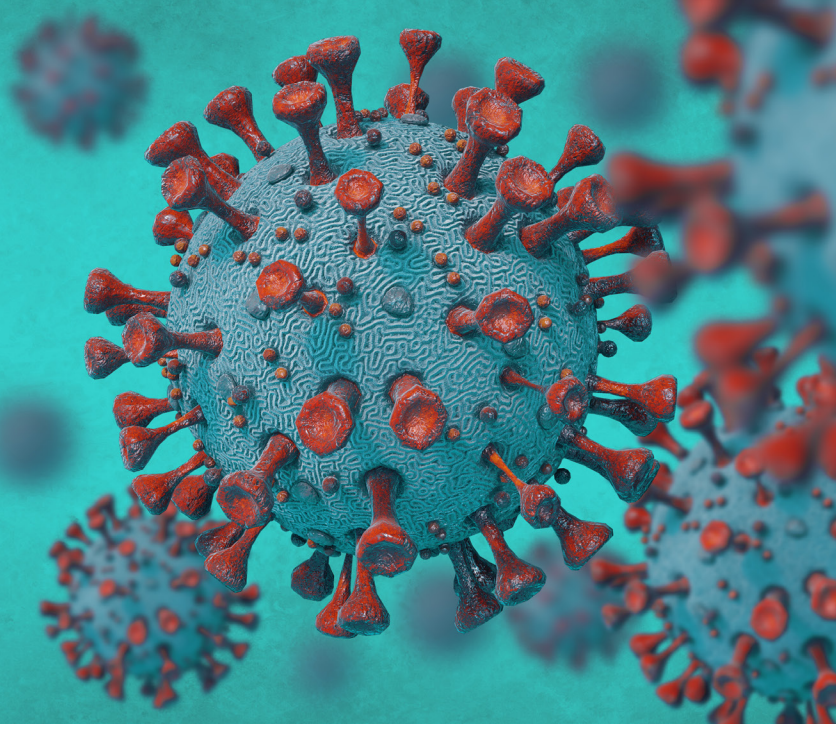
Continuing Education

PHARMACIST CE:

Neurological Sequelae Associated with COVID-19



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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel coronavirus variant first reported in December 2019 in Wuhan, China. The virus causes CoronaVirus Disease 2019, or COVID-19, which often presents as respiratory illness. Since its discovery, more than 200 countries have reported over 200 million cases of the virus, resulting in nearly 4.4 million deaths worldwide (as of this writing).[1] The long-term physiologic consequences of a COVID-19 infection remain unknown, with particular concern relating to the central nervous system (CNS). This review aims to summarize current literature surrounding the neurologic sequelae associated with COVID-19.

CE FOR **PHARMACISTS**

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Learning Objectives

- Describe the neurological signs and symptoms which may present during or after COVID-19 infection
- Recognize the proposed mechanisms in which viruses can breach the blood brain barrier
- Compare COVID-19 associated "brain fog" with myalgic encephalomyelitis/chronic fatigue syndrome
- Define anosmia and dysgeusia and appreciate how their mechanisms related to COVID-19 may differ
- Identify patients who may be at greater risk for cerebrovascular disease or neuromuscular disorders due to COVID-19

ABBREVIATIONS

ACE2: angiotensin-converting enzyme 2
Ang II: angiotensin II
ARDS: Acute Respiratory Distress Syndrome
ATP: adenosine triphosphate
BBB: blood brain barrier
CFS: chronic fatigue syndrome
CK: creatine kinase
CNS: central nervous system
CSF: cerebrospinal fluid
CVD: cerebrovascular diseases
IL: interleukin
ME: myalgic encephalomyelitis
NMD: neuromuscular disorder
OSN: olfactory sensory neuron
RAAS: renin-angiotensin-aldosterone system
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
TNF: tumor necrosis factor

COVID-19 Neuropathophysiology

An estimated 36% of patients diagnosed with COVID-19 experience CNS-related symptoms.[2] A systematic review published in January 2021 describing the neuropathophysiology of this viral illness found the most common neurological symptoms to be altered mental status (43.8%), delirium (28.1%), and cerebrovascular events (6.3%).[3] Additionally, post-mortem brain examination of patients with COVID-19 reveals swelling, obstructed blood supply, intracranial bleeding, neural artery damage, hypoxia, enhanced inflammation, and reduction of the white matter critical for electrical conduction.[3] Other effects related to the central nervous system include sensory dysfunction of taste and smell. Given the negative impacts of these conditions on patients' quality of life, a great need exists for further investigation surrounding the relationship between the virus and CNS physiology.

It is widely accepted that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor as a method of initial cell entry. This receptor, abundantly expressed in cells of the blood, kidneys, lungs, heart, and gastrointestinal system, is important for blood pressure regulation

and antiatherosclerotic mechanisms via the renin-angiotensin-aldosterone system (RAAS).[4,5] ACE2 receptors protect the body from cerebrovascular damage via breakdown of angiotensin II (Ang II), a potent vasoconstrictor and inflammatory mediator. Thus, the downregulation of ACE2 and resulting increase in levels of Ang II following viral infection play a role in disease progression and potential cerebrovascular dysfunction manifesting as a hemorrhage or stroke. ACE2 receptors found on neurons and glia provide some understanding about neural dysfunction that can occur in the CNS, although the role this enzyme plays in viral entry is still unclear.

Any virus reaching the CNS must first find a way to directly breach or indirectly bypass the highly selective, nearly impermeable blood brain barrier (BBB) which protects the brain from exposure to potentially harmful substances traveling through the bloodstream. Further insight into mechanisms of entry stems from prior coronavirus variants, which are known to penetrate the CNS by indirect infection of cerebrospinal fluid (CSF) or direct endothelial cell attack.[6] The mechanism of CSF invasion of SARS-CoV-2 may be related to olfactory epithelium damage in the nasal cavity. By way of the nasal mucosa, the virus could potentially circumvent the BBB by accessing the CSF surrounding and supporting the olfactory bulb in nearby structures. This theory is of particular interest given the large number of patients who lose their sense of smell. As ACE2 receptor expression is absent in olfactory sensory neurons, damage and dysfunction is likely related to other structures of the mucosa. However, evidence is conflicting, as low levels of SARS-CoV-2 have been found in the CSF of some patients, whereas in the majority, the virus has been primarily absent.[6] Although the virus may still be present at undetectable levels, these limitations warrant the investigation of other mechanisms related to the penetration of the BBB.[3]

In order for the virus to travel from the systemic circulation into the brain, it must pass through the tight endothelial cells making up the BBB. Three proposed mechanisms exist.[7] The first is intracellular invasion, which relies on viral attachment to ACE2 receptors expressed on endothelial cells as a passage to the CNS. Paracellular entry is also possible and requires the virus to go through the tight junctions that connect each cell. Lastly, SARS-CoV-2 may access the CNS by entering white blood cells that easily cross the BBB. Commonly referred to as "the trojan horse method," this evasion of the host response used by many viruses is an attractive theory for SARS-CoV-2, given ACE2 surface expression on monocytes, granulocytes, and neutrophils. Upon entry, viral infection of neurons and glia results in a common viral process known as budding, which effectively impairs neural function without necessarily destroying cells.[7]

These proposed mechanisms of viral entry are likely mediated by the release of host pro-inflammatory cytokines in response to infection. Toll-like receptors found at the BBB are specifically designed to identify and react to certain components of the coronavirus, triggering downstream pathways to enhance inflammatory responses.[8] A common phenomenon seen with this virus is the over-reaction of the immune system known as the cytokine storm. Interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor (TNF) are some of the cytokines thought to be responsible for BBB disruption and subsequently enhanced viral entry to the CNS.[8] Indirect passage via the nasal cavity, direct penetration of the BBB, and cytokine destruction of cells may work separately or in conjunction with one another to ultimately lead to the diverse and unpredictable neurological sequelae associated with SARS-CoV-2.

Brain Fog

"Brain fog" is an umbrella term used to describe the various neurological manifestations associated with cognitive dysfunction in current or recovered patients with COVID-19 infection. Common symptoms reported are confusion, trouble concentrating, and fatigue.[9] Additional symptoms, such as impaired memory and impaired cognition, may contribute to difficulty with word finding, executive function, and learning.[10] While presentation varies, these symptoms may have a profound impact on work productivity, learning, and daily functioning for patients far after recovery from the acute viral illness.

One proposed theory explaining the symptoms of brain fog is that a lack of oxygen supply to the brain results from enhanced metabolic demand from the virus. Mitochondria, which are responsible for producing nearly all of the body's energy in the form of adenosine triphosphate (ATP), depend on oxygen for their function.[9] As neurons rely on high amounts of energy, any disturbance in oxygen supply leads to neural dysfunction, which may manifest as impaired cognition. Mitochondria also play a less well known yet incredibly important role in immunity. While all viruses require host DNA machinery for survival, the coronavirus harnesses a unique ability to alter the mitochondrial genome to enhance its own survival and replication while simultaneously altering the host immune response.[9] Cerebral hypoxia triggers the release of pro-inflammatory markers, which subsequently activate immune cells. It is well known that SARS-CoV-2 can result in an over-reactive immune response to cause acute failure of almost every organ system.[9] Less understood is how the body's response to the virus in the long term may result in sustained activation of immune cells and inflammatory markers to cause persistent symptoms.

Much of what we know about brain fog stems from other widespread infections, such as the Russian flu, Spanish flu, and diphtheria outbreaks in the 18th and 19th centuries, which resulted in a small number of patients who went on to experience nonspecific changes in cognitive function.[11] These changes ranged from fatigue, headache, and impaired concentration to anxiety, paranoia, and delirium. Notably, previous infections and the coronavirus-associated brain fog share similarities with myalgic encephalomyelitis (ME), a condition better known as chronic fatigue syndrome (CFS). There is no agreed upon diagnostic criteria for ME/CFS, but it is characterized by extreme fatigue and cognitive dysfunction lasting six months or longer. It affects 0.2-2% of the population, and although the cause is generally unknown, presentation is strongly correlated with autoimmune disease and infection.[12] Historically, it has been overlooked by professionals, who mistakenly classify symptoms as related to a psychiatric etiology, but current research supports a physiologic etiology related to mitochondrial dysfunction. Many of

the proposed treatments for ME/CFS are related to improving mitochondrial function with antioxidants such as Coenzyme Q10 (also known as ubiquinone), NADH, and vitamin E, alone or in combination.[12] Although some small studies report promising results in ME/CFS, there is not enough evidence to recommend these as treatment. Since it is unclear whether ME/CFS is the same as, overlapping with, or distinctly different from brain fog, learning more about the mechanisms of each is crucial for future treatment development.

There are no clear associations to predict which patients are most likely to experience brain fog or long-term cognitive impairment from COVID-19. Although a high viral load is associated with increased confusion and cognitive dysfunction during acute illness, a number of young, healthy people who were not hospitalized during their course have still gone on to experience brain fog.[10] While all races, socioeconomic classes, and ages seem to be at risk, it is likely that females experience brain fog more commonly than males.[9,12] The idea that females may exhibit an overactive inflammatory response to infection is consistent with the knowledge that females have stronger immune systems and are far more likely to have an autoimmune disease compared to their male counterparts. We cannot know the exact prevalence of patients who will experience brain fog long term. A 2021 meta-analysis examining the prevalence of long-term effects reported fatigue in 42-73%, attention disorder in 19-36%, and memory loss in 0-55% of patients recovering from COVID-19.[13] Given that the symptoms of brain fog are non-specific and vary for patients, providers should be informed about how to screen for long-term impacts of COVID-19 infection.

Anosmia & Dysgeusia

A 2021 meta-analysis examining 107 global studies, including over 30,000 patients with confirmed COVID-19, found anosmia (loss of the sense of smell) and dysgeusia (loss of the sense of taste) to occur in 38.2% and 36.6% of patients, respectively.[14] A higher prevalence of anosmia in younger, female patients has been consistently found with a possibility that Caucasians experience anosmia at a three times greater rate than Asians.[14,15] While anosmia and dysgeusia may occur in other respiratory illnesses (e.g. influenza, Epstein-Barr virus, and rhinovirus), the authors found the prevalence to be ten and eight times greater, respectively, in COVID-19 infection.[14] Although anosmia or dysgeusia may be the first and only symptom identified, many patients experience smell and taste dysfunction concurrently with other symptoms or much later in the course of their illness.[14] The average time to resolution of anosmia occurs within 14 days of onset for the majority of COVID-19 patients.[16] However, some patients experience symptoms lasting 30 days or longer.[15,16] The variability of presentation and duration complicates identification of a plausible mechanism.

Smell occurs as a response to the binding of chemical odorants to olfactory sensory neurons (OSNs) in the nasal epithelium. OSNs deliver messages in the form of action potentials to the olfactory bulb to ultimately communicate with the olfactory cortex in the CNS. Nasal blockage due to congestion can interfere with this delivery and is commonly associated with respiratory illness. Of note, the loss of smell for COVID-19 patients occurs at much greater rates and frequently independently from congestion, a much less common symptom reported for this novel virus compared to previous variants.[16] Although direct damage to the OSNs has been proposed as a method of coronavirus entry to the CNS and as an explanation for smell dysfunction, the lack of ACE2 receptors found on OSNs suggests surrounding structures likely play a more prominent role. Sustentacular cells, which surround, support, and nourish the olfactory nerves, have been found to express ACE2 receptors.[14] This theory is consistent with studies that have identified SARS-CoV-2 accumulation in sustentacular cells but not olfactory sensory neurons.[14] Lastly, TNF and IL-6 have been found

to be increased in COVID-19 patients with anosmia, compared to COVID-19 patients with a preserved sense of smell.[17] The cytokine storm may act peripherally to induce cell death in the olfactory epithelium in the nasal cavity or centrally by attacking the olfactory center in the brain.

While smell is responsible for the majority of taste, the presence of patients with dysgeusia without anosmia suggests the possibility of distinct mechanisms relating to taste.[14] Taste is delivered to the CNS via the chorda tympani branch of the facial nerve (cranial nerve VII) which travels through the middle ear to ultimately deliver messages to the gustatory cortex. Viral loads in the nasopharynx could easily reach the chorda tympani via the eustachian tube, leading to the middle ear, resulting in taste disturbance. The large amount of ACE2 receptors found on the taste buds compared to the rest of the oral cavity could also result in direct inflammation and cell death from the virus.[14] Interestingly, both the sustentacular cells and taste buds take about one to two weeks for regeneration, consistent with the typical time period for recovery in patients.[14] Comparatively, OSNs can take up to a month or longer. As a smaller subsection of patients do experience persisting symptoms, there may be more than one mechanism at play.

The loss of smell with or without the loss of taste can be debilitating for a person's quality of life. While pharmacological treatments including oral and topical corticosteroids, intranasal vitamin A, caroverine, or alpha lipoic acid have been considered, there is no evidence to suggest recommending these as treatment for post-COVID-19 anosmia at this time.[18] "Olfactory training" has been investigated for patients who do not experience spontaneous recovery. This technique is preferred to pharmacological treatments (which have little to no evidence), especially given the low cost and low risk of adverse effects.[19] The olfactory training process repeatedly exposes the patient to four intense odors (phenyl ethyl alcohol: rose; eucalyptol: eucalyptus; citronellal: lemon; and eugenol: cloves) twice daily for 12 weeks with a goal to potentially enhance regeneration of olfactory cells. Past studies have shown significant improvement for post-infectious olfactory dysfunction; however, there is no current evidence related specifically to COVID-19.[19]

Cerebrovascular Diseases

Coinciding with SARS-CoV-2 infection, negative effects on the cerebrovascular system and subsequent cerebrovascular diseases (CVD) have been noted. A balanced hormone-regulated RAAS system is essential for maintaining a healthy vasculature. Viral hijacking of the ACE2 receptors results in elevated Ang II and leads to excessive vasoconstriction and weakened blood vessels. Elevated blood pressure and a decreased cerebral blood flow inhibit the delivery of oxygen and vital nutrients to critical areas of the brain, ultimately leading to ischemia and stroke.

A 2021 systematic review and meta-analysis assessed more than 13,000 patients diagnosed with COVID-19 for a pooled outcome of acute CVD, including the clinical subtypes of ischemic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis.[20] Of these patients, 2.5% had correlating CVD. A subgroup analysis further differentiated these outcomes, showing a higher likelihood of a CVD occurring in severe cases of infection (5.6%) compared to non-severe cases (0.6%), an important implication for inpatient providers.

Intracranial hemorrhagic stroke, a clinical subtype of CVD associated with COVID-19 infection, results from a leakage or rupture of a cerebral blood vessel. Elevated cytokine levels are thought to contribute to its development through the weakening of cerebrovascular endothelial cells via extracellular matrix degradation.[21] Thinning of the epithelium weakens vessel walls, thereby increasing the risk of hemorrhagic events. Large population studies estimate that intracranial hemorrhagic stroke occurs in 0.5% of COVID-19 patients.[21,22] Paradoxically, high levels of these inflammatory markers may also be associated with induction of hypercoagulable states. Blood hypercoagulability promotes clot formation and resulting ischemic stroke, estimated to occur in approximately 1-3% of COVID-19 patients. This mechanism may explain why patients, with or without prior risk factors, may also be at a higher risk of thrombus formation and consequential ischemic stroke.[21,22] Additionally, a retrospective cohort study conducted at two academic hospitals in New York compared the rate of ischemic stroke associated with COVID-19 infection with the rate associated with influenza infection.[23] This indirect comparison showed nearly an 8-fold increase in the likelihood of stoke associated with SARS-CoV-2, once again highlighting the severity of this novel coronavirus compared to other respiratory illnesses. Overall, CVD remains one of the leading causes of death in the 21st century; thus, awareness of SARS-CoV-2 cerebrovascular involvement is crucial for early recognition and effective management.

Neuromuscular Disorders

Viral proteins have the capability to mimic host proteins on peripheral nerves, leading to axonal attack and myelin degradation.[24] Vulnerability of the nerves leads to varying symptoms of neuromuscular disorders (NMDs), including nerve and muscle pain, weakness, cramping, numbness, and wasting. While molecular mimicry has been discovered for other SARS viruses, it is still unknown whether the SARS-CoV-2 virus uses this mechanism. Viral infections may lead to the development of a new NMD, exacerbation of an existing NMD, or the unmasking of a previously undiagnosed NMD in patients.

There is a well-established correlation between the development of Guillain-Barré Syndrome (GBS) and other viral infections (e.g. influenza, H1N1, Zika, EBV) which cause the host immune system to aggressively attack its own nervous system.[24] GBS often presents as weakness and tingling in limbs and in severe cases may progress to full paralysis. Of the observed cases that have appeared in conjunction with SARS-CoV-2 infection, a similar symptomatic pattern is seen as with other viral infections. Symptom onset of paresthesia, limb weakness, ataxia, and facial paralysis typically present five to ten days after infection with progression over one to four days.[25]

A systematic review in China found that nearly 30-50% of patients infected with COVID-19 present with myalgias, making it one of the most prevalent symptoms of the infection. Additionally, 44-70% of these cases were associated with elevated creatine kinase (CK).[24,26] While elevated CK suggests myositis, or moderate muscle inflammation, cases of the more serious

rhabdomyolysis remain rare. The use of nondepolarizing neuromuscular blockers in ventilated patients with Acute Respiratory Distress Syndrome (ARDS) enhances the risk of an elevated CK and development of rhabdomyolysis. If left uncontrolled, renal dysfunction can occur. Careful monitoring of muscular and renal enzymes in patients hospitalized with SARS-CoV-2, especially in cases of ARDS, is recommended.[26]

For those with existing NMDs (e.g. myasthenia gravis and amyotrophic lateral sclerosis), viruses are responsible for nearly 30% of exacerbations, making prevention of any viral infection a priority in this population. Additionally, viral infection may lead to the unmasking of existing NMDs in some patients who were previously undiagnosed.[27] While there is limited data on the specific relationship between COVID-19 infection and neuromuscular disorder onset, exacerbation, and unmasking, it is presumed that this virus would follow similar patterns. It is well known that long-term immunosuppressive therapies used to manage NMDs put patients at an increased risk for infection. However, patient- and disease-specific characteristics further quantify this risk. Shared clinical decision-making is essential to assess the patient's risk versus benefit of temporarily discontinuing immunosuppressive therapies during a COVID-19 infection.[24]

Conclusion

Inconsistencies in patient presentation and limitations in early available evidence highlight the challenges of comprehensively summarizing the neurological manifestations of COVID-19. As discussed, brain fog, anosmia, dysgeusia, cerebrovascular disease, and neuromuscular disorders are among the common signs and symptoms coinciding with COVID-19 infection. Although COVID-19 cases are declining, as of this writing, with vaccine development and complete resolution of neurological symptoms occurs for many patients, there still remains a large population who experience persistent and residual effects of the illness. No available treatments have been approved for the management of COVID-19-related neurological symptoms; however, all providers, including pharmacists, can play a role in identifying patients who may face diminished quality of life due to these long-lasting effects. As evidence continues to emerge, more insights will be gathered related to the prevalence and potential management strategies of the various neurological sequelae associated with COVID-19.

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Assessment Questions

1. Some studies estimate the percent of patients diagnosed with COVID-19 who experience CNS-related symptoms to be about:
   a. <10%
   b. 10-20%
   c. 30-40%
   d. >75%

2. Which enzyme does SARS-CoV-2 rely on for cell entry?
   a. Acetylcholinesterase (AChE)
   b. Angiotensin-converting enzyme 1 (ACE1)
   c. Angiotensin-converting enzyme 2 (ACE2)
   d. Acetaldehyde dehydrogenase (ALDH2)

3. Which of the following is a method of SARS-CoV-2 entry into the CNS that relies on white blood cells in order to evade the host response?
   a. CSF invasion
   b. "The trojan horse method"
   c. Intracellular invasion
   d. Paracellular invasion

4. Which of the following is NOT a cytokine associated with the cytokine storm occurring in response to COVID-19?
   a. IL-6
   b. IL-1
   c. IL-18
   d. TNF

5. A patient with "brain fog" may experience which of the following symptoms?
   a. Fatigue
   b. Confusion
   c. Learning Difficulties
   d. All of the above
   e. A & B only

6. Which of the following is **NOT** likely to occur following COVID-19?
   a. Dysgeusia
   b. Anosmia
   c. Fatigue
   d. Rhabdomyolysis

7. **True or False:** The mitochondria plays a role in both energy production AND immune response.
   a. True
   b. False

8. Myalgic encephalomyelitis (ME)/Chronic fatigue syndrome (CFS) is best described as:
   a. A condition that shares overlapping features with brain fog but is distinctly different based on a strict set of diagnostic criteria
   b. A condition that shares overlapping features with brain fog but may also be caused by autoimmune disease
   c. A condition that shares overlapping features with brain fog but is primarily due to a psychiatric rather than physiologic etiology
   d. A condition that was highly contagious during widespread infections in the 18th century but is rarely seen today

9. **True or False:** Only patients with severe COVID-19 illness as noted by a high viral load have been found to develop brain fog.
   a. True
   b. False

10. Which of the following is **NOT** true regarding loss of smell and taste in COVID-19?
    a. Anosmia (loss of smell) may occur at any time during the course of a COVID-19 infection
    b. Twice as many Asian patients with COVID-19 experience dysgeusia (loss of taste) compared to Caucasian patients
    c. Higher prevalence of anosmia (loss of smell) has been found in younger patients
    d. Anosmia (loss of smell) and dysgeusia (loss of taste) may occur at 10 times the rate in COVID-19 patients compared to other respiratory illnesses

11. Which of the following statements is correct about olfactory training?
    a. It can only be done in the office of a trained olfactory specialist, which is typically not covered by insurance
    b. It is a safer alternative to topical corticosteroids but has been found to be less effective
    c. It is a low-cost treatment option that may enhance olfactory cell regeneration
    d. It involves the patient smelling various household items (candles, detergent, spices, etc.) three times a day until their sense of smell returns

12. **True or False:** While cerebrovascular diseases such as ischemic stroke or intracerebral hemorrhage occur in a small number of COVID-19 patients, the risk remains low compared to patients with influenza.
    a. True
    b. False

13. Which of the following **correctly** describes a consequence of the cytokine storm?
    a. Lowered white blood cell activity leading to the loss of smell
    b. Weakening the blood brain barrier leading to enhanced CNS penetration
    c. Strengthening of blood vessels leading to vasoconstriction and stroke
    d. Immunosuppression leading to exacerbation of neuromuscular disorders

14. A treatment consideration for patients with an existing neuromuscular disorder infected with COVID-19 might be:
    a. Preference for nondepolarizing neuromuscular blockers
    b. Discussing initiation of NSAIDs for pain
    c. Closely monitoring liver enzymes
    d. Temporarily discontinuing immunosuppressive therapies

15. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
    a. Yes
    b. No

16. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

17. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

18. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

19. How useful was the educational material?
    a. Very useful
    b. Somewhat useful
    c. Not useful

20. How effective were the learning methods used for this activity?
    a. Very effective
    b. Somewhat effective
    c. Not effective

21. Learning assessment questions were appropriate.
    a. Yes
    b. No

22. Were the authors free from bias?
    a. Yes
    b. No

23. If you answered "no" to question 22, please comment (email info@pswi.org).

24. Please indicate the amount of time it took you to read the article and complete the assessment questions.

CE FOR **PHARMACISTS**

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8) a b c d
9) a b c d
10) a b
11)_____
12)_____
13)_____
14) a b c
15) a b c
16) a b
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