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REVIEW ARTICLE

Serotonin syndrome vs neuroleptic malignant syndrome: A contrast of causes, diagnoses, and management

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BACKGROUND: Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are uncommon but potentially life-threatening adverse reactions associated with psychotropic medications. Polypharmacy and the similar presentation of SS and NMS make diagnosis of the 2 syndromes problematic.

METHODS: A MEDLINE search was performed for the period 1960 to 2011 for case reports, review articles, and studies pertaining to SS and NMS.

RESULTS: The majority of available literature on SS and NMS consists of case reports, case-control studies, and retrospective reviews. In addition, diagnostic criteria have been developed to aid in the diagnosis and management of SS and NMS.

CONCLUSIONS: SS presents as mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia. Similarly, NMS presents as muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability. However, the clinical laboratory profile of elevations in creatine kinase, liver function tests (lactate dehydrogenase, aspartate transaminase), and white blood cell count, coupled with a low serum iron level, distinguishes NMS from SS among patients taking neuroleptic and serotonin agonist medications simultaneously. For both SS and NMS, immediate discontinuation of the causative agent is the primary treatment, along with supportive care. For NMS, dantrolene is the most effective evidence-based drug treatment whereas there are no evidence-based drug treatments for SS. A 2-week washout of neuroleptic medication minimizes the chance of recurrence.

KEYWORDS: differential diagnosis, neuroleptic malignant syndrome, serotonin syndrome

INTRODUCTION

Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are potentially life-threatening adverse reactions to psychotropics. SS originates from an excess of CNS serotonin (5-HT), usually because of serotonin agonist polypharmacy or drug-drug interactions involving serotonin agonist drugs.[1] In 1991, Sternbach presented the first comprehensive SS review that characterized the presentation of 38 patients drawn from 12 clinical reports.[2] The incidence of SS is unknown because many cases go unrecognized and/or unreported. On the other hand, any drug that is a dopamine antagonist is capable of precipitating NMS, which was first reported as an adverse drug reaction associated with the antipsychotic haloperidol in 1960.[3,4] NMS frequency estimates range from 0.07% to 2.2%.[5-8] Factors that explain the frequency variance include differing diagnostic criteria, misdiagnosis as SS, duration of antipsychotic exposure, and variable antipsychotic dosing practices. One group reported decreasing the NMS rate in a hospital population from 1.1% during an initial 31-month survey period to 0.15% over a subsequent 47-month period simply by making the staff aware of NMS risk factors.[8] Because of common polypharmacy of serotonin agonist and dopamine antagonist agents among individual mental health patients and the similarity of the presentation in SS and NMS, the diagnosis and treatment of these syndromes can be problematic. Our goal is to sort out the diagnostic and treatment confusion.

Etiology and pathophysiology

SS. Case reports indicate that SS is most likely to occur when serotonin agonist drugs are combined in patient treatment. Specific drug classes and drugs include the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs, ie, venlafaxine, duloxetine), triptans, trazodone, nefazodone, L-tryptophan, meperidine, buspirone, carbamazepine, mirtazapine, tramadol, linezolid, and methylenedioxymethamphetamine (MDMA or Ecstasy).[9,10]

In 1960, SS was described as an "indolamine syndrome" that was thought to be caused by elevations in serotonin and tryptamine.[11] The syndrome presented in patients receiving an MAOI and L-tryptophan concurrently.[11] Although many theories have been proposed for the mechanism of SS, the most creditable is that excess 5-HT in the CNS, which may occur because of excess precursors of 5-HT and its agonists, increase release of 5-HT, decrease uptake of 5-HT, and/or slow 5-HT metabolism.

NMS. As stated, all dopamine-blocking drugs are capable of precipitating NMS.[5-7] Even clozapine, an antipsychotic with very low affinity for dopamine-2 (D2) receptors in the nigrostriatal tracts, has been associated with at least 14 cases of NMS.[12-15] Additionally, the abrupt withdrawal of dopaminergic agonist drugs used to treat Huntington's disease and Parkinson's disease, such as levodopa[16] and amantadine,[17] has been shown to produce NMS-like conditions.

Numerous hypotheses have been proposed to explain the pharmacologic mechanisms of NMS. However, distillation of these hypotheses results in 2 divergent explanations of NMS pathophysiology. The first emphasizes CNS neurotransmission aberrations and the role of dopaminergic hypofunction in particular.[18] The second endorses peripheral sympathetic autonomic nervous system hyperactivity as the primary culprit.[19] Regardless, none of the hypothesized mechanisms fully explain the signs and symptoms of NMS.[20]

Risk factors

SS. Specific risks factors for SS have not been identified beyond serotonin agonist polypharmacy, such as the potentially fatal combination of an MAOI and an SSRI. Therefore, simply avoiding serotonin agonist polypharmacy can minimize risk.

NMS. Proposed NMS risk factors include exposure to high-affinity D2 receptor drugs, the presence of psychomotor agitation, the use of long-acting depot antipsychotics, neuroleptic polypharmacy, genetic predisposition, external heat load, sex, age, and history of NMS.[20] Unfortunately, assessing the clinical importance of the many proposed risk factors for NMS is difficult because of the conflicting and uncontrolled data in NMS literature. In many cases, it is not apparent if the risk factors truly are related to NMS or if they are simply a confounding variable resulting from some other aspect of the case.

First- vs second-generation antipsychotics. NMS is associated with both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), simply because they are all D2 receptor antagonists. Early clinical hypotheses that SGAs might be "NMS-proof" were unfounded. There are case reports of SGA-induced NMS. A series of 44 cases of NMS associated

with use of the SGAs clozapine, risperidone, and olanzapine concluded that one-third of these cases met stringent criteria for NMS.[21] The SGAs were less commonly associated with a temperature >38°C ($P < .05$) and 40°C ($P < .01$) compared with FGAs. However, the temperature difference may be an artifact, because more recent cases of NMS are diagnosed earlier and do not progress to hyperthermia. It is difficult to determine if the incidence of NMS will be reduced with the increased use of SGAs because comparative trials would require at least 500 exposures to detect a single case of NMS because of the rarity of its occurrence.

Antipsychotic dose and intramuscular antipsychotics vs psychomotor agitation. Higher doses of antipsychotics are a risk factor for developing NMS. Affected patients usually are exposed to higher antipsychotic doses titrated upward at a faster than normal rate, oftentimes as multiple intramuscular (IM) injections in agitated patients.[20] Two case-control studies of 18 and 15 NMS cases vs 36 and 45 controls, respectively, verified that acute IM antipsychotic exposure increases NMS risk, with an odds ratio of 35.7 in the latter study.[20,22] The case-control studies reported a correlation between psychomotor agitation and NMS. This may be a classic case of the logical fallacy that correlation proves causation. The studies indirectly demonstrate that agitated patients were administered significantly higher doses of antipsychotics, thereby increasing the probability of developing NMS.

Antipsychotic potency. Although it has been suggested that high-potency antipsychotics such as haloperidol vs low-potency antipsychotics such as chlorpromazine are a risk factor for developing NMS,[23,24] this hypothesis remains to be proven. The suggestion likely is related to the clinical observation that haloperidol is more commonly prescribed for agitation than chlorpromazine because of the latter agent's dose-limiting side effect of orthostatic hypotension.

History of NMS. Patients with a history of NMS are at increased risk for recurrence. This issue is discussed in detail in the section titled "Rechallenge."

Concomitant medications. Not surprisingly, more than one-half of reported NMS cases involved concomitant psychotropics.[20,25,26] Of particular interest is the antipsychotic-lithium combination, which was thought to predispose patients to NMS. Two case-control studies failed to confirm that the antipsychotic-lithium combination is associated with increased NMS risk.[20,26]

Malignant hyperthermia. Despite the clinical similarities between NMS and malignant hyperthermia (MH), little evidence supports a relationship between these disorders. A review of 48 patients with a history of NMS showed that none experienced MH after receiving anesthesia.[27] Other studies have used a standard in vitro test to identify patients who are susceptible to MH, and patients with a history of NMS were not found to be susceptible.[28,29] Despite these negative findings, some clinicians recommend a conservative approach to using anesthesia in patients with a history of NMS.[30,31] This includes using a competitive neuromuscular blocker to reduce muscle tone and prevent musculoskeletal damage during the tonic phase.[30] Additionally, succinylcholine should be avoided because of its potential to cause rhabdomyolysis and hyperkalemia in patients with active muscle disease.[30]

Studies have failed to confirm the other proposed risk factors of age, sex, external heat load, and use of depot antipsychotics. NMS has been reported in all age groups,[20] with 55 cases of NMS reported in children.[32-34] Clinical presentation was similar to adults. The postulation that men are more likely than women to experience NMS, although unproven, may be indirectly related to men usually receiving a larger IM dose when agitated. The suggestion that high environmental temperatures are a risk factor for NMS[35] was not supported by a case-control study of 37 NMS cases.[36] Finally, despite a study suggesting depot antipsychotics increase the NMS risk,[26] 2 subsequent case-control studies failed to confirm this finding.[20,22] Therefore, the only legitimate risk factor that appears to be sustained after rigorous scrutiny is the exposure of affected patients to rapidly escalating neuroleptic doses.

Clinical presentation

SS. SS varies significantly among patients in its clinical presentation. It was not until 1991 that the term *serotonin syndrome* appeared in medical literature.[2] In a report of 12 SS cases, Sternbach[2] categorized the presenting signs and symptoms into the 3 general areas of mental status changes, autonomic nervous system disturbances, and neurologic manifestations. Mental status changes, including mood changes and a clouded sensorium, were observed in the majority of cases (82%), whereas restlessness and agitation were seen in the minority of cases (28%). Autonomic disturbances included tachycardia, diaphoresis, labile blood pressure, shivering, tachypnea, mydriasis, and sialorrhea. Hyperthermia occurred in

34% of cases and was associated with increased severity. Neurologic manifestations included tremor, myoclonus, hyperreflexia, ankle clonus, muscle rigidity, and ataxia.

After the first SS case series report (n = 12) by Sternbach in 1991, Keck et al summarized the 133 subsequent case reports consisting of 168 patients.[37] Highly variable mental status changes occurred in 85% of patients. Symptoms ranged from anxiety, agitation, mood and affect changes, and delirium, to coma. Changes in vital functions included labile blood pressure, hyperthermia, tachycardia, and tachypnea. Mydriasis and sialorrhea also were described. Laboratory abnormalities were identified as nonspecific or secondary to complications of the syndrome. Leukocytosis occurred in 8% of cases. Rhabdomyolysis occurred in 27% of cases and was associated with increased creatine kinase (CK) levels secondary to muscle rigidity and damage. Rhabdomyolysis advanced to myoglobinuria-induced renal failure in 4% of the cases. Six cases presented with elevated serum hepatic enzymes; 3 were fatal.[37]

NMS. Similar to SS, there is substantial variation in NMS clinical presentations. Most, but not all, NMS patients exhibit the 4 cardinal symptoms: muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability.[23] "Lead pipe" rigidity is the most common neurologic finding, but rigidity may present in a less severe form, such as akinesia, dyskinesia, waxy flexibility, or cogwheel rigidity.[38] Fever or hyperpyrexia usually exceeds 38°C and occasionally exceeds 41°C.[23] Mental status changes include stupor, coma, delirium, and catatonia. Autonomic instability presents as tachycardia and fluctuations in blood pressure, with or without respiratory distress.[23] NMS resulting from SGA vs FGA exposure may differ in presentation severity; one report noted that 40% of patients did not have muscle rigidity, and temperature and CK increases were not as pronounced.[13]

The extreme skeletal muscle rigidity resulting in muscle necrosis explains the commonly observed elevations in CK, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).[36] In cases of severe muscle damage, rhabdomyolysis and myoglobinuria may lead to renal failure.[38] In one prospective study of NMS, leukocytosis was observed in 15 of 20 cases, with white blood cell (WBC) counts usually ranging from 10,000 to 20,000/mm^3, with an upper limit of 40,000/mm^3.[25] Concomitant lithium treatment contributed to the WBC counts >20,000/mm^3. Low serum iron levels are associated with NMS.[40] A study of patients with catatonic rigidity discovered that low serum iron levels were observed in all patients who developed NMS, whereas no patients with normal serum iron progressed to NMS.[40] Iron is a cofactor for tyrosine hydroxylase, the enzyme that mediates the rate-limiting step of catecholamine synthesis. Therefore, an iron deficiency should result in decreased synthesis of dopamine, which would be exacerbated by dopamine antagonist drugs.[41] A snapshot of the prevalence of the clinical features and laboratory abnormalities of NMS can be discerned from 24 consecutive cases of NMS collected between 1981 and 1987.[25] Hyperthermia, tachycardia, delirium, diffuse slowing of electroencephalogram (in 7 patients), and diaphoresis were seen in all patients. Nearly all patients experienced rigidity (96%), muteness (96%), dehydration (92%), and tremulousness (92%). Less commonly observed presenting signs and symptoms were incontinence (54%), hypertension (42%), labile blood pressure (33%), and dyspnea (29%). Laboratory abnormalities included elevations in low serum iron (95%), proteinuria (91%), CK (91%), LDH (91%), AST (83%), leukocytosis (75%), myoglobinuria (67%), ALT (59%), and thrombocytosis (56%).

The diagnostic confusion associated with differentiating NMS from SS stems from the 4 cardinal NMS symptoms of muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability also being present, although to a lesser degree of severity, in SS patients. This issue becomes a diagnostic dilemma in patients simultaneously receiving serotonin agonist and dopamine antagonist drugs. The overlap of signs and symptoms confuses the differential diagnosis, whereas the clinical laboratory results are enlightening. A laboratory profile that includes elevated low serum iron, proteinuria, CK, LDH, AST, and leukocytosis occurs in ≥75% of NMS cases. Therefore, it is recommended that particular attention be given to the laboratory data during the differential diagnosis of NMS and SS.

Course

The serotonin drug agonist polypharmacy insult that precipitates SS travels a transient course usually lasting <1 week and can resolve spontaneously despite continued serotonin agonist exposure. However, although rare, fatalities can result from myoglobinuria-induced renal failure, generalized seizures, and disseminated intravascular coagulation. In the Keck et al summary of the SS literature,[37] generalized seizures were fatal in 6 of 14 sei-

zure-related cases and 3 of 4 disseminated intravascular coagulation-related cases.

NMS usually occurs 1 to 2 weeks after the start of therapy or after a significant and abrupt increase of the antipsychotic dose.[23] The frequency of mortality resulting from NMS is difficult to calculate. In a retrospective review of 202 NMS cases, the mortality rate was 18.8%.[42] When stratified by date of publication, the mortality rates were 28% before 1980, 23% from 1980 to 1983, and 12% from 1984 to 1987. The downward trend likely is a result of better diagnosis and treatment. Predictors of mortality were myoglobinuria (47%) and rhabdomyolysis (56%). In 54 prospectively evaluated NMS cases, no deaths were reported.[5,6,25,26,43] These data suggest that retrospective reviews of case reports overestimate true NMS mortality, perhaps because severe and fatal cases of NMS are more likely to be reported than mild cases.

Differential diagnosis

Similar to all drug toxicity reactions, SS and NMS are diagnoses of exclusion. Disorders to be ruled out include infection, tumor, seizure, acute lethal catatonia, MH, and anticholinergic drug intoxication. Given the similarity in presentation and symptoms of NMS and SS, the most effective approach to distinguishing between these syndromes is to obtain an accurate medication history. Medication histories that are positive for both serotonin agonist and dopamine antagonist drugs are problematic. However, more severely ill patients should lead the clinician to suspect NMS rather than SS. Additionally, multiple diagnostic criteria are available to assist in diagnosis.

Three sets of diagnostic criteria for SS have been described. Sternbach suggested that criteria should include at least 3 of the following features for diagnosis: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.[2] Radomski et al developed a second criterion for SS.[44] After ruling out psychiatric, infectious, metabolic, endocrine, or toxic causes, the diagnosis requires the presence of ≥4 major symptoms or 3 major and 2 minor symptoms after addition or dosage increase of a serotonergic agent to an established serotonergic treatment. Major symptoms include consciousness impairment, elevated mood, coma, myoclonus, tremor, shivering, rigidity, hyperreflexia, and fever. Minor symptoms include restlessness, insomnia, impaired coordination, mydriasis, akathisia, and tachycardia. Lastly, the clinician must ensure that there was no initiation or dosage increase of antipsychotic treatment before symptom presentation. The most recent set of diagnostic criteria for SS are the Hunter Serotonin Toxicity Criteria.[45] The Hunter criteria require one of the following features or groups of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature >100.4°F, and ocular or inducible clonus.

There are various sets of criteria to aid in the diagnosis of NMS.[46] These are primarily useful as a research tool to help assure consistent diagnosis of NMS. However, the clinical diagnostic standard is set by DSM-IV-TR criteria. For a diagnosis of NMS,[47] the required criteria are the development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic/antipsychotic medications not caused other substances, medical conditions, or mental disorders. Additionally, ≥2 of the following symptoms must be present: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, labile blood pressure, leukocytosis, and evidence of muscle injury (elevated CK).[47] The DSM-IV-TR criteria are useful in differentiating NMS from SS.

Diagnostic considerations. By contrasting the NMS DSM-IV-TR criteria with the 3 sets of SS criteria, the following clues to the differential diagnosis emerge. Severe rigidity is suggestive of NMS, whereas any form of myoclonus suggests SS. Dramatically increased CK and WBC counts and low serum iron levels are laboratory findings more likely indicative of NMS, whereas no laboratory findings are particularly helpful for identifying SS. Gastrointestinal symptoms of nausea, vomiting, and diarrhea are more likely to be indicative of serotonin hyperactivity, whereas these findings usually are not seen with NMS. Finally, changes in vital functions and mental status are common to both disorders, limiting the value of these changes in differential diagnosis.

Treatment

SS. Non-evidence-based symptomatic treatment agents include dantrolene for hyperthermia induced by muscle contraction. There are no controlled trials because of the inherent ethical and logistical issues of conducting controlled drug toxicity treatment trials. Signs and symptoms of SS usually resolve within 1 week of discontinuing

or reducing the dose of the causative drug. Case reports theorize that cyproheptadine, a serotonin and histamine antagonist, is a potentially effective antidote.[48] An SS management guideline was developed that recommends discontinuation or dose reduction of the offending agent and supportive measures as needed.[44] Symptomatic treatment agents include dantrolene for hyperthermia induced by muscle contraction, benzodiazepines for muscle rigidity, anticonvulsants for seizures, and appropriate cardiac medications for labile blood pressure. Propranolol and cyproheptadine also were suggested as adjunctive therapy, along with ventilation for neuromuscular paralysis and dialysis for kidney failure in severe cases.

NMS. NMS becomes a self-limiting condition after the offending agent has been discontinued. Most sources suggest that NMS will resolve completely with supportive care within 1 to 2 weeks unless a depot antipsychotic is involved.[21]

Supportive care. Discontinuation of the causative agent is the single most important NMS treatment intervention. Continued successful neuroleptic treatment of psychotic patients has been reported,[49] but other reports suggest that this practice is associated with an unfavorable outcome.[5,8,27] As-needed supportive measures of fluid replacement, fever reduction, and support of cardiac, respiratory, and renal function are indicated. Uncommon complications such as pneumonia and thromboembolism may require rigorous monitoring, and severe cases of renal failure may require hemodialysis. NMS-induced hyperthermia may be difficult to treat using traditional methods. Endovascular and external cooling techniques for patients who fail antipyretic medications has been proposed.[50]

Pharmacologic treatments. Dopamine agonists and skeletal muscle relaxants are the 2 most common pharmacologic treatments for NMS.[51] Dopaminergic drugs such as bromocriptine or amantadine are used to counteract the dopamine blockade that produces the NMS symptoms. Dantrolene is a skeletal muscle relaxant used to decrease rigidity and, possibly, fever.

In a literature search, Sakkas et al identified 734 NMS cases that were treated with supportive care alone or bromocriptine, dantrolene, or amantadine alone or in combination with other specific treatments.[51] The diagnostic criteria used to identify cases of NMS were not reported. The 3 outcome efficacy measures were the reporting clinician's opinion of improvement rate, recurrence of NMS after discontinuation of specific treatment, and mortality. Among these 3 outcomes measures, recurrence of NMS following discontinuation of a specific treatment was the most useful because these cases included an objective measure of the specific treatments' effects, eg, recurrence of fever, rigidity, etc. The comparison of mortality rates between supportive care alone and a specific treatment is problematic because this study included every known case of NMS. Many of the historical cases were almost certainly treated differently from modern cases, because identification and treatment of NMS have improved over the years. In addition, because supportive care probably has improved since NMS was first reported, including older cases in the analysis would tend to make supportive care alone appear less effective than specific treatments that have only been used in recent years. Therefore, being aware of these methodological problems, the relapse rates for the single-drug treatments were 29% for amantadine, 18% for bromocriptine, and 6% for dantrolene. The supportive care mortality rate was 21% vs rates of 6%, 8%, and 9% for amantadine, bromocriptine, and dantrolene, respectively. Counter to these mortality figures is the analysis by Shalev et al of previously published case reports that concluded there were no differences between supportive care (7 of 52, 14%) and any specific treatment with amantadine, bromocriptine, or dantrolene alone or in combination (4 of 43, 9%).[42] However, this negative finding may result from a type 2 statistical error, in light of the findings of Sakkas et al.[51]

Electroconvulsive therapy (ECT). There are 2 case reports that consider the effectiveness of ECT for NMS.[27,52] Because ECT effectively treats acute lethal catatonia (ALC), it stands to reason that ECT might effectively reverse skeletal muscle rigidity in NMS. Mann et al found ECT effective in 20 of 27 cases and partially effective in 3 cases of ALC.[52] Two patients in this series developed serious cardiovascular complications during ECT, including cardiac arrest in one patient and ventricular fibrillation in the other. Therefore, it is not surprising that in the Davis et al NMS series, 24 of 29 patients improved with ECT. Three of these patients improved despite continued antipsychotic treatment.[27] Of the 5 nonresponders, all continued to receive antipsychotics. Trollor and Sachdev described 55 NMS cases treated with ECT.[53] The mean number of ECT treatments was 10, with the average onset of response occurring at 4 treatments. Of the cases in which ECT was

the primary treatment, the complete recovery rate was 63% and the partial recovery rate was 28%. The authors recommended ECT for severe NMS cases in which there is a high risk of complications, dysphoria with psychotic features is the primary disorder, and catatonia (muscle rigidity) is the major symptom. Although controversial, the use of anesthetic agents in NMS patients is feasible. Trollor and Sachdev noted that a muscle relaxant, usually succinylcholine, was used in 50% of cases. The use of succinylcholine did not result in MH or any laboratory abnormalities, although other case reports have reported these occurrences.[53]

Treatment recommendations. Bromocriptine and dantrolene are the 2 most widely used specific treatments for NMS. Bromocriptine, an inexpensive oral drug, directly opposes the dopamine effects of antipsychotics. However, this action may worsen a psychotic patient's mental status. Injectable dantrolene is reserved for patients who cannot take oral medication; a switch to oral dantrolene should be made as soon as possible. The most serious adverse effect of dantrolene is severe hepatotoxicity. Although rare, it may occur after prolonged exposure to high dosing. Although Shalev et al found no difference in efficacy between drug treatment and supportive therapy,[42] data from Sakkas et al are more compelling because of the larger size of the study population.[51] There is no evidence that combining ≥2 specific treatments improves response. Therefore, combinations are recommended only if a single agent has failed to produce a response.

Rechallenge

SS. There are no data regarding rechallenging a patient who has recovered from SS.

NMS. Patients with a history of NMS have a 30% to 50% risk of recurrence after antipsychotic rechallenge.[18,54-56] There is a strong inverse correlation between time to recurrence of NMS symptoms and time of antipsychotic rechallenge, according to a review of 41 cases.[56] If the antipsychotic was reintroduced within 5 days of resolution of the initial episode of NMS, the recurrence rate was 63%, whereas if >5 days had elapsed, the recurrence rate decreased to 30%. Of interest, 4 of 7 cases were successfully rechallenged using the same antipsychotic that initially caused NMS. It has also been reported that there is a higher recurrence rate if rechallenge occurs before resolution of NMS symptoms.[54] Caroff and Mann found that if a patient was switched to a low-potency antipsychotic (chlorpromazine, thioridazine, etc.), NMS recurrence rate decreased from 30% to 15%.[24] In a 15-patient series, 13 were rechallenged successfully with an antipsychotic.[18] Five patients (33%) experienced recurrence of NMS on the first rechallenge. In every case in which 2 weeks had elapsed after the episode of NMS, rechallenge was successful. Likewise, rechallenges were more likely to be successful if a lower dose of antipsychotic was used.

To date, only 1 case has been reported in the literature in which a patient experienced NMS and subsequently developed SS. The patient was a 24-year-old woman who experienced NMS after 6 days of treatment with haloperidol. Six years after the NMS incident, she developed SS within 24 hours after fluoxetine treatment. The patient died after failed attempts to treat SS.[57]

Most NMS patients require continued antipsychotic treatment. Approaches to preventing recurrence of NMS include reassessment of the indication for the antipsychotic, waiting 2 weeks after resolution of NMS before rechallenging, use of a different subclass of antipsychotic and/or an antipsychotic with a different potency, and rechallenge with the lowest possible dose with a slow titration. Alternative treatments for agitation, such as benzodiazepines, should be considered. Benzodiazepines may be effective alone for agitation or, if given in combination with an antipsychotic, also may allow for lowering of the antipsychotic dose. Finally, avoiding long-acting depot antipsychotics in patients with a history of NMS is advised.

CONCLUSIONS

SS presents as mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia. Similarly, NMS presents as muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability. However, the clinical laboratory profile of elevations in CK, liver function tests (LDH, AST), and WBC, coupled with a low serum iron level, distinguishes NMS from SS among patients taking neuroleptic and serotonin agonist medications simultaneously. For both SS and NMS, immediate discontinuation of the causative agent is the primary treatment, along with supportive care. For NMS, dantrolene is the most effective drug treatment. A 2-week washout of neuroleptic

medication minimizes the chance of recurrence. For SS, although symptomatic drug treatments are recommended, controlled clinical trials to support their use are unavailable. ■

DISCLOSURE: The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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