Differentiating serotonin syndrome and neuroleptic malignant syndrome

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ABSTRACT

Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are two rare, but serious adverse reactions associated with psychotropic medications. While the disorders may share certain features, there are differences in how they are managed and treated. This article reviews the risk factors, clinical presentation, and treatment of SS and NMS.

KEYWORDS

serotonin syndrome, neuroleptic malignant syndrome, psychotropic, adverse effect

INTRODUCTION

Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are two rare, but potentially life-threatening adverse reactions of psychotropics that have gained attention over the past few decades. These two medication-induced disorders share certain clinical features/manifestations. Differentiating between these serious disorders is crucial due to differences in their management and treatment. It is important to raise awareness about the similarities and distinguishing factors in their presentation.1

SS generally develops from concurrent use of multiple serotonergic agents; however, it can also occur after initiation of a single serotoninergic agent. Drug interactions that result in excess serotonin in the central nervous system (CNS) may also precipitate serotonin syndrome.2-4

There are several theories as to the mechanism of SS. Elevated levels of serotonin can occur due to drugs that cause an increase in release, decreased uptake or metabolism of serotonin, or excess serotonin precursors or agonists. Medications and drug classes that are implicated in occurrences of SS include the following: TCAs, SSRIs, SNRIs, MAOIs, triptans, nefazodone, buspirone, mirtazapine, carbamazepine, tramadol, linezolid, MDMA (ecstasy), dextromethorphan, St. John's wort, lithium, methadone, cocaine, levodopa, reserpine, and amphetamines.3-4 The incidence of SS with the use of these various agents is largely unknown.5

NMS is precipitated by use of neuroleptic agents. The incidence of NMS varies with a range of 0.02-2.4% in patients being treated with neuroleptics.6 These agents include dopamine antagonists such as antipsychotics and antiemetics. Also, abrupt withdrawal of dopamine agonists, for instance, those used in the management of Parkinson's disease, may produce signs and symptoms correlating with NMS. Interestingly, NMS does not necessarily correspond with high doses of antipsychotics, as it can occur with lower doses as well.3,7

RISK FACTORS

SS. Concurrent use of serotonergic agents has been the solitary risk factor identified in SS as of late.2,3 A list of agents that may be associated with SS can be found in Table 1.1 The individual risk with each serotonergic medication listed in the table is largely unknown, but avoiding concomitant use of multiple serotonin enhancing medications can help minimize the risk of developing SS.3,8 Talarico et al presented two cases of SS due to drug interactions involving use of citalopram with two CYP 2D6 inhibitors, cimetidine and topiramate. Each patient's symptoms resolved within a week of discontinuation of the offending agents.8

Another risk for SS may be with use of illicit drugs, especially when used in patients concurrently taking a serotonin enhancing drug.9-11 One case, reported by Jokovic, showed that “bath salts,” a synthetic derivative of cathinone, induced a state of serotonin toxicity. Cathinone is a naturally occurring psychostimulant. These synthetic cathinones are believed to enhance release of monoamines and block their reuptake, resulting in symptoms consistent with SS. Additionally, use of cocaine in patients taking antidepressants, specifically SSRIs, was found to be one of the most common causes of serotonin toxicity.11 MDMA used concomitantly with other drugs has been connected with a number of fatalities. MDMA exerts its effects via increasing neurotransmitters, serotonin, norepinephrine, and dopamine, in the CNS. Combining MDMA with other serotonin-modifying agents increases the risk of fatalities due to serotonin toxicity.12

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Table 1. Examples of medications that may precipitate serotonin syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>phenelzine, tranylcypromine, isocarboxazid, moclobemide, nialamide, iproniazid, selegiline, procarbazine, linezolid</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCAs)</td>
<td>clomipramine, imipramine, amitriptyline, nortriptyline</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</td>
<td>Venlafaxine, duloxetine, milnacipran</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines, amphetamine derivatives, MDMA</td>
</tr>
<tr>
<td>Serotonin antagonists</td>
<td>Ondansetron, granisetron</td>
</tr>
<tr>
<td>Other serotonin modulators</td>
<td>Nefazodone, vilazodone</td>
</tr>
<tr>
<td>Herbal products</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Antimigraine agents</td>
<td>Triptans</td>
</tr>
</tbody>
</table>

NMS. Common risk factors for NMS identified in literature include use of first- &/or second-generation antipsychotics (FGA, SGA). Use of higher doses of FGA & SGA, rapid escalation of dosing, switching among agents, higher potency agents, and long-acting depot formulations are also risk factors for developing NMS that have been recognized in case studies. NMS may also precipitate from medications that are not antipsychotics, which can also antagonize the actions of dopamine.

Table 2 provides a list of medications associated with NMS.

First-generation and second-generation antipsychotics are dopamine receptor antagonists, which produce a state of dopaminergic hypofunction. NMS can occur after a single dose of an agent or after years of treatment with the same agent. Development of this syndrome is idiosyncratic. Case series demonstrate that the probability of developing NMS increases with higher doses of antipsychotics or in those patients exposed to higher doses titrated faster than the normal rate. Multiple IM injections can increase the probability of producing NMS and have been implicated in case-control studies. It remains uncertain as to whether higher potency agents are a definitive risk factor for NMS. However, it has been noted that patients with prior history of NMS are at an increased risk for recurrence.

Table 2. Medications associated with neuroleptic malignant syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical antipsychotics</td>
<td>pimozide, droperidol, haloperidol, fluphenazine, trifluoperazine, thiothixene, perphenazine, loxapine, molindone, mesoridazine, thiioridazine, chlorpromazine</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole</td>
</tr>
<tr>
<td>Other dopamine antagonists</td>
<td>metoclopramide, prochlorperazine, promethazine</td>
</tr>
</tbody>
</table>

CLINICAL PRESENTATION

SS. Diagnosis of SS is essentially a subjective decision since there are no laboratory tests to confirm diagnosis. For that reason, a detailed past medical history and physical examination are vital to obtain with each case that presents with clinical findings suggestive of SS. Sternbach Criteria and the Hunter Serotonin Toxicity Criteria are two different sets of diagnostic criteria used to help define and recognize patients with SS. The Hunter Criteria (Table 3) is the most recent set of diagnostic criteria developed and appears to be more accurate than the original Sternbach criteria. Description of symptoms, onset of symptoms, and the rate of changes are essential for differential diagnosis. SS usually presents within 24 hours of initiation or change in a medication. The course of the syndrome typically lasts less than a week and may spontaneously resolve.

Table 3. The Hunter Serotonin Toxicity Criteria

- Diagnosis of serotonin toxicity can be made if patient is taking a serotoninergic agents and has one of the following:
  - Spontaneous clonus is present
  - Inducible or ocular clonus and agitation or diaphoresis is present
  - Inducible or ocular clonus and hypertonia and temperature >38°C are present
  - Tremor and hyperreflexia are present

According to various case reports, signs and symptoms of SS can be classified into three general areas: alteration in mental status, autonomic nervous system disturbances, and neurologic manifestations. Mental status changes may involve restlessness, mood changes, agitated delirium, anxiety, and disorientation. Autonomic disturbances such as tachycardia, diaphoresis, hyperthermia, fluctuating blood pressure, nausea, emesis, diarrhea, tachypnea, and mydriasis are signs and symptoms that may present depending on the degree of severity of the syndrome. Manifestations of
Neuromuscular findings may include deep tendon hyperreflexia, tremor, muscular rigidity, myoclonus, and ataxia. Patients’ symptoms are often variable. The degree of serotonergic activity in the presenting patient may be reflected by the intensity of clinical findings and help direct management.1,4,7,8,16

NMS. Neuroleptic malignant syndrome is generally characterized by a variety of symptoms, some of which may be shared with SS. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for NMS include the following symptoms: severe muscle rigidity, hyperpyrexia (>38°C), mental status alteration, and autonomic instability. Changes in mental status usually present as agitated delirium and confusion in a majority of patients.7,18 Fluctuations in blood pressure, along with tachycardia, are typical signs of autonomic dysregulation. In contrast to SS, patients with NMS present with “lead pipe” muscle rigidity as well as hyporeflexia.3,14,19 Table 4 outlines the overlapping and discriminating symptoms of the two syndromes.27 Rapid, increasing signs of extrapyramidal symptoms (EPS) is an important key feature of NMS. EPS, associated with conventional antipsychotics, occurs in about 95% of NMS cases. The potential for atypicals to produce EPS symptoms in NMS is comparable to that of conventional antipsychotics.6 NMS generally presents within 1-3 days of exposure to a dopamine antagonist or withdrawal of a dopamine agonist. A laboratory profile of a patient with NMS should exhibit low serum iron levels, and considerably elevated creatine kinase (CK) and white blood cells.13,18,19 Laboratory findings may be useful in differentiating the two syndromes.

TREATMENT
SS. The mainstay of therapy for SS is supportive care, which may involve oxygen administration, normalization of vital signs, continuous cardiac monitoring, and administration of intravenous fluids (Table 5).3,4 Patients with labile blood pressure should be treated with short acting agents such as esmolol or nitroprusside, while avoiding the longer acting agents to prevent prolonged hypotension. Patients suffering from hypotension due to MAOI therapy can be treated with low-doses of norepinephrine, epinephrine, or phenylephrine. Benzodiazepines may be used for sedation to help control agitation. Patients with a temperature of 41°C or higher should be intubated and active cooling measures should be initiated as needed. Also, appropriate administration of cyproheptadine may be an option if supportive care fails to improve symptoms. Treatment of SS with bromocriptine, dantrolene, or propranolol is not recommended.1-4

NMS. Due to lack of FDA-approved treatments for NMS, recommendations often originate from case series. Dopamine antagonists should be discontinued immediately in patients suspected of NMS (Table 6).7,14 Like SS, the mainstay treatment of NMS is supportive care, which includes hydration via IV fluids, resolution of abnormal electrolytes, external cooling measures for severe hyperthermia, and management of end organ complications. Benzodiazepines such as lorazepam 1-2 mg IV every 4-6 hours can be considered in milder cases of NMS.7,13,14 Amantadine and bromocriptine are two dopaminergic agents that can be used in managing NMS as well. These drugs may help with reversal of symptoms such as rigidity, accelerate recovery, while decreasing mortality. Due to evidence of NMS recurrence when bromocriptine was withdrawn too early, case reports propose that it should be used for 10 days, even after symptoms have resolved.1,7,21

Table 4. Characteristics of SS and NMS5,7

<table>
<thead>
<tr>
<th></th>
<th>Serotonin Syndrome</th>
<th>Neuroleptic Malignant Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitated by</td>
<td>Serotonergic agents</td>
<td>Dopamine antagonists</td>
</tr>
<tr>
<td>Onset</td>
<td>Variable, usually &lt; 24 hours</td>
<td>Variable</td>
</tr>
<tr>
<td>Similar features</td>
<td>Vital signs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTN, tachycardia, tachypnea, hyperthermia (&gt;40°C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucosa</td>
<td>Sialorrhea</td>
</tr>
<tr>
<td>Overlapping features</td>
<td>Skin</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td></td>
<td>Variable: agitated state, coma</td>
<td>Diaphoresis, pallor</td>
</tr>
<tr>
<td></td>
<td>Mental status</td>
<td>Variable: stupor, coma, alertiveness, delirium</td>
</tr>
<tr>
<td></td>
<td>Muscles</td>
<td>“Lead pipe” rigidity in all muscle groups</td>
</tr>
<tr>
<td></td>
<td>Increased tone, particularly in lower extremities</td>
<td></td>
</tr>
<tr>
<td>Differentiating features</td>
<td>Reflexes</td>
<td>Hyperreflexia, clonus</td>
</tr>
<tr>
<td></td>
<td>Hyperactive</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td></td>
<td>Pupils</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Bowel sounds</td>
<td>Normal, decreased</td>
</tr>
</tbody>
</table>

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Table 5. Treatment of serotonin syndrome

- Discontinuation of serotonergic agents
- Provide supportive care:
  - Oxygen therapy, IV fluids, continuous cardiac monitoring
- Use of benzodiazepines such as lorazepam to help eliminate agitation, neuromuscular abnormalities, and correction of mild increases in HR and BP.
- Hyperthermia should be treated with standard measures, while avoiding antipyretics such as APAP. Patients with temperature of >41°C should be sedated and intubated.
- Cyproheptadine may be administered if supportive care fails to relieve symptoms and improve vital signs.

Table 6. Treatment of NMS

- Discontinuation of dopaminergic antagonists
- Provide supportive care:
  - IV fluids, resolution of electrolyte abnormalities, external cooling for hyperthermia, management of complication such as cardiovascular, respiratory, &/or renal failure, & coagulopathies
- Use of benzodiazepines such as lorazepam to help improve catatonic symptoms (mutism, immobility).
- Severe hyperthermia should be treated with external cooling measures.
- Dopamine agonists such as Bromocriptine (initiate at 2.5 mg BID- TID, up to 45 mg/day) or amantadine (200-400 mg/day in divided doses) may be used to help reverse NMS symptoms.
- Dantrolene, a skeletal muscle relaxant (1-2.5 mg/kg IV, then 1 mg/kg Q6 hours if symptoms reduce with 1st dose), may also be used to relieve symptoms of “lead-pipe” rigidity. This medication can be administered with dopamine agonists.
- Electroconvulsive therapy for treatment-resistant patients with severe cases of NMS.

Dantrolene, a skeletal muscle relaxant, is also frequently used in case reports to help relieve NMS effects on the different muscle groups. Dantrolene is available in oral and intravenous forms and may be administered with the dopamine agonists listed above. However, due to cardiovascular adverse effects, dantrolene may not be given with calcium channel blockers.

Unlike SS, electroconvulsive therapy (ECT) has demonstrated effectiveness in resolving symptoms of NMS. ECT is generally reserved for severe cases in patients that have not responded to supportive care or pharmacological therapy. Case series involving ECT have shown improvement with muscle rigidity and reduction in the rate of mortality.

RECHALLENGE OF NEUROLEPTICS IN NMS

Recurrent NMS is a possibility for patients restarting neuroleptics. There is about a 30-50% risk of recurring NMS in patients who are rechallenged with antipsychotics. According to case reports, waiting at least two weeks after symptoms of NMS had resolved helped minimize risk of recurrence. Other approaches to preventing recurrence of NMS can be found in Table 7.

Table 7. Managing patients with a history of NMS.

- Rechallenge with a different antipsychotic class
- Wait a minimum of 2 weeks before rechallenge
- Rechallenge with lower potency neuroleptic
- Titration should be performed slowly, starting with lower doses
- Avoid concurrent administration of lithium carbonate
- Avoid dehydration
- Monitor frequently for s/s of NMS

CONCLUSION

SS and NMS are rare, serious medication-induced disorders with certain overlapping features. SS can present with restlessness, agitation, HTN, tachycardia, diarrhea, tremor, myoclonus, hyperreflexia, diaphoresis, hyperthermia, and tachypnea. Symptoms of patients presenting with NMS include: HTN, tachycardia, tachypnea, diaphoresis, stupor, hyperthermia, lead pipe rigidity, hyporeflexia, and decreased bowel sounds. The similarities in presentation can make diagnostic decisions problematic. Prompt recognition and discontinuation of the causative agents is imperative in preventing serious complications in both disorders. When considering treatment options, clinicians must be able to differentiate between the two syndromes since each condition is treated differently. Looking at the precipitating agents and laboratory findings may aid in making the correct diagnosis. Additionally, raising awareness among clinicians about SS and NMS can help increase early recognition and allow for prompt management.

REFERENCES