SEROTONIN SYNDROME IN A PATIENT WITH DUAL DIAGNOSIS-CASE STUDY

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Abstract

Introduction: Serotonin syndrome is a rare but potentially life-threatening condition. In most cases, this complication is caused by taking two serotonergic medications simultaneously, leading to excessive serotonin concentration in the body. Selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), as well as irreversible monoamine oxidase inhibitors (MAOIs) and their combination with other serotonergic substances, are associated with symptoms of serotonin syndrome.

Case study: A patient who was prescribed sertraline (an SSRI) for a depressive episode suffered fractures in a traffic accident during the treatment, and tramadol was prescribed for her pain. Since both drugs tend to increase serotonin levels in the body, a complication in the form of serotonin syndrome developed. With timely recognition and treatment, the symptoms of serotonin syndrome resolved without lasting consequences.

Conclusion: Numerous drugs and substances can induce serotonin syndrome, often in combination with antidepressants. Therefore, it is of great importance that doctors are aware of comorbid conditions that necessitate the use of the mentioned drugs in order to prevent serotonin syndrome. If it does occur, adequate and successful treatment is crucial.

Keywords: Serotonin syndrome, risk, treatment, SSRI, SNRI
INTRODUCTION

Serotonin syndrome (SS) represents a not-frequent but potentially life-threatening reaction due to an excessively high concentration of serotonin in both the peripheral and central nervous systems (1-4). Most frequently, serotonin syndrome occurs when two or more medications that affect serotonin levels are administered simultaneously, when the dose of one serotonergic medication is suddenly increased, or due to intoxication or overdoses of various substances with serotonergic properties.

Serotonin syndrome was first described in 1937 as an adverse effect in a patient taking iproniazide, an irreversible monoamine oxidase inhibitor (IMAO). Symptoms can manifest in various patients regardless of age and sex. Serotonin syndrome can even be diagnosed in a newborn if it was exposed in utero to serotonergic substances (4,5,6). Usually, antidepressants are the most common drugs that affect serotonin levels, leading to the occurrence of serotonin syndrome. Nevertheless, there are numerous other substances that can cause symptoms of SS either by themselves or in combination. The fact is that under therapeutic dosage and monitoring, a single serotonergic antidepressant will not cause serotonin syndrome if not administered with other serotonergic substances (2-5).

Serotonin (5-HT) was identified in 1937 by Asero Erspamer. Over 90% of the body's serotonin is synthesized in enterochromaffin cells, about 5% in thrombocytes and other organs, and only 5% in the central nervous system (CNS) (1,6). Nonetheless, serotonin remains one of the most important neurotransmitters, regulating neurophysiological and behavioral processes, pain perception, mood, anger, anxiety, appetite, sleep, libido, and thermoregulation. In peripheral areas of the body, serotonin plays an important role in vasoconstriction, muscle contraction, and thrombocyte aggregation, among other functions (5,6,7).

A deficiency of serotonin in CNS synapses is associated with the emergence of depressive and anxiety disorders (5-8). There is an abundance of evidence that drugs which increase intrasynaptic serotonin concentration in the CNS alleviate symptoms of depression and anxiety (7,8,9).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are the most commonly prescribed drugs for anxiety and depressive disorders. Most people can safely take antidepressants under the guidance of a healthcare professional. Adverse effects might arise when two or more serotonergic drugs are combined or when they are overdosed (1,2,9,10,11).

When the combination of serotonergic antidepressants is deemed necessary, doctors should exercise caution and regularly monitor the patient’s condition. Symptoms resembling those of serotonin syndrome can be similar to symptoms of a mental disorder, a comorbid somatic problem, or a result of intolerance to a specific medication. The diagnosis of serotonin syndrome in most cases includes mental changes, dysfunction of the neurovegetative system, and neuromuscular changes (clonus, tremor). Nonetheless, it is crucial to gather all data about comorbid somatic disorders and other drugs/supplements prescribed to the patient for somatic issues (painkillers, antibiotics, etc.), as well as any use of illegal psychoactive substances, to avoid adverse reactions such as SS.
Symptoms of serotonin syndrome usually occur within a few hours to a day after an elevated level of serotonin in the CNS. When the serotonergic drug that is causing the rise in serotonin levels is excluded, symptoms typically disappear within 24-72 hours. However, if a prescribed antidepressant has a long half-life elimination time or has active metabolites, some mild symptoms may persist for a few weeks. Cases of chronic, mild clinical features of SS are described in the literature (10-14). Symptoms can vary in intensity, ranging from mild to moderate and severe. When serotonin syndrome remains unrecognized and is left untreated, severe symptoms can escalate to a life-threatening condition. Complications can include seizures, abnormal heartbeat, rhabdomyolysis, renal or heart failure, acidosis, disseminated intravascular coagulation, respiratory insufficiency, coma, and death (15-18). To prevent complications, a prompt diagnosis and treatment of SS should be initiated as soon as symptoms arise.

Most frequently, serotonin syndrome presents as mental confusion, agitation, neurovegetative dysfunction, and various forms of neuromuscular dysfunctions or even coma. The following is a list of the most common symptoms that occur in serotonin syndrome (Table 1).

<table>
<thead>
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<th>Table 1. Symptoms of Serotonin syndrome</th>
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<td><strong>Mild</strong>- Hypertension, intermittent tremor, mydriasis, tachycardia, diaphoresis, myoclonus, restlessness</td>
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<td><strong>Moderate</strong>- Hyperthermia (&gt;38°C), psychomotor agitation, confusion, hyperreflexia, tremor, hyperhidrosis, diarrhea, tachycardia, hypertension (&gt;140/90 mmHg), repeated rotatory movements of head and neck</td>
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<tr>
<td><strong>Serious</strong>- Myoclonus, horizontal oculogyric clonus, tachypnea, tremor, seizures, muscle rigidity, rhabdomyolysis, metabolic acidosis, coma or agitation, hypo or hypertension, renal insufficiency, disseminated intravascular coagulation (DIC), hyperthermia (&gt;41°C), death</td>
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Epidemiological data regarding serotonin syndrome (SS) are not well consolidated, but there is evidence suggesting that SS occurs in approximately 15% of cases involving intoxication with selective serotonin reuptake inhibitors (SSRIs). However, there is a suspicion that the actual number might be much higher due to cases of SS going unrecognized (2,3,17,19,20). There is evidence that various medications, opioids, and many illegal substances, either taken alone or in combination with other serotonergic substances, can contribute to serotonin syndrome (SS). As our understanding of SS improves, misdiagnosis and complications can be significantly reduced, which can lead to a decrease in the mortality rate associated with serotonin syndrome.

Here is a list of medications and other substances that could potentially cause serotonin syndrome (SS):

**Antidepressants**

Selective Serotonin Reuptake Inhibitors (SSRIs): fluoxetine, citalopram, escitalopram, sertraline, paroxetine
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran
Tricyclic Antidepressants (TCAs): clomipramine, amitriptyline, imipramine, desipramine, nortriptyline, doxepin
Monoamine Oxidase Inhibitors (MAOIs): selegiline, tranylcypromine, phenelzine
Serotonin Modulators: trazodone, nefazodone
Norepinephrine Reuptake Inhibitor (NRI): bupropion

There is evidence suggesting that mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSa), does not cause SS due to its dual action. However, some articles claim the opposite.

**Other medications that can cause SS include:**

Opioid painkillers: tramadol, hydrocodone, oxycodone, fentanyl
Migraine headache drugs: sumatriptan, zolmitriptan, eletriptan, rizatriptan, almotriptan
Drugs for treating HIV/AIDS: ritonavir
Cough medication: dextromethorphan
Antibiotics: linezolid
Antiemetics: metoclopramide, droperidol, granisetron, ondansetron
Mood stabilizer: lithium
Illegal substances: LSD, ecstasy, cocaine, amphetamine
Other drugs: olanzapine, risperidone, valproate, tryptophan, levodopa, buspirone
Herbal supplements: Asian and American Ginseng, St. John's wort, Syrian rue

Serotonin syndrome (SS) is not solely attributed to an increased level of serotonin in the synaptic space; it also involves the overstimulation of 5-HT2A receptors, while agonism of 5-HT1A receptors can contribute through pharmacodynamic interaction (18,19,20). The mechanisms of serotonin syndrome encompass various factors, including elevated serotonin synthesis, hyperactivation of serotonin receptors, inhibition of serotonin reuptake, slower serotonin
metabolism, and potential inhibition of CYP 450 enzymes. However, other neurotransmitters also play a role in the development of serotonin syndrome, such as the increased level of norepinephrine. Alterations in the sensitivity of NMDA receptors and changes in GABA neurotransmission have been observed in serotonin syndrome (7,11,20). Evidence suggests that numerous other neurotransmitters influence the clinical signs and symptoms of serotonin syndrome.

Diagnosing SS is typically a process of exclusion, as there is no specific test available for serotonin syndrome. The diagnosis relies on clinical assessment. Other conditions, such as neuroleptic malignant syndrome (NMS), intoxication with anticholinergic drugs or sympathomimetics, neurological disorders, and viral illnesses, should be ruled out in the diagnostic process (2,4,7,11,15). Diagnostic procedures, including blood and urine tests, toxicology and alcohol screening, electrolyte level assessment, thyroid function testing, spinal tap, chest X-ray, and CT scan of the brain, may be conducted. If all tests yield negative results and the criteria specified by the Hunter criteria are met, a diagnosis of serotonin syndrome can be made.

Distinguishing between SS and NMS is always necessary. This distinction can be difficult, especially if a patient was using both antipsychotics and serotonergic antidepressants. Symptoms of serotonin syndrome can emerge rapidly, often within hours of co-medication or a dose increase of serotonergic substances, particularly when medications affecting serotonin levels are combined. In our patient, symptoms appeared in less than a day, despite not using antipsychotic medication (although even SSRIs can cause NMS). In NMS, symptoms usually arise over a few days after initial antipsychotic use or a dosage increase. Main NMS symptoms include bradykinesia, hyperreflexia, extrapyramidal rigidity, leukocytosis, elevated body temperature, confusion, somnolent consciousness, or psychomotor agitation, often accompanied by increased blood creatine phosphokinase (CPK) enzyme levels (4,5,21,22).

In serotonin syndrome, the most important symptoms include muscle rigidity, tremor, clonus, and dilated pupils along with dryness of the mouth's mucosa. In diagnosis, medical history is crucial, particularly the patient's illness history, medication usage, and observation of symptoms.

The first evaluated criteria were introduced by Sternbach in 1991 (15,17,20). For diagnosis, the presence of 3 out of 10 symptoms should be positive: altered consciousness, agitation, hyperreflexion, myoclonus, diaphoresis, hyperthermia, tremor, diarrhea, dyscoordination, and trembling. These should be accompanied by the use of serotonergic drugs or an increased dosage within the last 24 hours.

Later, Hunter Toxicity Criteria Decision Rules were introduced, with greater sensitivity (84%) and specificity (over 97%). According to the Hunter criteria, therapy with serotonergic drugs in combination with one of the symptoms is necessary to confirm the diagnosis of serotonin syndrome. The qualifying symptoms are myoclonus, tremor with hyperreflexia, muscle rigidity in combination with hyperthermia, and ocular or induced clonus (12,14,15).

**CASE REPORT**
A 54-year-old female patient has been undergoing psychiatric treatment for 5 years with a diagnosis of depressive disorder. The patient experienced remission for the last three years, but following her mother's passing, she developed symptoms of anxiety, sleep disturbances, and reduced appetite. Her treatment involved increasing the dosage of sertraline up to 150 mg/day and adding mirtazapine at 30 mg/day, which resulted in a decrease in the intensity of her depressive symptoms. During this time, the patient was involved in a car accident resulting in a broken arm and four ribs. At the Surgery unit, she was given tramadol for the severe pain, reaching doses of up to 400 mg/day. After less than a day, the patient reported experiencing intense tremors, anxiety, restlessness, diaphoresis, confusion, and instability. She visited her psychiatrist, who diagnosed serotonin syndrome based on the Hunter criteria. The patient's psychiatric medications were reduced to 50 mg/day of sertraline and 15 mg/day of mirtazapine, and diazepam was added to the therapy at a dosage of 10 mg/day. Tramadol was discontinued and replaced with paracetamol. Over the course of a few days, the symptoms subsided; however, the patient continued to experience insomnia, leading to an increase in the dosage of mirtazapine to 30 mg/day. In the subsequent period, the patient achieved clinical remission without further signs of serotonin syndrome.

**DISCUSSION**

Upon correct diagnosis, the initial management involves discontinuing the use of precipitating drugs or other contributing substances. Benzodiazepines can be administered to address myoclonus, and supportive measures should be taken based on the type and severity of symptoms. In the first hour, intestinal decontamination with activated charcoal may be prescribed if the patient has ingested large doses of serotonergic medication. If hypotension is evident, sympathomimetics are recommended, while short-acting antihypertensive drugs like nitroprusside are preferable in cases of hypertension or tachycardia. Hyperthermia treatment includes using benzodiazepines to reduce myoclonus and applying cold compresses; however, antipyretic agents are ineffective as the elevated body temperature results from muscular activity. Severe cases may call for the administration of serotonin antagonists such as cyproheptadine. Hospitalization is necessary when symptoms are of moderate to severe intensity. In our patient's case, her symptoms were mild to moderate, and with adjustments in sertraline and mirtazapine dosages, discontinuation of tramadol, and additional supportive measures like diazepam, her serotonin syndrome symptoms lessened.

In most cases, prompt recognition and treatment of serotonin syndrome lead to symptom resolution without lasting consequences. Supportive measures should be continued until symptoms abate, usually within 24 hours after discontinuation of serotonergic substances. This was the case with our patient.

Accurate diagnosis is crucial, as misdiagnosing serotonin syndrome as neuroleptic malignant syndrome (NMS) might lead to inappropriate treatment. For example, bromocriptine, a drug used in NMS, can be contraindicated and worsen the clinical presentation of serotonin syndrome due to its interaction with D2 receptors.

Medical personnel should remain vigilant about the potential for serotonin syndrome. When there is a need for two serotonergic medications in higher doses, close monitoring becomes essential.
Patients with comorbid mental disorders, particularly anxiety and depressive symptoms alongside chronic pain, require careful observation. If feasible, the effective dosage of pain-relieving medication (e.g., tramadol) and serotonergic antidepressants should be minimized.

**CONCLUSION**

Serotonin syndrome can develop in approximately 14-16% of patients who overdose on serotonergic drugs or substances. Early identification plays a crucial role in preventing the progression to more severe symptoms. When symptoms and signs of serotonin syndrome are recognized, it is advisable for medical practitioners to consider prescribing serotonergic antidepressants, if necessary, at the lowest effective dosage or to explore alternative classes of antidepressants. It is essential to avoid combining two medications that affect serotonin, particularly in higher dosages. However, in most cases, SSRI or SNRI antidepressants, even at higher dosages when administered individually, do not typically induce serotonin syndrome. Various other drugs have the potential to influence serotonin levels in the human body, and the best approach to preventing serotonin syndrome is to minimize the combination of different medications in patients. Combining opioids with other serotonergic drugs, due to their serotonin-norepinephrine reuptake inhibition, tends to pose the most significant concern in this regard.

**Abbreviations**

CNS- Central Nervous System
CT scan- Computerised Tomography scanning
CPK- Creatinine Phosphocinase
GABA- Gama-amynobutricaccide
Imao- Irreversible Monoaminooxidase inhibitors
5HT- 5-Hydroxytryptopohan
5HT1a, 5HT2a- 5-Hydroxytryptopohan receptors
NaSSA- Noradrenergic and specific serotonergic antidepressants
NMIDA- N-methyl-D-aspartate receptor
NMS- Neuroleptic Malignant Syndrome
NRI- Norepinephrine reuptake inhibitor antidepressants
SNRI- Serotonin and norepinephrine reuptake inhibitor antidepressant
SS- Serotonin Syndrome
SSRI- Selective Serotonin Reuptake Inhibitor antidepressant
X-RAY- Radiation

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Sažetak

SEROTONINSKI SINDROM KOD PACIJENTKINJE SA DUALNOM DIJAGNOZOM-PRIKAZ SLUČAJA

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Uvod: Serotoninski sindrom predstavlja retko, ali po život potencijalno ugrožavajuće stanje. Najčešće do ove komplikacije dolazi kod istovremene primene dva serotonergična leka koji prekomerno povise nivo serotonina u organizmu. Najčešće se primena SSRI (selektivni inhibitori ponovnog preuzimanja serotonina) i SNRI (inhibitori ponovnog preuzimanja serotonina i noradrenalina), kao i IMAO (irezverzibilni inhibitori monoaminooksidaze) povezuju sa pojavom serotoninskog sindroma, najčešće u kombinaciji sa drugim serotonergičnim sredstvima.

Prikaz slučaja: Pacijentkinja kojoj je zbog depresivne epizode ordiniran sertralin (SSRI) tokom lečenja je u saobraćajnoj nesreći zadobila prelome, te joj je zbog bolova ordiniran tramadol. Obzirom da oba leka imaju tendenciju da povećaju nivo setotonina u telu, razvila se komplikacija u vidu serotoninskog sindroma. Pravovremenim prepoznavanjem i tretmanom, simptomi serotoninskog sindroma su se povukli bez trajnih posledica.

Zaključak: Brojni lekovi i supstance mogu da uzrokuju serotoninski sindrom, najčešće u kombinaciji sa antidepresivima. Od velike važnosti je stoga da se lekari informišu o komorbidnim stanjima koje iziskuju primenu navedenih lekova kako bi se serotoninski sindrom prevenirao, a ukoliko se javi kako bi se adekvatno i uspešno lečio.

Ključne reči: serotoninski sindrom, rizik-lečenje, serotonin, SSRI, SNRI

REFERENCES


*Accepted papers are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of Sanamed. The final text of the article may be changed before the final publication. Accepted papers can already be cited using the year of online publication and the DOI, as follows: the author’s last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI. When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

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