CE 1.5 ANCC CONTACT HOURS

Rx 0.5 PHARMACOLOGY CREDITS

Neuroleptic malignant syndrome: A case report

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Abstract: Electroconvulsive therapy (ECT) is an increasingly popular treatment for drug-resistant depression that may have utility for some patients with neuroleptic malignant syndrome (NMS) who are unresponsive to pharmacotherapy. Using a case study as an example, this article discusses the diagnosis of a patient with NMS, the use of ECT as a treatment for NMS, and the importance of nursing care for these patients.

Keywords: ECT, electroconvulsive therapy, neuroleptic malignant syndrome, NMS, pharmacotherapy

JD, 64, WAS ADMITTED TO THE ED with signs of a possible stroke. He had a history of schizophrenia, depression, hypertension, Alzheimer disease, dyslipidemia, benign prostatic hyperplasia, and obstructive sleep apnea. His schizophrenia and depression were managed with the antipsychotic quetiapine.[1] Recently, JD had also been placed on lithium (an antimanic agent) and haloperidol (a first-generation [typical] antipsychotic) to treat psychosis characterized by paranoia, hallucinations, thought disorganization, and religious delusions.[2]

According to his family, JD had become nonverbal and was "sitting and staring into space." Concerned that he might be having a stroke, they called emergency medical services after he became rigid and nonresponsive.

Upon admission to the ED, JD remained unresponsive to verbal stimuli, responding only to noxious stimuli with facial grimacing. JD's Glasgow coma scale (GCS) score was 7

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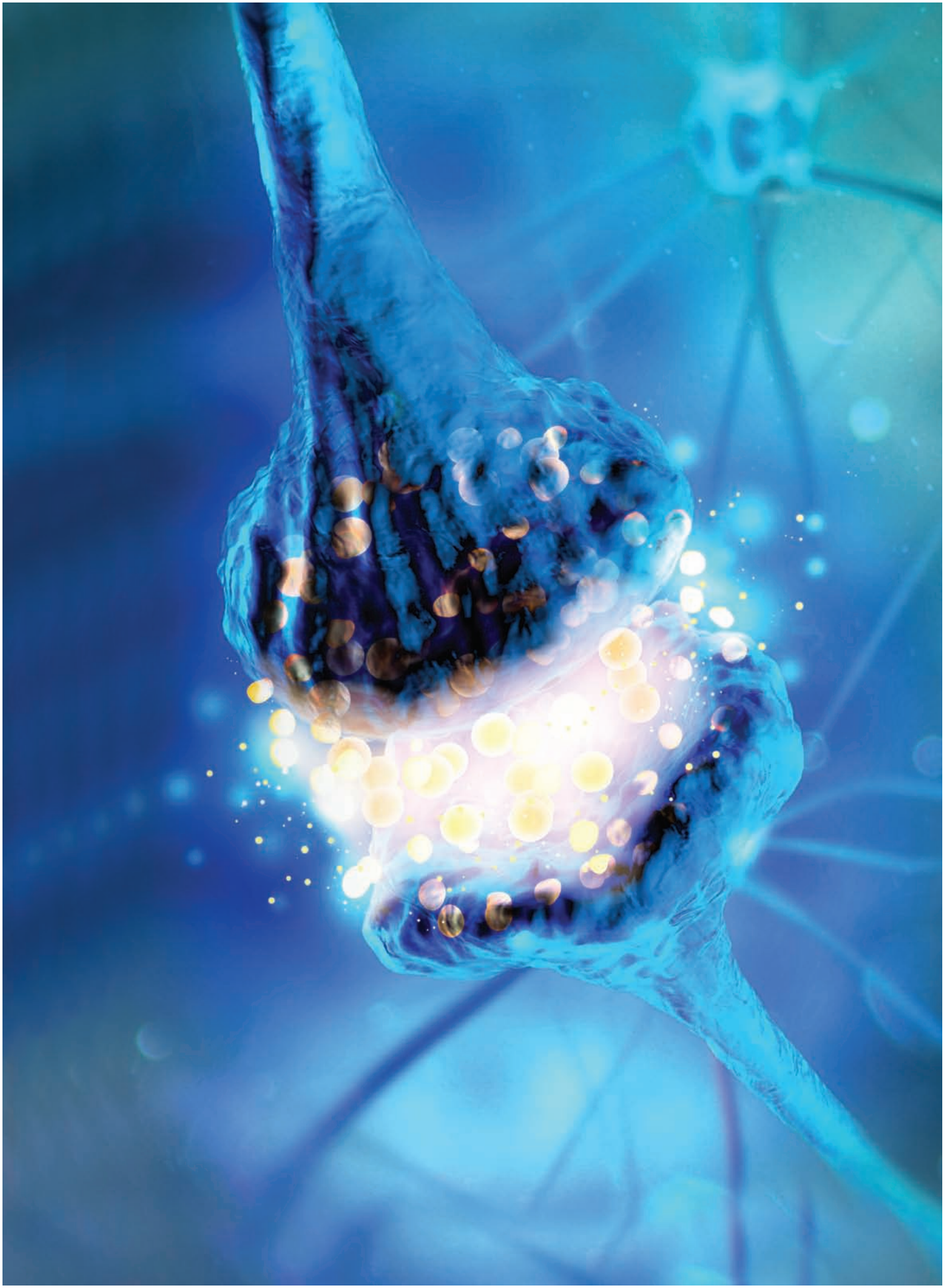


(see *Glasgow coma scale*). His vital signs included temperature, 104° F (40.0° C); sinus tachycardia, 137 beats/minute; respiratory rate, 28 breaths/minute; SpO_2, 92% on supplemental oxygen via nasal cannula at 2 L/minute; and BP, 158/88 mm Hg.[3] Other physical assessment findings included profuse diaphoresis and generalized muscular rigidity with superimposed tremor.[4]

JD's blood and urine specimen results showed no signs of an infection, but his serum creatine kinase (CK) levels were significantly elevated at 1,600 U/L (normal range, 38 to 174 U/L).[5] Computed tomography of the brain demonstrated no hemorrhage, arteriovenous malformation, tumor, midline shift, or other changes related to increased intracranial pressure. A lumbar puncture ruled out meningitis, encephalitis, bleeding, syphilis, and inflammatory disorders such as multiple sclerosis. JD was admitted to the neuroscience ICU (NSICU) for further management.

Glasgow coma scale[41]

Eye opening	
Spontaneous	4
Response to verbal command	3
Response to pain	2
None	1
Verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor response	
Follows commands	6
Localizing response to pain	5
Withdrawal response to pain	4
Flexion to pain	3
Extension to pain	2
None	1

The GCS is scored between 3 and 15, 3 being the worst and 15 the best. A score of 13 or higher correlates with mild brain injury, a score of 9 to 12 correlates with moderate injury, and a score of 8 or less represents severe brain injury.

Given his clinical manifestations, such as changes in mental status, muscular rigidity, hyperthermia, autonomic instability (tachycardia, tachypnea, profuse diaphoresis), and elevated serum CK levels, JD was diagnosed with neuroleptic malignant syndrome (NMS), likely caused by an adverse drug reaction related to haloperidol and antipsychotic medications.[4]

Using JD's case as an example, this article discusses the diagnosis and treatment of patients with NMS, including the use of electroconvulsive therapy (ECT). Although not considered a first-line treatment, ECT is an increasingly popular option for treating drug-resistant depression and may also be effective for patients with NMS who do not respond to pharmacotherapy.[4,6-8] This article highlights the importance of nursing care for patients with NMS who are treated with ECT.

Unpredictable and dangerous

NMS is an unpredictable and potentially fatal neurologic emergency that must be recognized and treated quickly.[6,7,9-11] It occurs in an estimated 0.2% to 3% of patients who have been prescribed antipsychotic (formerly called neuroleptic) medications.[4,11-15] It occurs in men more frequently than women by a ratio of 2 to 1 and may affect individuals of all ages.[16] With early recognition and prompt treatment, most patients will recover completely within 1 to 2 weeks.[9,10,13] Even with appropriate and timely treatment, however, mortality ranges from 10% to 20%.[14]

NMS is not a dose-dependent phenomenon. Rather, it is an idiosyncratic reaction to antipsychotic drugs that may occur after a single dose or one taken in the same quantity for many years.[4] It may also result from a dosage that is too high or increased too quickly. Additionally, it could be caused by a sudden change in medications that block dopamine, including antipsychotic agents such as risperidone, chlorpromazine, haloperidol, paliperidone, quetiapine, clozapine, and antiemetic agents such as metoclopramide and promethazine.[4,14-17]

An idiosyncratic reaction, or type B reaction, is an unpredictable adverse reaction to a drug that is not the consequence of a known pharmacologic property or patient allergy. Instead, it is an abnormal response to normal drug dosages that occurs unexpectedly due to genetic factors.[16,18] Symptom onset from these reactions typically occurs between 4 and 14 days after the initiation of a pharmacologic therapy, with 90% of patients developing symptoms within 10 days.[18]

Pathophysiology

Many researchers believe that NMS is caused by underlying pathophysiologic mechanisms and marked by sudden reductions in central dopaminergic activity due to blocked D2 dopamine receptors in the nigrostriatal, hypothalamic, and mesolimbic and cortical pathways.[16,18,19] It is associated with dopamine antagonist medications or rapid withdrawal from dopaminergic medications.[4,12,15,16] NMS is typically seen with antipsychotic agents such as haloperidol and fluphenazine.

Signs such as muscular rigidity and tremors are most likely due to interference with nigrostriatal dopamine pathways.[18-20] Sustained rigidity may lead to muscle breakdown, which releases myoglobin into the bloodstream. If not corrected, this can lead to myoglobinuria and acute kidney injury.[4,19,20] Muscle damage from tremors and prolonged rigidity leads to the release of CK into the bloodstream. Lab findings can validate the clinical manifestations of NMS, with more severe rigidity corresponding to elevations in a patient's CK levels. In patients with NMS, CK levels are usually more than 1,000 U/L, possibly reaching 100,000 U/L.[4]

Clinical manifestations of NMS are also related to sympathetic

nervous system hyperactivity, and autonomic signs are supported by increased urine and plasma catecholamine levels.[20] NMS may also share pathophysiologic similarities with malignant hyperthermia, which affects skeletal muscle and presents as a hypermetabolic crisis due to halogenated inhalational anesthetic agents or succinylcholine, as well as a defect in a patient's calcium regulatory proteins.[21,22] The increased release of calcium from the sarcoplasmic reticulum may cause dystonia, trismus, muscle rigidity, tremors, muscle breakdown, and hyperthermia.[16,18-21,23]

Risk factors

Patients may be at risk for NMS following the initiation of antipsychotic medications, when dosages are changed, when one antipsychotic drug is switched for another, or the administration route is changed from an oral to a parenteral or depot formulation.[4] As with JD, the concomitant use of lithium with other antipsychotic medications may also present a risk.[8-11,13]

NMS may be more likely in patients with acute disorders such as infection, trauma, and dehydration. Surgery and pregnancy are also risk factors. Similarly, comorbidities that affect the neurologic system are associated with NMS, including Parkinson disease, for which medications may be decreased, stopped too quickly, or rapidly switched.[10,11]

Additionally, several familial clusters of NMS have demonstrated an overrepresentation of a specific allele of the dopamine D2 receptor gene, suggesting a genetic predisposition.[4,18,20]

Diagnosis

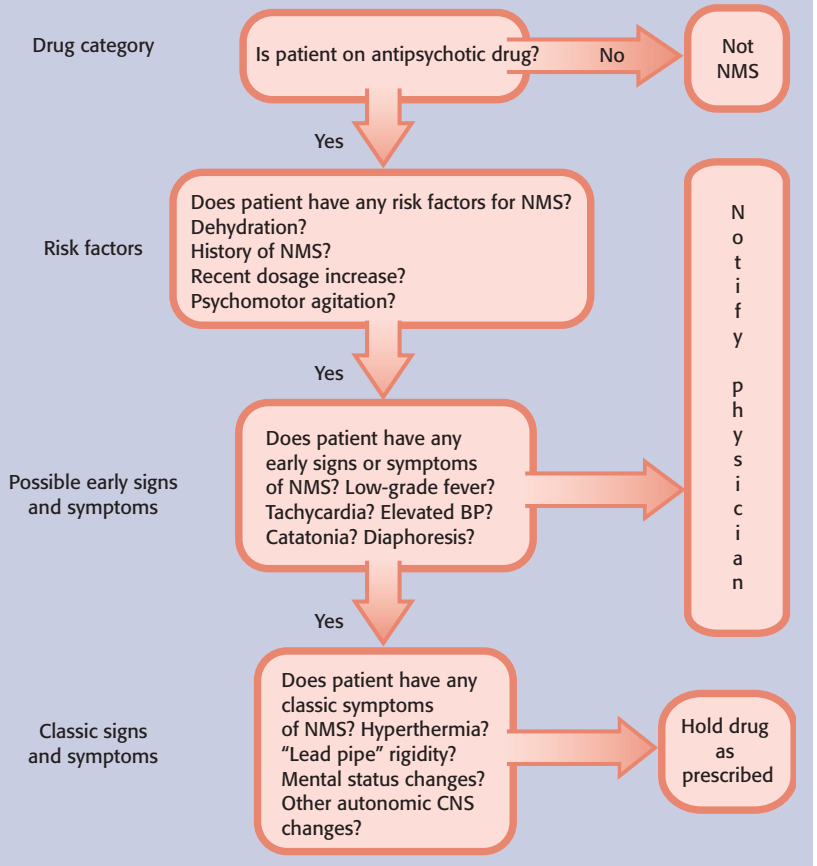
Two major criteria must be present for an NMS diagnosis, as well as two or more other criteria. Following patient exposure to a dopamine antagonist or withdrawal from a dopamine agonist, the major criteria are severe muscle rigidity and hyperthermia. (See *Is it NMS?*) Other criteria include but are not limited to changes in mental status and autonomic instability such as tachycardia, tachypnea, and labile BP.[23,24]

Although no one specific biomarker can be used to diagnose NMS, certain diagnostic studies may be helpful. These include acutely declining renal function studies and elevated serum CK levels, which can be profound and typically correlate to disease severity. Leukocytosis is common, with white blood cell counts ranging from 10,000 to 40,000/mm^3 (normal, 4,400 to 11,000 cells/mm^3 in adults) and an increased number of immature leukocytes.[19,20,23,25] Serum transaminases may also be mildly elevated. Healthcare professionals must work collaboratively to identify the cause of NMS and rule out differential diagnoses such as serotonin syndrome or malignant hyperthermia before the patient experiences permanent damage to the kidneys or other vital organs.

Management

The goal of treatment is to identify and discontinue the causative factor as soon as possible.[21,23] Potential causative factors may include psychotropic drug regimens or the cessation of dopaminergic therapies.[4] Supportive therapies include maintaining cardiopulmonary stability, treating dehydration, restoring normothermia, correcting electrolyte imbalances, and preventing acute renal failure.[19] Healthcare professionals may pursue additional interventions as well, such as initiating venous

Is it NMS?



Source: Boyd MA. *Psychiatric Nursing: Contemporary Practice*. 5th ed. Philadelphia, PA: Wolters Kluwer; 2014.

thromboembolism (VTE) prophylaxis and administering a benzodiazepine to treat muscle rigidity, akathisia, or psychomotor agitation if necessary. Benzodiazepines indirectly increase dopaminergic activity and have been found to enhance patient recovery.[10]

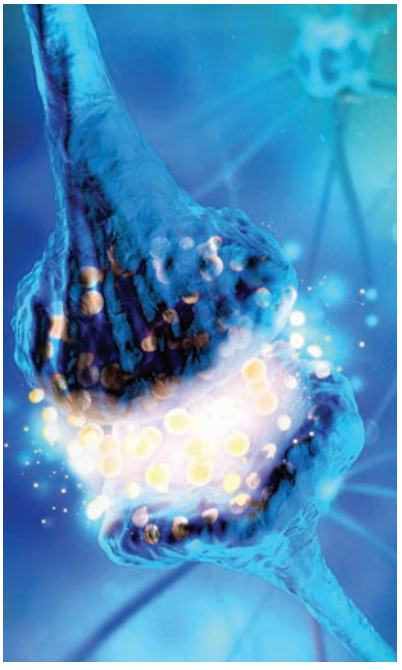
Markedly elevated BP can be lowered by administering clonidine or nitroprusside. Bromocriptine mesylate, a dopamine agonist, may be prescribed to restore lost dopaminergic tone.[26]

Patients must be assessed and treated for complications, including cardiomyopathy and VTE.[19,27] Additionally, patients' respiratory status must be closely monitored. Respiratory acidosis from chest wall rigidity or aspiration pneumonia may lead to respiratory failure and the need for endotracheal intubation and mechanical ventilation. Euthermia may be maintained by reducing the room temperature and using ice packs, ice water gastric lavage, antipyretics, and cooling blankets or garments such as vests and leg wraps.[28] Another pharmacologic therapy includes amantadine, a muscarinic antagonist, to reverse hyperthermia.[10]

In severe NMS, dantrolene sodium, a direct-acting skeletal muscle relaxant that inhibits calcium release from the sarcoplasmic reticulum, may be administered to prevent rhabdomyolysis.[29] By monitoring patient CK-MM levels, healthcare providers can determine the degree of muscle injury. Additionally, they can maintain euvolemia via I.V. fluids to prevent renal failure due to myoglobinuria.[4,19] Glucocorticoids also have dopaminergic and lysosomal membrane stabilization properties and may be used to treat patients with NMS.[10]

Treating JD with ECT

In the case example, JD was first treated by discontinuing lithium, quetiapine, and haloperidol. He then received I.V. dantrolene to reduce hyperthermia, CK levels, and rigidity. He was also treated with amantadine and glucocorticoids. Although JD's body temperature normalized and his rigidity improved slightly, pharmacologic interventions had minimal effect. At this point, ECT was considered.



ECT requires a multidisciplinary approach for optimal patient outcomes, including collaboration between anesthesia providers, nurses, psychiatrists, pharmacists, and other providers.

ECT is a therapeutic procedure performed under general anesthesia that delivers a small electric current to the brain, triggering a generalized seizure and changing brain chemistry.[7,30,31] ECT is used mainly to treat severe depression, but it may also be indicated in patients with other disorders, including NMS. ECT may help with temperature regulation in patients with NMS, altering levels of consciousness and reducing diaphoresis.[32]

In patients with NMS who do not respond to other therapies, or when nonpharmacologic psychotropic treatment is needed, ECT may be performed.[4] Patients with NMS who are treated with ECT have lower mortality than those treated with supportive care alone.[7,30]

ECT may be considered in older adults who cannot tolerate adverse reactions to pharmacotherapy, in those for whom standard pharmacologic treatments have failed, and in those who prefer it or have experienced success with it in the past.[7]

A typical course consists of 6 to 12 treatments, individualized to each patient. Standard practice in the US is to give ECT three times per week.[33] ECT usually continues until the patient experiences remission from the signs and symptoms of NMS.

The healthcare team must be cognizant of the associated risks and contraindications, as ECT is considered a high-risk procedure for some patients. This includes but is not limited to those with increased intracranial pressure, recent myocardial infarction, recent cerebral hemorrhage or ischemic stroke, brain tumors, cardiac conduction defects, aortic and cerebral aneurysms, high-risk pregnancies, retinal detachments, or pheochromocytoma. Patients taking theophylline for pulmonary disorders may be at increased risk of status epilepticus, as are those taking St. John's wort.[9,30,34]

Nursing considerations

Nurses caring for patients with NMS who are undergoing ECT must act as patient advocates, particularly for those who cannot communicate such as JD.[9,31] Although ECT is typically performed as an outpatient procedure, JD received inpatient treatment due to his NMS-impaired mental status. ECT may be performed in the

postanesthesia care unit (PACU) or in a designated suite. Nurses who assist in the procedure should follow facility-specific policies and procedures regarding patients who require general anesthesia.

Pre-ECT. ECT requires a multidisciplinary approach for optimal patient outcomes, including collaboration between anesthesia providers, nurses, psychiatrists, pharmacists, and other providers. Nurses obtain a thorough health history and perform medication reconciliation, noting any drugs or herbal medications with implications for patients receiving ECT such as ginkgo biloba, kava, ginseng, St. John's wort, and valerian.[19,35] For example, St. John's wort may increase the ECT seizure threshold.[36] They also perform a comprehensive physical assessment, including baseline vital signs.[4,10,13]

Nurses collaborate with the treatment team to provide pre-ECT education to patients and families. The risks, benefits, and alternative treatments related to ECT should be presented to the patient by the provider as part of informed consent. As demonstrated in JD's case, not all patients with NMS can provide informed consent. In these cases, a patient's designated healthcare proxy or advocate must be included in the pre-ECT review.

Patients (or their proxies) should be informed that they will receive general anesthesia and muscle relaxants; therefore, they should not feel or remember any events immediately before or after the ECT.[37,38] Afterward, they may experience lingering effects such as memory loss or headaches, but these are usually minimal.[37] Patients may also experience temporary confusion, nausea, muscle pain, and jaw pain.[31,34]

Patients should not ingest food for 6 to 8 hours or clear liquids for a period of 2 hours before the procedure, except small quantities of water when taking certain medications such as cardiac, antihypertensive, and antireflux medications.[33,38] Otherwise, many drugs are typically discontinued the evening before the procedure, especially for patients on antiseizure medications.[35] Adequate peripheral venous access will also be obtained.

Intra-ECT. During the procedure, the patient is placed in the supine position. Vital signs are continuously monitored, including cardiac rate and rhythm, oxygen saturation, electroencephalography (EEG), and electromyography. Nurses must follow institutional guidelines to maximize and maintain patient safety during ECT, including padding side rails.

I.V. methohexital, a rapid, ultrashort-acting barbiturate anesthetic, is commonly used as an induction agent, in addition to skeletal muscle relaxation to minimize the motor seizure and prevent musculoskeletal injury.[39] The standard agent for muscle relaxation is succinylcholine, a depolarizing neuromuscular blocker.[38] Nondepolarizing muscle relaxants such as cisatracurium, mivacurium, or rocuronium are used only for special circumstances in which succinylcholine cannot be used, such as in patients with a family history of malignant hyperthermia, skeletal muscle myopathies, or known hypersensitivity.[37,38,40]

The electric current used to induce the seizure passes briefly through the brain via two electrodes applied to the scalp. Psychiatrists typically position the stimulating electrodes in one of three ways: bilateral, right unilateral, or bifrontal. Most therapeutic ECT seizures last 15 to 70 seconds on the EEG. Short seizures (less than 15 seconds) may not be maximally effective, and prolonged seizures (longer than 2 to 3 minutes) may be associated with increased cognitive impairment.

Post-ECT. Nurses should monitor patients during their recovery period to assess for adverse reactions to the general anesthesia, such as dizziness, hypotension, nausea, vomiting, and respiratory depression. Patients' neurologic status should be monitored for any deficits compared with their pre-ECT state.[34,37] They should be monitored closely for possible adverse reactions such as spontaneous seizures, and fall precautions should be in place.[31] Postprocedure pain medications are not typically required.

Hydration and supportive care are essential for all patients with NMS following ECT. Many patients remain in the PACU for 1 to 2 hours following the procedure. Once patients are stable and meet the PACU discharge criteria, they may be transferred to the medical-surgical, psychiatric, or same-day surgery units before being discharged home. JD was transported back to the NSICU for continued assessment and care.

JD's progression

JD's case is unusual in that, despite pharmacologic interventions and multiple ECT procedures, he remained febrile and comatose for more than a month. Palliative care and hospice were consulted according to his family's wishes. ECT therapy was discontinued and JD died peacefully with his family at his side. The cause of death was NMS.

NMS mortality has decreased from 30% to approximately 10% to 20% over the past 2 decades.[14,28-32] With increased awareness and appropriate interventions, nurses and other healthcare professionals can continue to help improve the odds for patients who experience this rare life-threatening disorder. ■

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