Improving the early identification of malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome for anesthesia providers

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Abstract

Background: Serotonin syndrome (SS), Neuroleptic Malignant Syndrome (NMS) and Malignant Hyperthermia (MH) are all potentially life-threatening conditions that share similar clinical features. Anesthesia providers need to be able to recognize the hallmark features and management priorities of each condition.

Purpose: The purpose of this Doctor of Nursing Practice (DNP) project was to investigate the use of a cognitive aid tool to help clinicians differentiate malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), and serotonin syndrome (SS) in a clinical case scenario presentation. This DNP project aimed to improve the clinician's ability to identify and appropriately manage each condition through prompt intervention.

Methods: The DNP student designed a cognitive aid tool and conducted a mixed-method investigation of the use of the cognitive aid by anesthesia providers during case scenario presentations involving SS, NMS, and MH. Assessment of the anesthesia provider's initial knowledge of the management of each condition without using a cognitive aide was determined through responses to survey questions. After a baseline response from the participants was obtained, a cognitive aid tool was introduced to the participants. The participants were asked to respond to a second series of case scenarios involving either NMS, SS, or MH. Their responses were collected (post-cognitive aid responses) and compared to the initial responses (pre-cognitive aid responses).

Results: Anesthesia providers demonstrated improved mean score responses to the case scenario presentations after the introduction of a cognitive aid tool and educational presentation. The outcome of the DNP project indicated an enhanced ability to identify and prioritize the

management of a patient experiencing either SS, NMS, or MH through the use of a cognitive aid tool.

Recommendations and Conclusions: A cognitive aid tool is a practical and effective resource to improve recognition of these rare and life-threatening conditions during case scenario presentations.

Keywords: Malignant Hyperthermia, Serotonin syndrome, Neuroleptic Malignant Syndrome, Management priorities, and Cognitive Aid

Background and significance

Serotonin syndrome [SS], neuroleptic malignant syndrome [NMS], and malignant hyperthermia [MH] are rare but potentially life-threatening conditions that have overlapping clinical presentations, which are easily confused, especially in the anesthetized patient.

Serotonin syndrome occurs when there is an excess of the neurotransmitter serotonin, causing symptoms ranging from mild to life-threatening. Serotonin syndrome can develop from the combination of just two serotonergic medications within a few hours of administration. Opioid analgesics can inhibit the reuptake of serotonin by the serotonin transporter. Fentanyl is one of the most commonly administered drugs associated with serotonin syndrome in anesthesia (Baldo and Rose, 2020). Methylene blue, used commonly as a dye in surgical procedures or as a treatment for vasogenic shock, has also been implicated in causing serotonin toxicity (Nicolaou and Lee, 2016). Patients with a psychiatric history may be taking anti-depressants such as selective serotonin reuptake inhibitors or other serotonergic medications before surgery (Smith et al., 2015). The incidence of serotonin syndrome during general anesthesia is not well known (Garel et al, 2021). As the use of serotonergic medications becomes more pervasive, however, it is likely the incidence of this syndrome will increase in surgical patients.

Neuroleptic malignant syndrome results from excessive dopamine receptor blockade accompanying the use of neuroleptic or anti-psychotic medications. NMS has a slow onset (can develop over days) and is defined by autonomic instability, bradykinesia, muscle rigidity, and hyperthermia. Along with anti-psychotic medications, risk factors for NMS include dehydration, excessive exercise or agitation, or alcohol use (Viveiros, 2021). The incidence rate of NMS varies between 0.02 and 2.4% and the mortality is between 10-20% (Debeljak and Plesničar, 2021).

Malignant hyperthermia is characterized by tachycardia, a rapid increase in end-tidal carbon dioxide, muscle rigidity, and hyperthermia. MH can develop rapidly after the administration of inhalational anesthetic agents or depolarizing neuromuscular blocking agents. The muscle rigidity seen in MH or NMS differs from that in SS. SS has a characteristic lower limb hyperreflexia as opposed to the marked rigidity in NMS and MH.

Each condition requires rapid identification and treatment but follows a distinct management pathway. Immediate cessation of the offending medication is critical in managing each condition. For a patient with malignant hyperthermia, this means discontinuing volatile anesthetic agents, whereas for a serotonin crisis, the offending agent may be fentanyl. In addition, the administration of dantrolene can save a patient experiencing MH or NMS, whereas dantrolene may worsen serotonin toxicity (Baldo and Rose, 2020, p.56).

Early diagnosis and prompt treatment can be life-saving measures. As the number of risk factors for SS, MH, or NMS grows, the incidence of each syndrome will increase, requiring providers to be adept at making the diagnosis as well as adequately managing each unique syndrome.

Purpose

The purpose of this Doctor of Nursing Practice (DNP) project is to improve anesthesia providers' ability to promptly identify and appropriately manage the treatment of malignant hyperthermia [MH], neuroleptic malignant syndrome [NMS], and serotonin syndrome [SS] by conducting an educational intervention and providing a cognitive aid tool.

Review of Current Evidence

Surgical patients are commonly prescribed a lengthy list of medications. With an increasing number of prescribed anti-depressant medications among the general population, anesthesia providers need to be aware of the risk of serotonin toxicity from the administration of routinely administered perioperative medications. This literature review aims to identify the overlapping clinical presentations of MH, NMS, and SS and the challenges anesthesia providers face in identifying and appropriately managing each condition.

Search Strategy

A general literature search was conducted for each condition, NMS, MH, and SS. A search in PubMed using the keywords "malignant hyperthermia," "neuroleptic malignant syndrome," AND "serotonin syndrome" was performed, but NOT case report was performed. The CINAHL, DynaMed, Access Anesthesiology, Critical Care journals, Scopus, and Google Scholar were searched using the terms "malignant hyperthermia," "neuroleptic malignant syndrome," and "serotonin syndrome." Across each database, searched articles that were not clinically relevant or did not address the specific identification or management of these conditions were excluded from the literature review. In the recent literature, there were several case reports of the individual syndromes (Hencken et al., 2016) or comparing two of the conditions for example, serotonin syndrome and neuroleptic malignant syndrome (Uddin et al., 2017; Viveiros, 2021; Debeljak and Plesnicar, 2020; Aussedat et al., 2020; Dosi et al., 2014;

Nisijima, 2015). No systematic reviews, random control studies, or non-experimental studies were found in the current literature addressing the use of clinical aides in the operating room to help anesthesia providers quickly differentiate NMS, MH, or SS. SS, NMS, and MH are difficult to identify due to a broad differential diagnosis.

The correct diagnosis of serotonin syndrome, neuroleptic malignant syndrome, or malignant hyperthermia is challenging because of their overlapping clinical presentations. Autonomic instability, tachycardia, hyperthermia, and muscle rigidity are common to both malignant hyperthermia and serotonin toxicity (Baldo and Rose, 2020). Neuroleptic malignant syndrome may also present with autonomic instability, hyperthermia, and muscle rigidity but is more likely to cause bradykinesia. There are subtle differences that distinguish the clinical presentation of SS from MH or NMS. The muscle rigidity in NMS and MH is different than in SS. Clonus and hyperreflexia are typically present in the lower limbs in SS but not in NMS. The subtle differences in each condition make it challenging to identify each syndrome without a clinical reference or experience. As the number of factors increasing a patient's vulnerability to develop serotonin toxicity continues to grow (Wang et al., 2016; Davis et al., 2013), the frequency of this syndrome will increase, requiring more providers to be adept at diagnosing and managing these syndromes. Failure to appropriately manage these conditions can be life-threatening. There is a need for increased awareness within the anesthesia community as well as other perioperative team members of agents causing serotonin syndrome (Aussedat et al., 2020; Debeljak and Plesnicar, 2020) and to be able to differentiate SS from NMS or MH.

The peri-operative period is a vulnerable time for polypharmacy to occur, leading to an increased opportunity for these dangerous syndromes to present in surgical patients.

The peri-operative period is a time of increased risk of serotonin syndrome in patients undergoing anesthesia. It is during this period when opioids and other serotonergic medications are often given together. This increases the likelihood of the patient developing serotonin toxicity post-operatively (Baldo and Rose, 2020, p.44). When serotonergic medications are administered as components of anesthesia care and are followed by additional serotonergic agents in the post-anesthesia care unit for pain management, there is ample opportunity for a patient to develop serotonin syndrome. Subtle symptoms may go unnoticed by providers as the offending medication continues to be administered. There are numerous drugs capable of contributing to the development of serotonin syndrome, including fentanyl, meperidine, tramadol, metoclopramide, ondansetron, and others (Francescangeli, 2016; Nicolaou and Lee, 2016; Smith et al., 2015).

The inability to identify SS, NMS, or MH can delay the emergence from anesthesia.

Serotonin syndrome can delay recovery from anesthesia, and every minute patients spend in the operating room increases the cost to the patient (Smith et al., 2015). Early recognition and treatment of serotonin syndrome are essential to avoid poor post-operative outcomes (Baldo and Rose, 2020). An increased length of stay because of serotonin toxicity increases the patient's risk of developing infection, immobility, and other post-operative complications.

Importance of simulation and cognitive aides

Current practice guidelines focus on emergency manuals or guidelines addressing malignant hyperthermia. Malignant hyperthermia intervention carts are often located near the operating room. These carts provide helpful information and access to resources for managing malignant hyperthermia. Educational sessions, along with structured simulation experiences,

provide a safe, accessible, and cost-effective method of increasing awareness and practical tools for anesthesia providers to use to improve patient outcomes.

Theoretical Model

Nola Pender's Health Promotion Model (HPM) is the theoretical framework for the basis of this DNP project. The HPM focuses on people's commitment to beneficial and valuable behaviors. In the context of this DNP project, the beneficial behavior is using a clinical resource to help select life-saving measures at critical moments in the operating room. In addition, the HPM addresses the competence relating to the behavior as a factor that will increase the individual's likelihood of repeating it. Cognitive aids that are simplistic, concise, and easily accessible can help improve crisis performance (Ziewacz, et al., 2011). The Health Promotion Model also discusses situational influences on a person's commitment to health-promoting behavior. Crisis scenarios that involve rare anesthetic events are situations in which it is easy to forget critical interventions, medication dosages, or available resources during high-stress moments. Cognitive aids can be beneficial tools for anesthesia providers to develop competence through educational simulation-based training scenarios.

Methods

Study Design

The DNP student designed a cognitive aid tool and conducted a mixed-method investigation of the use of the cognitive aid tool by anesthesia providers during case scenario presentations involving SS, NMS, and MH. The anesthesia provider's responses to the case scenarios were recorded on paper surveys before and after the introduction of cognitive aid tool. In addition, post-cognitive aid survey responses were collected at a follow-up meeting which occurred fourteen days after the initial participant survey.

Translational Framework

The evidence-based framework selected as a resource for this DNP project was the Iowa Model Revised: Evidence-Based Practice to Promote Excellence in Health Care. As an Evidence Based Practice (EBP) model developed by nurses, the Iowa Model is renowned for being intuitively understandable (White and Spruce, 2015, p.52), and it is a widely used framework.

This DNP project aimed to explore the utility of a cognitive aid tool used among anesthesia providers to help differentiate rare but life-threatening conditions that may occur during the peri-operative period. The step-by-step framework provided by the Iowa Model was instrumental in the execution of this DNP project.

As a heuristic model, the Iowa framework encourages the use of a practical method sufficient to meet the goals of a rigorous DNP project. The Iowa model has been demonstrated as a realistic framework to help graduate students gain a deeper understanding of the EBP process (Lloyd, D'Errico, and Bristol, 2016) and ultimately can help cultivate more EBP champions in the clinical practice setting.

Cognitive aid development

A single 8.5" by 11" double-sided sheet contained concise information to identify and treat MH, NMS, and SS.

Case scenarios

Each case scenario (a total of nine scenarios: three scenarios presented before the use of a cognitive aid, three case scenarios after the introduction of the cognitive aid tool and three follow-up case scenarios presented two weeks after the initial presentation) focused on one critical event (a patient experiencing either MH, serotonin crisis, or neuroleptic malignant syndrome under general anesthesia). The presented crisis events aimed to understand better how anesthesia providers manage the treatment of these patient crisis scenarios and evaluate their

responses with and without using a cognitive aid. There were nine case scenarios presented in the following order: three pre-cognitive aid case scenarios, three post-cognitive aid case scenarios, and three follow-up survey case scenarios. Responses to the pre-cognitive aid case scenarios before the post-cognitive aid case scenarios and follow-up survey questions had minimal influence (if any) on the participants' responses, as each case scenario presented different unique clinical situations. An opportunity to discuss the correct responses to each scenario followed after the final presentation (follow-up cognitive aid survey questions) so that the discussion could not influence the participants' responses to any of the survey questions. The case scenarios were presented in a classroom setting in the clinical site facility. The DNP student read aloud each scripted case scenario (and provided the scenarios on a single sheet of printed paper) and asked the participants to identify each scenario crisis event and prioritize the management of each patient. An overall score for each set of case scenarios (pre-, cognitive aid, post-cognitive aid, and follow-up cognitive aid survey responses) was determined based on how many of the case scenario events were correctly identified and managed (one point granted for each correct response) by the anesthesia provider.

Sample

The DNP project sample included certified registered nurse anesthetists (CRNAs). The clinical site where the DNP project was conducted employs over 100 CRNAs and 50 physician anesthesiologists. A statistically significant number of respondents participated in this project.

Practice setting

The project was presented at two clinical sites within one healthcare system. The first clinical site was a 500-bed tertiary care facility. The second site was a 175-bed tertiary care facility. More than 32,000 general and specialized surgeries, including orthopedic,

otolaryngology, pediatric, dental, and cosmetic surgeries, were performed at the clinical sites' surgery centers over the past year. Minimally invasive surgeries for the spine, heart, and thoracic, as well as laparoscopic techniques, robot-assisted surgeries, and stealth-guided neurosurgery options, were available to patients at these clinical sites.

Recruitment of participants

Clinicians were recruited to participate in a series of operating room emergency case scenarios based on convenience sampling at the clinical site. Participant recruitment methods consisted of an informational poster printed and placed in the anesthesia provider lounge a week before the in-person presentation meeting was scheduled.

DNP Project Implementation Plan

- The DNP graduate student designed a cognitive aid tool to distinguish the identification and treatment priorities of SS, NMS, and MH.
- A total of nine crisis scenarios of surgical patients experiencing each condition under general anesthesia were created for review by the clinicians.
- A classroom at the clinical site to present the crisis scenarios and PowerPoint presentation was requested and reserved.
- Participants were asked to identify and manage the treatment of each scenario (a total of 3 scenarios) before using a cognitive aid. The DNP graduate student collected the clinicians' responses on a single sheet of paper (pre-cognitive aid survey questions that the DNP graduate student provided)
- After collecting the pre-cognitive aid survey questions, the graduate student presented the cognitive aid and reviewed the critical features of the aid with the clinicians, utilizing a PowerPoint presentation and a physical copy of the cognitive aid tool.

- Three additional case scenarios (post-cognitive aid survey questions) were introduced to the participants (approximately fifteen minutes after the pre-cognitive aid survey questions). The DNP student recorded how many clinicians responded to the scenarios using the cognitive aid and those who elected to respond to the post-cognitive aid survey without using the cognitive aid.
- The DNP graduate student collected the post-cognitive aid survey questions. The opportunity to provide feedback from the anesthesia providers about the reality of integrating a cognitive aid specific to SS, NMS, and MH into the clinical setting was provided.
- A follow-up survey announcement was made at the initial meeting to take place approximately 14 days later. The participants' responses were recorded on a single sheet of paper and collected by the DNP graduate student. Use of the cognitive aid tool in the follow-up survey case scenarios was optional.

IRB approval statement

IRB approval was obtained from the University of North Carolina at Greensboro and the clinical site. Appropriate IRB guidelines were followed throughout the DNP project implementation and data collection stages. Minimal risks of harm to the project participants were anticipated.

Measurement tools

Appendices to include the cognitive aid tool, case scenarios, and survey questions, as well as the scoring guide for appropriate identification and management of each condition used to score the participants' responses. The ideal cognitive aid encourages an effective sequence of

interventions and limits erroneous tasks (Marshall, 2013). To date, there is no formal standard for developing or evaluating cognitive aids used in anesthetic emergencies.

Data collection process

The clinicians' pre-intervention responses to three case scenarios were recorded on paper surveys and collected before the introduction of the cognitive aid. The DNP graduate student's cognitive aid was presented and distributed to the participants. A ten-minute PowerPoint presentation was presented on the clinical features of SS, NMS, and MH, along with the treatment options. A second series of case scenarios were reviewed with the participants. Post-intervention responses to the clinical case scenarios were recorded and collected after the distribution of the cognitive aid to the clinicians. Informed consent was not needed to be obtained to collect participant responses.

The educational presentation and pre- and post-cognitive aid survey responses were conducted over a one-day meeting. Approximately two weeks after the initial presentation, a follow-up survey was collected from the clinicians at both clinical sites. The participants had the opportunity to use the cognitive aid tool to answer the follow-up survey questions.

The DNP student collected and intended to safeguard the paper responses from the participants until September 01, 2024. The paper responses will then be discarded at the clinical site facility's confidential paper refuse grey bin. The DNP student paid for the DNP project survey printed materials (about $20 US dollars).

Data Analysis

A convenience sample of clinicians was obtained for the data set. De-identified data was collected. Pre-cognitive aid and post-cognitive aid survey responses were collected on paper surveys and the data was entered into a Microsoft Excel file for data analysis.

Statistical Analysis

The paired t-test is an appropriate method to analyze the data of this QI DNP Project because it is used to test whether the mean difference between pairs of measurements (participant survey responses) is zero or not. The paired t-test data was analyzed using Microsoft® Excel® for Microsoft 365 MSO (Version 2308 Build 16.0.16731.20310) 64-bit Data Analysis feature.

Pre-cognitive and post-cognitive aid survey responses were compared using the paired t-test. The difference in mean survey responses of the participants approached significance.

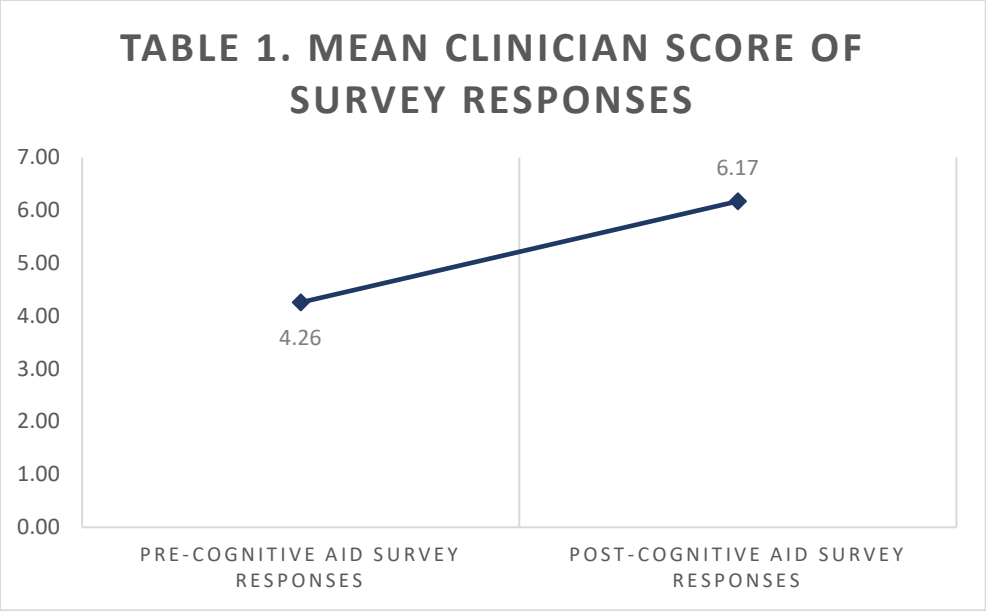
The primary analysis was the post-cognitive aid comparison of the survey responses to the pre-cognitive aid survey responses. This outcome is presented as median scores and was compared using the paired t test.

Results

Thirty-five participants completed all three scenarios and fully completed both the pre- and post-cognitive aid survey questions. Thirty-eight pre-cognitive aid surveys and thirty-six post-cognitive aid surveys were collected. Three pre-cognitive aid surveys could not be linked to post-cognitive surveys, and one post-cognitive survey could not be linked to a pre-cognitive survey.

A statistically significant improvement in the participants' responses was demonstrated during the project period ($p < 0.000021$).

Thirty-five participants' responses were analyzed before and after implementing a cognitive aid. Results of the mean pre-cognitive aid survey score and the mean post-cognitive aid survey score are shown in Table 1.



Discussion

Improvement in overall mean scores of the clinician responses to the post-cognitive aid surveys suggests an effective educational presentation and useful cognitive aid tool. Interestingly, one pre-cognitive aid score of 2 improved to a score of 8 in the post-cognitive survey. The sample size of thirty-five participants provided informative results.

All respondents answered the post-cognitive aid survey questions using the cognitive aid tool. No respondent scored 100% on either the pre- or post-cognitive aid survey. Some of the scores decreased after the presentation/cognitive aid tool introduction. A possible reason for a decrease in the post-cognitive aid scores is that the tool needed to be more adequately explained to each user. It is possible that further explanation or instructions were needed to use the tool as designed. Another possible area to improve the DNP project would be to include more case scenarios to highlight the clinician's understanding of the clinical case scenarios and appropriate interventions. In addition, the select all that apply scoring did not allow for partial marks of

correct responses. The opportunity for partial credit could have influenced more dramatic pre- and post-cognitive aid survey scores.

Conclusion

Early suspicion and prompt treatment of serotonin syndrome, malignant hyperthermia, or neuroleptic malignant syndrome can be life-saving measures utilized by the skilled anesthesia provider. These high acuity, low occurrence events make it challenging for anesthesia providers to respond appropriately to these events without using a reliable and practical resource. This DNP project demonstrated that the use of a cognitive aid tool can help experienced anesthesia providers to respond appropriately to clinical case scenarios involving malignant hyperthermia, serotonin syndrome or neuroleptic malignant syndrome. Educational presentations and case scenario presentations provide a safe, accessible, and cost-effective method of increasing awareness of effective management of these conditions. A possible future direction based on the findings of this DNP project includes establishing a cognitive aid as a free online resource for clinicians to access as needed. The creation of the cognitive aid as an online resource reduces the need for excess documents to be attached to the anesthesia workstation. It can decrease clutter in the operating room. The availability of the cognitive aid used in this DNP project through a trusted online resource could impact a much broader audience of clinicians, helping to increase awareness of managing these life-threatening conditions.

The results and recommendations of the DNP project were summarized and prepared for the chief CRNA at the clinical site through email. In addition, the DNP graduate student presented the DNP project findings at two separate graduate showcase in-person events which were available for the public to attend.

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Appendix A

Recruitment flyer

Appendix B

Pre-cognitive aid Case scenarios

Based on the following case scenarios please select the diagnosis of either serotonin syndrome (SS), malignant hyperthermia (MH), or neuroleptic malignant syndrome (NMS) and describe initial management priorities for each condition.

1. A 32-year-old male with a 5-year history of schizophrenia is admitted to the ED with AMS (he is verbally unresponsive), rigidity in the upper and lower extremities, fever, and muscle spasms. He started haloperidol a week ago. Initial laboratory findings show:
   -WBC, urea, creatinine and CK levels are all elevated
   -ABG shows mixed acidosis
   -UA proteinuria and hemoglobinuria
   -Elevated AST and ALT along with troponin I

2. A 63-year-old female presents for mastectomy and sentinel lymph node biopsy. PMH of anxiety and depression, HTN and CKD. No history of anesthetic complications noted. Patient was given IV versed, induced with propofol, fentanyl and succinylcholine. She was maintained with nitrous oxide and isoflurane. Her intraoperative course was uncomplicated. She received fentanyl, ondansetron, and hydromorphone prior to extubation. In PACU she was hypertensive and febrile and seemed confused. She later became agitated and hyperreflexia (mainly in her lower limbs). She was given more hydromorphone and became unresponsive. She was sedated for ventilation. Her BP became normotensive an hour after intubation. It is later discovered that she ingested more than her usual amount of sertraline tablets prior to surgery.

3. A 27-year-old male undergoing routine orthopedic surgery. He is induced with fentanyl propofol and succinylcholine and maintained with sevoflurane. During the maintenance phase, the patient's HR increases from 87 to 107 bpm. The volatile anesthetic is increased. The end-tidal CO2 rapidly rises from 40 to 85 mmHg, the patient's temperature also increases. An increase in minute ventilation does not alter the EtCO2.

Post-cognitive aid Case scenarios

4. A 68-year-old male with a history of alcohol abuse and on multiple antipsychotic medications was hospitalized for SAH after sustaining a fall. Over the course of his hospitalization, he was started on olanzapine for intermittent periods of agitation. 10 days after the initiation of this medication he became somnolent, febrile, and extremely rigid in his upper and lower extremities. His BP at this time was labile. Laboratory values showed elevated WBC, CPK, and AST/ALT. A CT scan showed resolution of the initial SAH and no new cerebrovascular abnormalities. His CSF was normal. Blood, urine, and sputum cultures showed no growth in 48 hours.

5. A 22-month-old female presents for repair of her cleft lip and palate. She is mask induced and maintained with sevoflurane. The surgery proceeds without any complications. At the end of surgery, the patient is slow to emerge. About 30 minutes after the end of surgery the child is given

glucose and Narcan. Another 30 minutes passes and the patient now has a disconjugate gaze and very stiff extremities. Her EtCO2 rises to 78 mmHg and the patient's temperature increases as well.

6. A 34-year-old woman with alcoholic cirrhosis presents with hematemesis. The patient undergoes EGD for which she is given midazolam, lidocaine, propofol, and fentanyl. Following the procedure, the patient becomes somnolent and develops muscle rigidity. The patient was given rocuronium and etomidate for urgent intubation. After intubation the patient becomes more rigid, diffusely diaphoretic and displays oscillating eye movements. The patient's temperature increases to 102° F. The laboratory findings are suggestive of rhabdomyolysis.

Follow-up survey Case scenarios

7. A 23-year-old male with history of severe depression (currently taking SSRIs) is scheduled for knee surgery. He receives IV versed 2mg. The patient is induced with propofol and fentanyl and an LMA is placed. The patient is maintained on a propofol infusion along with a remifentanil drip. Shortly after surgical preparation is complete the surgeon reports patient movement (bilateral lower extremity clonus at the ankle). The patient's eyes are inspected (a horizontal nystagmus is observed). The patient was also diaphoretic, the core temperature displayed normothermia and there was no major change in vital signs at the time. The anesthetic was deepened, and the patient's lower extremity clonus continued.

8. A 32-year-old male presents for an emergent laparoscopic appendectomy. A rapid sequence induction with rocuronium is performed and Isoflurane used to maintain the patient. The surgery is completed without complication. Neostigmine and glycopyrrolate are used to reverse the neuromuscular blockade and mitigate the effects of neostigmine administration. The patient is slow to emerge. After 20 minutes the patient becomes rigid, cyanotic, tachycardic, hypertensive and begins to shake violently. The end tidal CO2 rises from 45 to 92 mmHg. At the same time the temperature increases above 42° C.

9. A 19-year-old male on the third day of his new antipsychotic medication regimen develops excessive perspiration, hypersalivation, rigors, a fever above 40°C. He presents with agitation initially, but then becomes akinetic. GCS of 6/15 (M4V1E1). He develops hypertonia in all four limbs (lead-pipe rigidity). Lab findings show elevated serum creatine kinase. Blood cultures and CSF analysis are normal.

Appendix C

Pre-Cognitive Aid Survey Questions

Please enter your father's first initial:
Please enter your mother's first initial:
Please enter the two digits corresponding to the month you were born:
Please enter your favorite song title:

Case Scenario responses: Please write down what you believe each case scenario best represents (either malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS) or serotonin syndrome (SS))

Case Scenario 1: _____
Case Scenario 2: _____
Case Scenario 3: _____

Select all that apply for each question

1. Common features of severe Serotonin Syndrome (SS) include:
    a. It is a rare, but life-threatening syndrome caused by anti-dopaminergic agents
    b. It develops slowly (over weeks) after administration of several serotonergic agents
    c. Ocular clonus, hyperreflexia (especially in the lower limbs), and tremors
    d. It develops within 24 hours of administration of a halogenated anesthetic gas
2. Common features of Neuroleptic Malignant Syndrome (NMS) include:
    a. Results in severe hyporeflexia
    b. Muscle rigidity is severe (lead-pipe like rigidity)
    c. Can lead to severe muscle break down
    d. Dantrolene is an effect treatment option as it can inhibit the hyperactive muscle cell
3. SS, NMS and Malignant Hyperthermia (MH) management priorities include:
    a. Discontinue the offending agent
    b. Send labs for CK levels
    c. Administer a benzodiazepine
    d. Provide supportive care (active cooling, reduce tachycardia and muscle rigidity)
4. Dantrolene can worsen SS but not NMS
    a. True
    b. False
5. SS can be alleviated by:
    a. benzodiazepine
    b. cyproheptadine
    c. chlorpromazine
    d. dantrolene
6. Offending serotonergic agents include:
    a. Methylene blue
    b. SSRIs
    c. Fentanyl
    d. Ondansetron
7. The clonus observed in SS is more rigid (lead-pipe like) than in NMS
    a. True
    b. False

Post-Cognitive Aid Survey Questions

Please enter your father's first initial:
Please enter your mother's first initial:
Please enter the two digits corresponding to the month you were born:
Please enter your favorite song title:

Case Scenario responses: Please write down what you believe each case scenario best represents (either malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS) or serotonin syndrome (SS))

Case Scenario 4: _____
Case Scenario 5: _____
Case Scenario 6: _____

Select all that apply for each question

1. Common features of severe Serotonin Syndrome (SS) include:
    a. It is a rare, but life-threatening syndrome caused by anti-dopaminergic agents
    b. It develops slowly (over weeks) after administration of several serotonergic agents
    c. Ocular clonus, hyperreflexia (especially in the lower limbs), and tremors
    d. It develops within 24 hours of administration of a halogenated anesthetic gas
2. Common features of Neuroleptic Malignant Syndrome (NMS) include:
    a. Results in severe hyporeflexia
    b. Muscle rigidity is severe (lead-pipe like rigidity)
    c. Can lead to severe muscle break down
    d. Dantrolene is an effect treatment option as it can inhibit the hyperactive muscle cell
3. SS, NMS and Malignant Hyperthermia (MH) management priorities include:
    a. Discontinue the offending agent
    b. Send labs for CK levels
    c. Administer a benzodiazepine
    d. Provide supportive care (active cooling, reduce tachycardia and muscle rigidity)
4. Dantrolene can worsen SS but not NMS
    a. True
    b. False
5. SS can be alleviated by:
    a. benzodiazepine
    b. cyproheptadine
    c. chlorpromazine
    d. dantrolene
6. Offending serotonergic agents include:
    a. Methylene blue
    b. SSRIs
    c. Fentanyl
    d. Ondansetron
7. The clonus observed in SS is more rigid (lead-pipe like) than in NMS
    a. True
    b. False

Follow- up (Post-Cognitive Aid) Survey Questions

Please enter your father's first initial:
Please enter your mother's first initial:
Please enter the two digits corresponding to the month you were born:
Please enter your favorite song title:

Case Scenario responses: Please write down what you believe each case scenario best represents (either malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS) or serotonin syndrome (SS))

Case Scenario 7: _____
Case Scenario 8: _____
Case Scenario 9: _____

Select all that apply for each question

1. Common features of severe Serotonin Syndrome (SS) include:
    a. It is a rare, but life-threatening syndrome caused by anti-dopaminergic agents
    b. It develops slowly (over weeks) after administration of several serotonergic agents
    c. Ocular clonus, hyperreflexia (especially in the lower limbs), and tremors
    d. It develops within 24 hours of administration of a halogenated anesthetic gas
2. Common features of Neuroleptic Malignant Syndrome (NMS) include:
    a. Results in severe hyporeflexia
    b. Muscle rigidity is severe (lead-pipe like rigidity)
    c. Can lead to severe muscle break down
    d. Dantrolene is an effect treatment option as it can inhibit the hyperactive muscle cell
3. SS, NMS and Malignant Hyperthermia (MH) management priorities include:
    a. Discontinue the offending agent
    b. Send labs for CK levels
    c. Administer a benzodiazepine
    d. Provide supportive care (active cooling, reduce tachycardia and muscle rigidity)
4. Dantrolene can worsen SS but not NMS
    a. True
    b. False
5. SS can be alleviated by:
    a. benzodiazepine
    b. cyproheptadine
    c. chlorpromazine
    d. dantrolene
6. Offending serotonergic agents include:
    a. Methylene blue
    b. SSRIs
    c. Fentanyl
    d. Ondansetron
7. The clonus observed in SS is more rigid (lead-pipe like) than in NMS
    a. True
    b. False

Appendix D

Scoring for each response to the case scenario and survey question: 1 point will be granted for each correct response and no points for incorrect or incomplete responses (Score out of 10 possible points for each survey).

Pre-cognitive aid survey correct responses: 10 points
1. NMS (Hallmark features: AMS, rigidity in the upper and lower extremities, haloperidol use, elevated CK levels and lab values indicative of rhabdomyolysis)
2. SS (Hallmark features: myoclonus, hyperreflexia in lower limbs, sertraline use)
3. MH (Hallmark features: dramatic increase in EtCO2, tachycardia)
4. c
5. a, b, c, d (all answer choices)
6. a, c, d
7. a
8. a, b, c
9. all answer choices
10. b

Post-cognitive aid survey correct responses: 10 points
1. NMS (Hallmark features: Lead-pipe rigidity, AMS, febrile, multiple antipsychotic use)
2. MH (Hallmark features: dramatic increase in EtCO2, febrile)
3. SS (Hallmark features: ocular clonus, rigidity, autonomic hyperactivity, rapid onset after serotonergic agents given)
4. c
5. a, b, c, d (all answer choices)
6. a, c, d
7. a
8. a, b, c
9. all answer choices
10. b

Follow-up survey correct responses: 10 points
1. SS (Hallmark features: prescribed SSRIs, lower extremity clonus, nystagmus)
2. MH (Hallmark features: dramatic increase in EtCO2, febrile)
3. NMS (Hallmark features: onset of antipsychotic medication, akinesis, lead-pipe rigidity, elevated CK labs)
4. c
5. a, b, c, d (all answer choices)
6. a, c, d
7. a
8. a, b, c
9. all answer choices
10. b

Appendix E

PowerPoint Presentation Hyperlink:

Improving the early identification of MH, NMS, SS (3).pptx

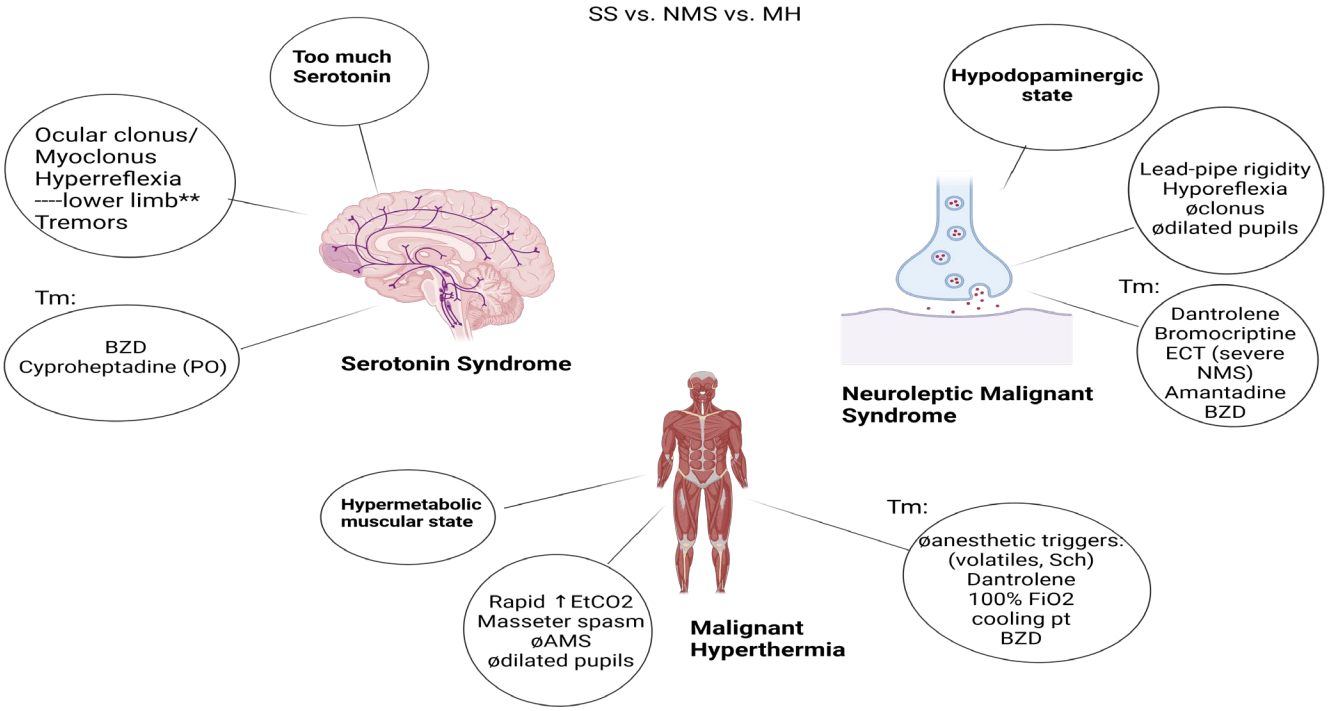
Appendix F

Cognitive Aid- Front side

	What is it?	Hallmark clinical features	Triggers	Treatment
Serotonin Syndrome	Too much serotonin	Autonomic hyperactivity Hyperthermia Myoclonus Ocular clonus AMS N/V Hyperreflexia (lower limb**) Hyperkinetic Ataxia Tremors Develops rapidly after administration of serotonergic agents	anti-depressants (SSRIs) ondansetron, metoclopramide, opioids (fentanyl, meperidine, tramadol), linzolide, methylene blue	BZD cyproheptadine (PO) chlorpromazine - (contraindicated in NMS)
Malignant Hyperthermia	Hypermetabolic muscular state	Rapid ↑ EtCO2 Hyperthermia Tachycardia Tachypnea Acidosis (mixed) Hyperkalemia Muscle rigidity masseter spasm øAMS ø dilated pupils	Volatiles Succinylcholine	Dantrolene/ ryanodex 100 % FiO2 cooling pt BZD
Neuroleptic Malignant Syndrome	Too little dopamine	Autonomic instability high EtCO2 hyperthermia Extreme muscle rigidity Lead-pipe rigidity hyporeflexia bradykinetic AMS (akinetic mutism) elevated serum CK (+ lab values suggestive of rhabdo) ødilated pupils øclonus S/S develop over days to weeks	Metoclopramide, haloperidol, promethazine	•**Dantrolene/ryanodex** •**Bromocriptine** •**ECT** (bold = contraindicated in SS) Amantadine Resolution can take >1 wk in spite of appropriate tm

Version 1.0 August 2023

Cognitive Aid- Back side



Version 2.0 August 2023