, only anecdotal case evidence for cyproheptadine (4 mg po Q4H around the clock) supports this strategy and more research is required.

Several treatments should be approached with caution. β-blockers with 5-HT_{1A} antagonism and a long duration of action (e.g., propranolol) may inadvertently cause hypotension and shock in patients with autonomic instability as a result of their mechanism of action. Bromocriptine, a dopamine agonist, has been implicated in the development of serotonin syndrome. Dantrolene has demonstrated no effect on survival in animal models and its clinical use in humans has led to increased temperature and resultant death in one case report.[1,8,13]

Contributors to the Storm

When examining the root causes of serotonin syndrome, all potential contributors must be taken into account. Clinically, a number of patient-specific, genetic, medication use, drug and disease state concerns need to be considered when assessing a patient's risk for developing serotonin syndrome.

To prevent serotonin syndrome, pharmacists should look at the therapeutic thought process governing the choice of medications. The acronym TAIDCC—Therapeutics, Accuracy of the medication, Interactions, Duplication, Compliance and Cost (Table 2)—is a useful, patient-centric approach to patient assessment.[14] Medications on profile or ingested that have serotonergic activity (Table 1) must be closely examined**,** including an assessment of therapy duplication, polypharmacy and any potential interactions. However, it should be noted that a growing body of evidence supports combining multiple serotonergic agents in certain situations (e.g., combining a serotonin–norepinephrine reuptake inhibitor (SNRI) and a noradrenergic and specific serotonergic antidepressant (NaSSA) in treatment-resistant depression).

GENETIC POLYMORPHISMS

Since drug interactions may significantly contribute to the development of serotonin syndrome, the effect of genetic polymorphisms must be considered. A polymorphism is a distinct population or ethnic difference apparent in gene expression or activity. Some cytochrome P450 (CYP) enzymes are prone to genetic polymorphisms, especially CYP2D6, CYP2C9, CYP2C19 and CYP2B6.[15]

feature

Patients can metabolize drugs at different rates. A ***poor metabolizer*** possesses two nonfunctional alleles and this phenotype is an autosomal recessive trait. These patients are more likely to have enhanced or diminished effects from medications that are substrates of this isozyme, depending on whether the drug is an active compound or prodrug, respectively. [15] An ***extensive metabolizer*** may result from gene duplication (e.g., there can be up to 13 copies of CYP2D6). These patients may experience therapeutic failure or inadvertent toxicities of medications activated by the affected isozyme.[16]

As CYP2D6 metabolizes 25–30% of all medications, the possibility of being a poor or extensive metabolizer of CYP2D6 presents a very large and real concern. Less than two per cent of Asians, two to five per cent of African-Americans, and six to 10% of Caucasians are poor metabolizers of CYP2D6.[17,18] Medications with serotonergic activity that are processed through the CYP2D6 isozyme include dextromethorphan, codeine, some antipsychotics (e.g., risperidone), and some antidepressants (e.g., paroxetine, fluoxetine, duloxetine).[16,19]

Three allelic variants of the CYP2C9 gene associated with decreased enzyme activity have been identified.[16] Medications with serotonergic properties that may be affected by such genetic polymorphisms include amitriptyline and fluoxetine.[19]

CYP2C19 is completely absent in two to five per cent of Caucasians[20] and in 20% of Japanese, while two to five per cent of Caucasians and 12–23% of most Asian populations are considered to be CYP2C19 poor metabolizers.[17] Medications with serotonergic properties that are metabolized by CYP2C19 include imipramine, amitriptyline, citalopram and clomipramine.[16,19] However, there is little clinical evidence of excessive or adverse drug effects in people who are CYP2C19 deficient, which may in part be secondary to challenges with obtaining genetic phenotyping.

Genetic polymorphisms are also associated with CYP2B6, but it is responsible for metabolizing a smaller number of medications with serotonergic properties (e.g., methadone).[19] Han Chinese are CYP2B6 poor metabolizers.[21,22]

CYP3A4 is responsible for metabolizing 50% of all medications, including several commonly used medications with serotonergic properties (e.g., citalopram, venlafaxine, ondansetron, fentanyl, methadone, quetiapine, ziprasidone, St. John's wort).[19] Polymorphisms of the 3A4 system are only now being explored.[16,23]

Pharmacists can particularly make a difference by focusing on 2D6, which is the CYP isoenzyme that metabolizes many antidepressants. In taking a thorough medication history, an easy "field" test question can be asked in the community pharmacy, such as: "If you have taken codeine in the past, what was your experience with respect to pain relief and side effects?" Approximately 10% of codeine is metabolized by CYP2D6 to its active metabolite, morphine. Patients who are poor CYP2D6 metabolizers will have little to no pain relief from codeine, whereas ultra-rapid metabolizers make excess morphine, leading to possible adverse effects. Consider what your patients define as a "codeine allergy." Is it an immunoglobulin IgE-mediated allergy or could it be a clue regarding an ultrarapid polymorphism? Patients who have a poor therapeutic effect or adverse response to usual doses of codeine may also experience unexpected responses to other serotonergic drugs that are metabolized by CYP2D6 (e.g., fluoxetine, paroxetine).[19]

Health status

The overall health status of the patient must be considered. In a patient with chronic renal failure, the metabolism of medications will be reduced because key enzymatic systems may be inhibited in the liver, intestine and kidney.[17] Significant reductions (1.5–3 fold) are noticeable for most pathways for CYP3A4, CYP2D6 and CYP2C19.[17] Decreased renal function may place patients taking certain serotonergic medications (e.g., venlafaxine) at greater risk for serotonin syndrome, as there is decreased clearance of the drug and subsequent increased levels of serotonin. In clinical practice, patients taking venlafaxine who have impaired renal function (i.e., creatinine clearance < 30 mL/min or serum creatinine > 200 µmol/L) or are on dialysis, should have their venlafaxine dose decreased by 50%.[24,25]

Liver disease may also induce changes in hepatic metabolism. As liver disease progresses and function deteriorates, clearance through a number of CYP systems is reduced, including the 1A2, 2C19, 2D6 and 2E1 systems, each to a different degree.[26,27] For example, paroxetine (metabolized via CYP2D6) clearance will be decreased in a patient with liver dysfunction and levels of this medication and serotonin will increase.[19] This may place a patient at increased risk for developing serotonin syndrome.

Polypharmacy

Polypharmacy is a key pandemic contributor to the perfect storm. The 2006 Brogan Ontario Drug Benefit summary identified that patients on atypical antipsychotics are also on three or more medications 67% of the time. Examples of medications implicated in polypharmacy include antidepressants, anxiolytics, analgesics and other antipsychotics, many of which have serotonergic activity.[28]

Opiates/opioids and surgical drugs

A number of opiates, including tramadol, morphine, codeine, pentazocine, meperidine, methadone, oxycodone and fentanyl, have serotonergic properties and cause subsequent serotonin release. The mechanism of action of tramadol also involves monoamine (including serotonin) reuptake inhibitory effects.[29] The serotonin release caused by opioids/opiates is a transient effect. Morphine has been shown to increase central serotonin levels by 50% in rat models.[30] Since 10% of codeine is metabolized to morphine, serotonergic effects may also be observed with codeine. Meperidine works by blocking presynaptic serotonin reuptake. As such, it may interact with other serotonergic agents and result in serotonin hyperstimulation.[7,31] Methadone has a much higher potency as a serotonin reuptake inhibitor than other opiates, leading to a higher risk of serotonin syndrome.[7,32] Caution must be used when methadone is taken with other medications affecting CYP3A4 isoenzymes, because interactions may result in increased levels of methadone and, therefore, serotonin.[19,32] The same can be said for fentanyl, which is a phenylpiperidine opioid with weak serotonergic activity.[7,33-35]

Medications that are used surgically within the operating room and immediately postoperative may place the patient at increased risk of serotonin syndrome, especially if the patient received an agent (e.g., fentanyl, ondansetron, morphine) that acts on serotonin prior to the procedure or intraoperatively.[33] Therefore, analgesic selection following an operation must be done with caution and with extra monitoring for early signs and symptoms of serotonin syndrome.

By understanding our patient as a whole, pharmacists are very well suited to prevent serotonin syndrome or divert the storm at its early stages of formation.

The Pharmacist's Role

When presented with a prescription or providing counselling on an OTC/herbal product with serotonergic properties (e.g., dextromethorphan, St John's wort) or when questions arise regarding use of an illicit substance with serotonergic properties (e.g., LSD, "ecstasy," DMT), pharmacists should always consider the patient's risk for developing serotonin syndrome. Awareness of other serotonergic medications (see Table 1) on the medication profile and awareness of impaired renal or hepatic status are key areas to consider. When three or more medications with serotonergic properties are being used by the patient at therapeutic doses in the absence of any other confounders (e.g., polymorphisms), the pharmacist can follow-up with the patient and monitor for signs and symptoms of serotonin syndrome. When in doubt, pharmacists should consider that any two serotonergic medications may lead to serotonin syndrome. At this point, education regarding serotonin syndrome should be provided to the patient and/or physician. Speaking first with the physician prevents misunderstanding and avoids inadvertent alarm for the patient.

If a patient displays signs or symptoms of serotonin syndrome (e.g., spasms or tremors with elevated blood pressure and cognitive changes), the patient must be assessed in the emergency department of the local hospital. This is a very fine clinical line as 40% of patients started on an SSRI go on to develop activation and agitation. Activation is not a medical emergency; it usually subsides as the medication is continued and may respond to a dose reduction. However, activation or agitation may also be viewed as evidence that the patient could have a risk factor for serotonin syndrome.

Conclusion

Given that serotonin syndrome is often under-recognized, underdiagnosed and under-reported, yet can have a significant impact on patient morbidity and mortality, it is essential that pharmacists be aware of the potential seriousness of this disorder. Knowledge of the medications that act on serotonin, completion of a thorough medication history and awareness of patient/family reactions to medications are all part of the preventive prescription. This is largely an avoidable condition that can be prevented using patient-centric patterns of practice. By understanding our patient as a whole, pharmacists are very well suited to prevent serotonin syndrome or divert the storm at its early stages of formation. pp

References found online at CanadianHealthcareNetwork.ca

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