According to the Centers for Medicare & Medicaid Services, approximately 1 in 10 adults in the United States is affected by depression. This overwhelming number of people affected are often treated with antidepressant medications. In fact, antidepressants are the prescription medications most frequently used by US adults between the ages of 20 and 59 years.

According to the Centers for Disease Control and Prevention, antidepressant use increased nearly 65% over the course of 15 years. Between 2011 and 2014, 12.7% of people aged 12 years and older reported antidepressant medication use in the last month vs 7.7% from 1999 to 2002. Of people treated within the last month, a quarter of them have been using antidepressants for more than 10 years. Moreover, use increases with age, ranging from 3.4% among people aged 12 to 19 years to 19.1% among people aged 60 years and older.

Antidepressants are the third most frequently mentioned medications during physician office visits, with a significant proportion written by primary care physicians. Moreover, a significant proportion of antidepressants are not being prescribed for the approved indications (eg, depression and anxiety), but are being used off-label.

Selective serotonin reuptake inhibitors (SSRIs) constitute the most widely used antidepressants. However, they are associated with significant toxicity. According to the 2016 annual report of the National Poison Date System, SSRIs were number 10 of the top 25 substance categories associated with reported fatalities.
In particular, SSRIs raise serotonin levels in the body, and when combined with other serotonergic agents, they can lead to a potentially fatal condition called serotonin syndrome (SS). The actual incidence of SS and associated morbidity is likely underestimated, as SS is frequently underdiagnosed and underreported and can easily be overlooked, especially when mild. It has been suggested that more than 85% of physicians are not familiar with the existence of SS or which drugs or drug combinations may cause it.

“In my experience, the majority of prescribers have absolutely no idea that [SS] even exists, let alone what causes it and what to do about it,” according to Irene Campbell-Taylor, MB ChB, PhD, a clinical neuroscientist based in Nova Scotia, Canada, with a private practice focusing primarily on geriatrics.

“It is alarming because SSRIs are among the most frequently prescribed antidepressants, and patients are not usually warned about other serotonergic agents that can interact with SSRIs and induce serotonin syndrome, a condition that can be lethal,” she told Psychiatry Advisor.

**Serotonin: Too Much of a Good Thing?**

SS is caused by drugs that either affect serotonin metabolism or act as direct serotonin receptor agonists, or both, and takes place in the setting of excess stimulation of central and peripheral serotonin receptors.

Decarboxylation and hydroxylation of tryptophan are responsible for producing serotonin (5-hydroxytryptamine [5-HT]). After this process, 5-HT is stored in vesicles and released into the synaptic cleft when it is stimulated. Monoamine oxidase-A is responsible for metabolizing 5-HT.

Serotonin can bind to at least 7 different families of 5-HT receptors, and no single receptor is responsible for the development of SS. However, evidence suggests that the 5HT-2A receptors are most implicated in the condition.

Serotonin plays an essential and far-reaching role in multiple systems and acts both peripherally and centrally. Peripheral serotonin is produced primarily in gastrointestinal tract and is responsible for stimulating vasoconstriction, uterine contraction, bronchoconstriction, gastrointestinal motility, and platelet aggregation.

Central serotonin, which is present in the midline raphe nuclei of the brainstem, functions to inhibit excitatory transmission. It also plays an important role in modulating wakefulness, attention, mood, affective and sexual
Drugs that can cause SS do so by inhibiting serotonin reuptake, increasing serotonin synthesis, decreasing serotonin metabolism, increasing serotonin release, or activating serotonergic receptors. The inhibition of cytochrome P450 enzymes by SSRIs can result in the accumulation of certain serotonergic drugs that are usually metabolized by these enzymes, leading to an “exacerbation loop in which the SSRI inhibits the metabolism of a certain drug, which in turn increases serotonergic activity.” Drugs that increase serotonin concentrations and their mechanisms of action are listed in Table 1. Additional drugs with serotonergic effects that can potentiate other serotonergic agents and cause SS are listed in Table 2.

From Subtle to Serious

“Serotonin syndrome tends to be underrecognized by physicians because you have to be careful and on the lookout, since its presentation can be subtle,” Peter R. Chai, MD, MMS, from the Division of Medical Toxicology, Department of Emergency Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, told Psychiatry Advisor.

The onset of SS can occur within hours of an exposure to a serotonergic agent, but can be delayed for as much as 24 hours.

“It is important to note that serotonin syndrome can progress from mild to florid and serious very quickly, especially in the setting of the combination of an SSRI or [serotonin-norepinephrine reuptake inhibitor (SNRI)] and a drug of abuse, such as cocaine,” warned Dr Chai, who is also an assistant professor at Harvard Medical School in Boston.

Dr Campbell-Taylor recounted the case of a patient who was being treated with an SSRI and took over-the-counter melatonin for insomnia.

“He woke up during the night with headache, dizziness, and his ‘face on fire,’ which is typically a sign of elevated blood pressure,” she reported.

“The fact that it wasn’t lethal is likely because he took a relatively small dose of melatonin and his symptoms abated without requiring hospitalization,” she added.

Diagnosis of Serotonin Syndrome

Autonomic, cognitive, and neuromuscular derangements are common in SS, together with signs such as fever, agitation, and clonus. However, the condition varies considerably from patient to patient. Moreover, many of these manifestations are nonspecific, making the syndrome challenging to diagnose.

It is essential to take a careful patient history, finding out what medications (prescription and over-the-counter) and dietary supplements the patient might have been using, for how long, and whether the dose was recently increased. It is also important to ascertain when the signs and symptoms began, relative to the exposure, and whether they were they rapid in onset.

Dr Chai emphasized that it is important as well to find out whether the patient recently stopped taking a serotonergic agent and began taking another one, as many of these drugs have long half-lives and may still be
There is no laboratory test that confirms SS and serum serotonin levels do not necessarily correlate with clinical findings. Instead, laboratory and other tests are used to rule out other diagnoses.\(^{11}\)

Classical symptoms of SS are listed in Table 3. The Hunter Serotonin Toxicity Criteria for diagnosing serotonin syndrome has become the standard algorithm to diagnose SS and is listed in Table 4. Differential diagnoses of SS are included in Table 5.

**Related Articles**

- MAOIs Better Than Tricyclic Antidepressants for Early Stage Treatment-Resistant Depression
- Sequential Addition of CBT or Antidepressants Effective in Nonremitting Depression
- Depression, Antidepressants, and Atrial Fibrillation: What Do We Know?

**Treating Serotonin Syndrome**

“Clinicians should be aware that serotonin syndrome is treatable once you recognize the hallmark features, and that the prognosis is generally favorable,” Dr Chai said.

First-line management involves discontinuation of the offending serotonergic agents and provision of supportive care, with the intensity of treatment depending on the severity of the syndrome.\(^{11}\) Mild cases typically resolve in 24 to 72 hours with conservative therapy, and patients do not necessarily require hospital admission.\(^{11}\) In contrast, patients with moderate to severe cases involving hypertonicity, hyperthermia, autonomic instability, or progressive cognitive changes require hospitalization.\(^{11}\) Management of mild, moderate, and severe cases are listed in Table 6.

**Prevention: The Role of Psychiatrists**

Dr Campbell-Taylor and Dr Chai both emphasized the critical role that psychiatrists can play in preventing SS.

*Be vigilant about what you are prescribing.*

Physicians and other prescribers should modify their prescription practices to avoid or at least minimize coprescription of drugs that have a high probability of inducing SS.\(^{11}\)

“Do not combine 2 serotonergic agents, such as an SSRI and SNRI, in treatment, and be vigilant during initiation of the medication or when increasing the dose, especially in patients naive to these drugs,” Dr Chai warned.

A computerized ordering system and medical software can ascertain whether there are potential interactions when multidrug regimens are required.\(^{11}\) Physicians who do not have access to this system should verify potential interactions with a pharmacist.

*Make sure you know what other agents your patient may be taking.*
“This requires thorough inquiring because many people don’t think to mention items taken for nonpsychiatric causes, such as cold remedies, antibiotics, or herbal supplements that the patient may regard as ‘natural’ and therefore perfectly safe,” she said.

**Educate patients about serotonin syndrome**

“Many drugs include instructions or warnings, such as not to take them in combination with alcohol or not to drive or use heavy equipment while being treated, but SSRIs do not carry those warnings, although there are warnings about suicidality,” Dr Campbell-Taylor pointed out. It therefore is incumbent on prescribers to inform patients about the risk for serotonin syndrome.

“I suggest that prescribers provide list of all products that patients should avoid while taking SSRIs, SNRIs, or other serotonergic agents,” she advised. “Patients should be told that if they have a cold or allergy or have difficulty sleeping, they should consult the prescriber before self-treating with an over-the-counter drug or herbal supplement.”

Part of education is educating patients and families about the risk for overdose and its associated symptoms, Dr Chai added.

**Consider nonpharmacologic approaches for treatment of mood disorders**

“The implications of this widespread SSRI use are staggering,” Dr Campbell-Taylor said. “It is incumbent on all medical professionals to educate themselves and their patients and avoid prescribing these drugs whenever possible.”

Evidence-based psychotherapies, such as cognitive behavioral therapy, are increasingly being regarded as potential first-line approaches to patients with mood disorders, and their use should be increased, together with other nonpharmacologic interventions, she advised.

**References**


Table 1

Mechanisms of Serotonin Syndrome

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of serotonin</td>
<td>Amphetamines/weightloss drugs</td>
<td>Phentermine, Bupropion, nefazodone, trazodone</td>
</tr>
<tr>
<td>uptake</td>
<td>Antidepressants</td>
<td>Bupropion, nefazodone, trazodone</td>
</tr>
<tr>
<td></td>
<td>Antiemetics</td>
<td>Granisetron, ondansetron</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Chlropheniramine</td>
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<tr>
<td></td>
<td>Opiates</td>
<td>Levomethorphan, levorphanol, meperidine, methadone, pentazocine, pethidine, tapentadol, tramadol</td>
</tr>
<tr>
<td></td>
<td>Drugs of abuse</td>
<td>Cocaine, MDMA</td>
</tr>
<tr>
<td></td>
<td>OTC cold remedies</td>
<td>Dextromethorphan</td>
</tr>
<tr>
<td>Inhibition of serotonin metabolism</td>
<td>Anxiolytics</td>
<td>Buspirone</td>
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<tr>
<td>-----------------------------------</td>
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<tr>
<td>Monoamine oxidase inhibitor</td>
<td>Furazolidone, isocarboxazid, linezolid, methylene blue, phenelzine, selegiline, Syrian rue, tranylcypromine</td>
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</tr>
<tr>
<td>Triptans</td>
<td>Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan</td>
<td></td>
</tr>
<tr>
<td>Increasing serotonin synthesis</td>
<td>Amphetamines/weight loss drugs</td>
<td>Phentermine</td>
</tr>
<tr>
<td>Dietary supplements</td>
<td>L-tryptophan</td>
<td></td>
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<tr>
<td>Drugs of abuse</td>
<td>Cocaine</td>
<td></td>
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<tr>
<td>Increasing serotonin release</td>
<td>Antidepressants</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Antimigraines</td>
<td>Dihydroergotamine, triptans</td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>Meperidine, oxycodone, tramadol</td>
<td></td>
</tr>
<tr>
<td>Drugs of abuse</td>
<td>MDMA</td>
<td></td>
</tr>
<tr>
<td>OTC cold remedies</td>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td>Parkinson disease treatment/amino acid</td>
<td>L-dopa</td>
<td></td>
</tr>
<tr>
<td>Activating serotonin receptors</td>
<td>Anxiolytics</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Mirtazapine, trazodone</td>
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<tr>
<td>Antimigraines</td>
<td>Dihydroergotamine, triptans</td>
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<td>Opiates</td>
<td>Fentanyl, meperidine</td>
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<td>Drugs of abuse</td>
<td>LSD</td>
<td></td>
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<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>Prokinetic agents</td>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Inhibition of various CYP450 microsomal oxidases</td>
<td>CYP2D6 inhibitors</td>
<td>Fluoxetine, sertraline</td>
</tr>
<tr>
<td>CYP2D6 substrates</td>
<td>Dextromethorphan, oxycodone, phentermine, risperidone, tramadol</td>
<td></td>
</tr>
</tbody>
</table>
CYP3A4 inhibitors  Fluconazole
CYP2C19 substrates  Citalopram

Table 2

Additional Drugs/Supplements Associated With Serotonin Syndrome

<table>
<thead>
<tr>
<th>Drug/Supplement</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimigraine medications</td>
<td>Carbamazepine, valproic acid</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Lansoprazole, omeprazole, pantoprazole</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Benazepril, lisinopril, enalapril, captopril</td>
</tr>
<tr>
<td>Cardioselective β-adrenergic blocking drugs</td>
<td>Atenolol, metoprolol, bisoprolol, esmolol</td>
</tr>
<tr>
<td>Digitalis glycoside</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Nonprescription product sold online as a Sibutramine weight-loss agent</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Factor Xa inhibitor oral anticoagulant</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Antiviral medications</td>
<td>Ritonavir, acyclovir</td>
</tr>
<tr>
<td>Herbal/dietary supplements</td>
<td>S-adenosyl-L-methionine, curcumin, ginseng, nutmeg, turmeric, melatonin, St. John's wort</td>
</tr>
</tbody>
</table>

Table 3

Signs and Symptoms of Serotonin Syndrome

- Agitation
- Akathisia
- Ataxia
- Clonus
- Confusion
- Diaphoresis
- Diarrhea
- Disseminated intravascular coagulation
- Fever
- Hyperreflexia
- Hypertension
- Muscular rigidity
- Multiorgan failure
- Mydriasis
- Rhabdomyolysis
- Shivering
- Seizures
- Tachycardia
- Tremor

Table 4

Hunter Serotonin Toxicity Criteria: Decision Rules

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presence of Serotonin Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous clonus</td>
<td>Yes</td>
</tr>
</tbody>
</table>

If the above is not present but there is...

Inducible clonus + agitation
OR
Inducible clonus + diaphoresis

If the above are not present but there is...

Ocular clonus + agitation
OR
Ocular clonus + diaphoresis

If the above are not present but there is...

Tremor + hyperflexia

If the above are not present but there is...

Hypertonic + temperature >38°C + ocular clonus
OR
Hypertonic + temperature >38°C + inducible clonus

If none the above are present

No

Table 5

Differential Diagnosis of Serotonin Syndrome

- Anticholinergic syndrome (primary)
- Malignant hyperthermia (primary)
- Neuroleptic malignant syndrome (primary)
- Tetanus
- Overdose of sympathomimetic drugs
- Meningitis
- Heat stroke
- Delirium tremens
- Sepsis

**Table 6**

**Managing Serotonin Syndrome Based on Severity**

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Mild hypertension, Tachycardia, Mydriasis, Diaphoresis, Shivering, Tremor, Myoclonus, Hyperreflexia</td>
<td>1. Discontinue the offending agent/agents· 2. Support (ie, stabilize vital signs, initiate cooling measures) 3. For mild agitation, fever, hypertension, tachycardia: benzodiazepines (diazepam) 4. Observe for ≥6 hours</td>
</tr>
<tr>
<td>Moderate</td>
<td>All the above plus· Temperature of ≥40°C, Hyperactive bowel sounds, Ocular clonus, Agitation, Hypervigilance, Pressured speech</td>
<td>All the above plus· 1. For severe agitation/hypothermia: 5-HT antagonist (cyproheptadine) 2. Admission to hospital for cardiac monitoring/observation</td>
</tr>
<tr>
<td>Severe</td>
<td>All the above plus· Temperature of ≥41.1°C, Dramatic swings in pulse rate, blood pressure, Delirium, Muscle rigidity</td>
<td>All the above plus· 1. For severe hypertension/tachycardia: esmolol or nitroprusside 2. Sedation and paralysis with a nondepolarizing agent and intubation/ventilation 3. Admission to intensive care unit</td>
</tr>
</tbody>
</table>

**TOPICS:** [DEPRESSION] [DEPRESSIVE DISORDER]

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