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Send correspondence to:
Megan Grant, Pharmacy Society of Wisconsin
701 Heartland Trail, Madison, WI 53717, phone: 608-827-9200, fax: 608-827-9292, thejournal@pswi.org

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It's Time for EPIC Leadership

by Melissa Theesfeld, PharmD

I recently had the privilege of attending the Decker-Temple Leadership Conference, a unique personal and professional growth opportunity hosted jointly by the Pharmacy Society of Wisconsin and the Iowa Pharmacy Association. Pharmacy leaders early in their careers from Wisconsin and Iowa gathered to hone their communication skills; discuss diversity, equity, and inclusion; and have a little fun getting to know their colleagues.

During our final session with the participants, we asked them to share how they were feeling and what they were taking away from the conference. It was perhaps the most engaging and emotional part of our time together. One of the participants called the Leadership Conference experience EPIC – engaging, passionate, inclusive, and caring. And he was right! The experience itself was EPIC. But as I reflected on the conference in the following weeks, I realized that, perhaps even more importantly, the people were also EPIC!

Our profession has been faced with tough challenges lately. In addition to the COVID public health crisis, we are navigating workforce shortages, an opioid crisis, drug pricing transparency issues, healthcare disparities, and payment for pharmacist-provided services. We have had to change our practices, change our roles, and change how we care for patients. But with all of these changes comes opportunity. Steve Jobs once said "Innovation is the ability to see change as an opportunity - not a threat." I think it is so important that everyone in our pharmacy profession embrace this mindset. Change is an opportunity. It is scary and overwhelming and time-consuming and hard. But change is an opportunity. It's an opportunity to innovate and be at the forefront of some really important healthcare solutions. It's an opportunity to be visible in our communities and serve patients who might not have other access to healthcare. And it's an opportunity to improve the lives of others around us.

All of this change requires EPIC leadership. Some of us have official, formal leadership roles. Others don't have the terms "manager" or "director" in their job title. But I believe that true leadership isn't about the job title we have or the position we hold. We can all be engaged, passionate, inclusive, and caring. We can all model these attributes in our mindset and actions. And we can all view change as an opportunity. Our influence as both formal and informal leaders extends broadly to affect our patients, colleagues, and communities. Regardless of title, others are looking to us and to our profession for advice, comfort, and reassurance. Our EPIC leadership is needed!

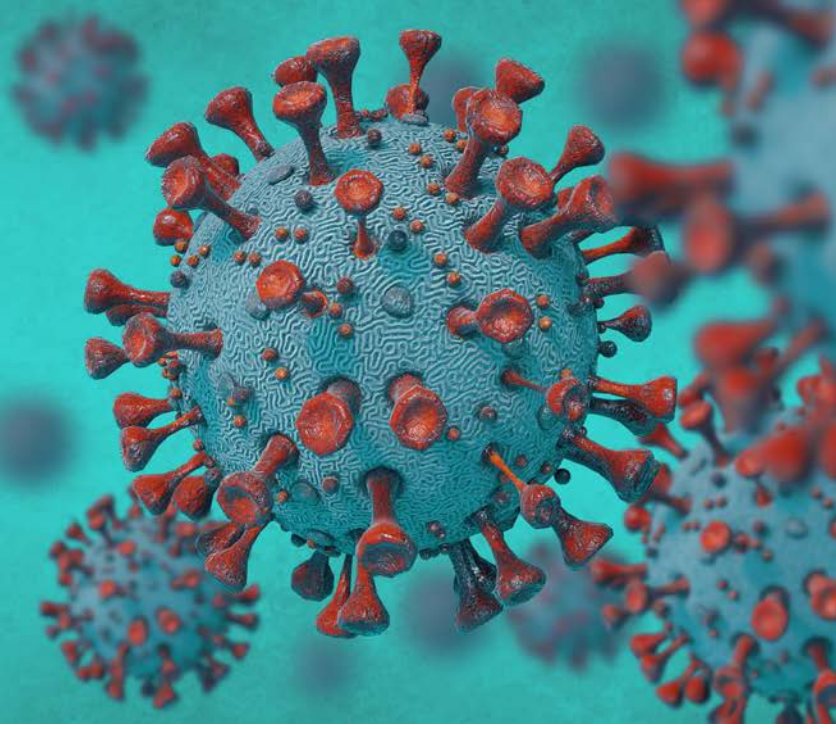
The rate of change in healthcare is not likely to slow down any time soon and the challenges we face probably won't get any easier to tackle. Our PSW community remains strong and is always working to do what is best for our patients. We all remain united as pharmacy professionals with PSW's "one voice, one vision" motto. I am excited to hear how your EPIC leadership has influenced others and affected change!

- Melissa Theesfeld, PharmD
PSW President

Continuing Education

PHARMACIST CE:

Neurological Sequelae Associated with COVID-19



by Megan Ballew, 2022 PharmD Candidate, Jamie Sterr, 2022 PharmD Candidate, Alexis Doering, 2023 PharmD Candidate, Cynthia May, 2022 PharmD Candidate, Hanna Lovstad, 2024 PharmD Candidate

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.

Megan Ballew, Jamie Sterr, Alexis Doering, Cynthia May, & Hanna Lovstad are Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

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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.

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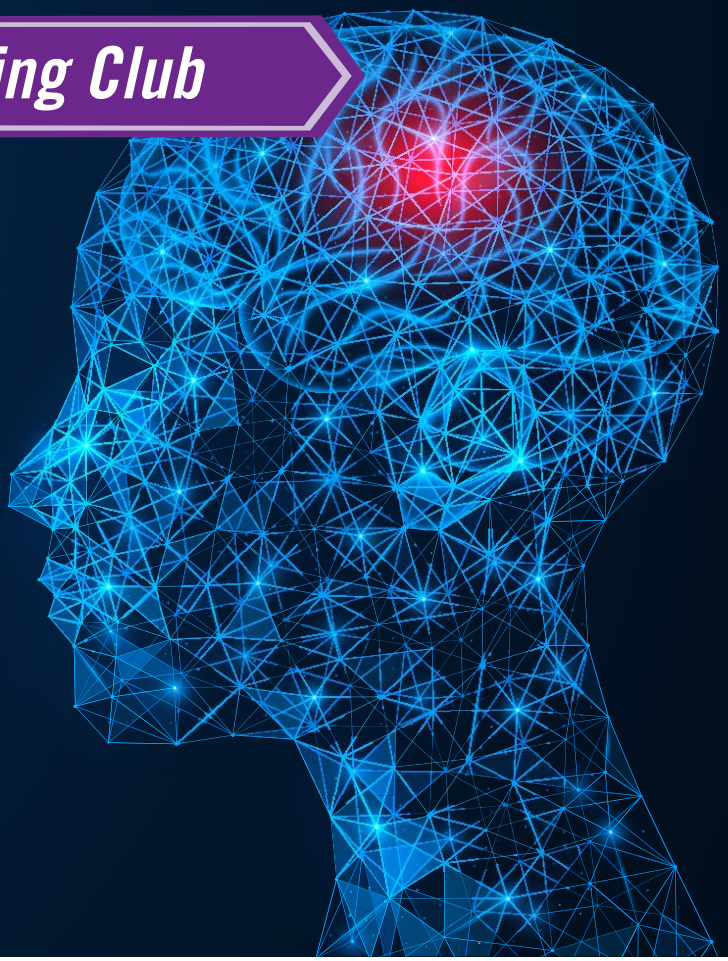

PHARMACIST CE:

CGRP Treatments: Their Role in Migraine Therapy

by Melissa Smith, 2023 PharmD Candidate, Alexandra Falk, PharmD, Ashley Alter, PharmD, Maddie Wiarek, 2022 PharmD Candidate, Kelsey Kapinus, 2023 PharmD Candidate, Beth Martin, RPh, MS, PhD

CE FOR **PHARMACISTS**

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Learning Objectives

- Describe the role calcitonin gene-related peptide (CGRP) has in migraine pathophysiology.
- Describe symptoms associated with migraine headache.
- Interpret the guidelines for initiating migraine prevention therapy and when patients with migraine are eligible for CGRP inhibitors.
- Identify the different routes and frequencies for each CGRP inhibitor.
- Identify the place in acute migraine therapy for CGRP antagonists, also known as gepants.

Migraine headache is the third most common disease worldwide, in both males and females.[1] Neurologists and primary care providers continue to encounter patients with migraines in their practice daily, with migraine accounting for the second leading cause of time spent living with disability worldwide.[2] There are different types of migraine; however, the most prevalent is migraine without aura (see Table 1). According to the third edition of the International Classification of Headache Disorders (ICHD), migraine without aura is characterized by headache with a combination of recurring neurological symptoms and specific features.[3] This can include recurrent headache attacks lasting 4-72 hours with moderate to severe pulsating or throbbing pain located on one side of the head (unilateral). Other disabling symptoms include nausea and/or vomiting, and sensitivity to light and sound. Patients with migraine headache usually need to stop all activities and rest. Some patients may describe an aura that precedes the migraine headache for 5-30 minutes, characterized by either visual or sensory changes, or speech or motor changes that are reversable. Aura is considered a prodrome, or warning sign, that signals migraine headache pain may follow. Migraine with aura is associated with increased cardiovascular and cerebrovascular risks and outcomes. Regardless of sex, patients who suffer from migraine with aura are at a greater risk for ischemic and hemorrhagic stroke as well as myocardial infarction.[4] Due to this relationship, choosing medications with lower risks for cardiovascular and cerebrovascular events is essential for patients experiencing migraines with aura.

The definitive cause and pathophysiology of migraines are not fully understood. However, neurotransmitter and neuromodulator release are associated with migraines, including the neuropeptides 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide (CGRP). The 5-HT receptor agonists, also known as triptans, have been the primary treatment used for acute attacks since the 1990s, and although triptans, available in tablet, nasal spray and injectable formulations, are safe and effective, some patients find they are less effective over time, experience side effects, or have contraindications to their use.[5,6] In this case, the migraine patient may resort to non-specific migraine treatments, like opioids or simple analgesics, which can result in medication overuse headaches.[7] Due to the varying

degrees of severity, frequency, and overall migraine characteristics from person to person, finding an optimal acute or preventive treatment for patients can prove challenging.[8] Oral medications currently used for preventive migraine treatment were not designed specifically for migraines, thus limiting their safety and efficacy profiles. Based on these treatment needs, the use of CGRP antagonists looks to be a promising approach to migraine management, as they were specifically designed as a preventative measure for migraine treatment.

Role of CGRP in Migraine

Present throughout the peripheral and central nervous system, CGRP is known as a vasodilator and is released during both spontaneous and triggered migraine attacks.[9] Due to CGRP's role in migraines, it was considered that blocking CGRP or its receptor may treat or prevent migraine attacks. While the first CGRP antagonists showed promise, liver toxicity was a concern and production ended.[10] However, the U.S. Food and Drug Administration (FDA) has recently approved several new drugs that target CGRP for either migraine prevention or acute migraine treatment. Four new monoclonal antibodies (mAbs) targeting CGRP and its receptor have been developed for migraine prevention therapy, successfully avoiding liver toxicity and providing other benefits (Table 2).[11] Targeting the CGRP ligand and receptor with mAbs adds specificity and longer half-lives while generally producing fewer side effects. In contrast to small-molecule receptor antagonists, mAbs are much larger, and thus unable to cross the blood-brain barrier. With regards to elimination, mAbs are eliminated by degradation into peptides, allowing for less potential for drug-drug interactions. Of the four mAbs currently approved, three work by blocking the CGRP ligand: eptinezumab, galcanezumab, and fremanezumab. Alternatively, erenumab targets and blocks the CGRP receptor.

Small-molecule CGRP antagonists, referred to as "gepants," are oral formulations available for the acute treatment of migraine in patients with either insufficient response or contraindication (e.g. coronary artery disease) to treatment with triptans.

TABLE 1. Symptoms of Migraine Headache[3]

Migraine Without Aura - at least five attacks fulfilling the following criteria:
Headache lasting 4-72 hours
Headache characterized by two or more of the following characteristics: • Unilateral location • Pulsating or throbbing • Intensity of pain moderate to severe • Aggravated by or causing avoidance of routine physical activity
Headache must also fulfill at least one of the following characteristics: • Nausea and/or vomiting • Sensitivity to light and sound
No evidence of other disease diagnoses to better explain symptoms
Migraine With Aura
Aura may also precede migraine headache for 5-30 minutes, characterized by at least one of the following more common fully reversible aura symptoms: • Visual Symptoms: » Changes in vision, vision loss, spots in visual field, flashes of light • Sensory Symptoms: » Numbness ■ Sensation of pins and needles moving slowly from origin to one side of the body, face and/or tongue • Speech and/or Language Symptoms: » Aphasia • Motor Symptoms: » Muscle weakness

Migraine Prevention Treatment with Anti-CGRP Monoclonal Antibodies Guidelines

Although migraine prevention therapy will not eliminate migraines altogether, its goal is to reduce the frequency, severity, and duration of migraine headaches. CGRP inhibitors are not currently the first line treatment for migraine prevention. The anti-CGRP mAbs have all been approved by the FDA for both episodic migraine (fewer than 15 migraine headache days per month) and chronic migraine headache (15 or more headache days per month). According to the American Headache Society (AHS), this class of medications can be prescribed to patients at least 18 years old who fall into at least one of the following three scenarios.[8]

First, in patients who have a diagnosis of ICHD-3 migraine with or without aura and experience 4-7 monthly headache days, they need to have experienced "both an inability to tolerate or have an inadequate 6-week trial of at least 2 other prevention medications."[8] In addition, they need at least moderate disability indicated by a MIDAS score >11 or HIT-6 >50. Medications that can be trialed first include topiramate, divalproex sodium/valproate sodium, beta blockers (metoprolol, propranolol, timolol, atenolol, and nadolol), tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), and other level A or B treatments according to the AHS guidelines.

Second, patients may qualify for CGRP inhibitors if they have an ICHD-3 migraine with or without aura diagnosis and experience 8-14 monthly headache days, with an inability to tolerate or a poor response to at least a 6-week trial of 2 of the following: topiramate, divalproex sodium/valproate sodium, beta blockers (metoprolol, propranolol, timolol, atenolol, and nadolol), tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), and other level A or B treatments according to the AHS guidelines.[8]

Lastly, patients are eligible for the CGRP inhibitors if they have a diagnosis of chronic migraine (15 or more headache days per month) and were unable to tolerate

or had an inadequate 6-week trial of 2 of the previously mentioned prevention medications or had an inadequate response to at least six months, or 2 quarterly injections, of onabotulinumtoxin A.[8]

If a patient fulfills any of the previous criteria, they are qualified to receive prevention treatment with CGRP inhibitors, which currently includes the aforementioned drugs: eptinezumab, erenumab, fremanezumab, and galcanezumab. The response to the initial use of anti-CGRP mAbs should be measured by patient-reported reduction of mean monthly headache days (i.e. > 50% reduction from baseline) or any of the validated outcome measures such as MIDAS, MPFID, HIT-6 by 5 or more points, or by 30% if the MIDAS baseline score was > 20.[8]

Erenumab

Erenumab-aooe, brand name Aimovig®, is a calcitonin gene-related peptide (CGRP) receptor inhibitor approved in the United States for the prevention of migraine in adults.[12] This medication was approved in May 2018 as the first CGRP inhibitor on the market. Amgen/Novartis manufactures erenumab as a once-monthly 70 mg/mL or 140 mg/mL subcutaneous auto-injection. As previously mentioned, this monoclonal antibody differs from the other CGRP antagonists currently on the market in that it is the only one to target the CGRP receptor, whereas the other medications target the CGRP ligand. It is also unique in that it is the only fully human product, with the others being humanized.

As erenumab was the earliest medication approved in this class, it has the most published data available. A systematic review from February 2019 concluded that erenumab was effective in the primary end point of monthly migraine days (MMD).[13] At week 4, the 70 mg dose reduced the migraine days by 1.3 compared to placebo (MD -1.3, 95% CI -1.6 to -1.0), and the 140 mg dose reduced the migraine days by 1.9 compared to placebo (MD -1.9, 95% CI -2.4 to -1.5). Both 4-week decreases were significant with a p-value of <0.001. There were also significant data for week 12 and 24 in the systematic review. By week 24, the 70 mg dose decreased migraine days by 1.6 compared to placebo (MD -1.6, 95% CI -2.2 to -1.0), and the 140 mg dose decreased the migraine days by 2.1 compared to placebo (MD -2.1, 95% CI -2.7 to -1.5). Both of these were significant with a p-value of <0.001.

Another systematic review examined the endpoint of ≥50% responder rate in migraine days per month.[14] This article found that erenumab significantly increased the ≥50% responder rate in migraine days per month compared to placebo (RR = 1.55; 95% CI: 1.35–1.77; P < .00001, I2 = 49%). A subgroup analysis broke down the different doses as well. Both doses currently on the market, the 70 mg dose (RR=1.54; 95% CI: 1.35–1.75; P < .00001; I2 = 0%), as well as the 140 mg dose (RR = 1.86; 95% CI, 1.59–2.19; P < .00001; I2 = 0%) significantly increased the ≥50% responder rate in migraine days per month.

With regard to side effects, erenumab is well-tolerated. According to the manufacturer, injection site pain and constipation are listed as the most common side effects.[12] The possibility of hypersensitivity reactions is also noted, like anaphylaxis and angioedema, which can occur with biologic medications. Although this is a risk, and documented in post-marketing surveillance, neither of the two systematic reviews reported any hypersensitivity reactions. Lanzetti et al.[13] found that only injection site pain differed significantly from placebo in terms of all adverse reactions. Zhu et al.[14] found no significant differences in any adverse event, minor or severe, in the erenumab group compared to placebo. Based on these data overall, erenumab is a safe, effective option for patients to help prevent migraines.

Fremanezumab

Fremanezumab-vfrm (Ajovy®) is another CGRP inhibitor approved in the United States for the prevention of migraines in adults.[15] Fremanezumab was approved on September 14, 2018, making it the second CGRP inhibitor available on the market. Fremanezumab is a subcutaneous injection that is available as either a prefilled syringe or an auto-injector as a dose of 225 mg/1.5 mL. While there is currently only one size syringe available, there are two dosing options. Fremanezumab can either be given as 225 mg monthly or 675 mg given every three months. If the quarterly option is chosen, it is administered as three consecutive injections of 225 mg.

The U.S. FDA approved fremanezumab for use in the United States based on the results from two clinical trials. The trial by Dodick et al.[16] compared fremanezumab to placebo for the prevention of episodic migraine for those who have not already failed multiple medication classes. Episodic migraine is defined as having less than fifteen headache days per month. This clinical trial had three study groups. The first study group received 225 mg of fremanezumab monthly, the second study group received a single dose of 675 mg of fremanezumab, and the third group was the placebo group. This trial had a study length of 12 weeks. At baseline, the monthly fremanezumab group had an average of 8.9 headache days per month, the quarterly fremanezumab group had an average of 9.2 headache days per month, and the placebo group had an average of 9.1 headache days per month. At the conclusion of the 12-week study, the monthly fremanezumab group had an average of 4.9 headaches per month, the quarterly group had an average of 5.3 headache days per month, and the placebo group had an average of 6.5 headaches per month. The monthly dosing group and the quarterly group both had a statistically significant difference compared to placebo, -1.5 days (P<0.001) and -1.3 days (P<0.001), respectively.

The clinical trial conducted by Silberstein et al.[17] compared fremanezumab to placebo for the prevention of chronic migraine. This trial defined chronic migraine as a headache of any duration or severity on greater than or equal to fifteen days per month and migraine on greater than or equal to eight days per month. Like the trial previously discussed, this trial also had three study groups. The monthly fremanezumab group received 675 mg at baseline and then 225 mg at weeks 4 and 8 and the quarterly group received only 675 mg at baseline, with the third group being placebo. At baseline, the average number of headache days per month for the monthly, quarterly, and placebo group were 12.8, 13.2, and 13.3 respectively. During the 12-week period the average number of headache days were 8.0, 8.5, and 10.4, respectively. The primary endpoint in this study was mean change from baseline in the average number of headache days. For the monthly group, the mean change from baseline was -4.6 +/-0.3 and difference

from placebo was -2.1 +/-0.3. The quarterly group had a mean change from baseline of -4.3 +/-0.3 and the difference vs placebo was -1.8 +/-0.3. Both of these comparisons were found to be statically significant (P<0.001 for both comparisons with placebo).

Since this medication has not been on the market long-term, it is difficult to say whether there are any long-term adverse effects of concern. Current data, though, suggests that Fremanezumab is safe and tolerable for patients.[17] With the two FDA approved doses, there was no statically significant difference found between the rate of adverse effects, except the 675 mg dose having a slightly higher frequency of sinusitis. The most common adverse event was found to be injection reaction pain. Overall, there was no significantly higher rate of adverse events with both doses of fremanezumab compared to placebo.

Galcanezumab

Galcanezumab-gnlm, trademarked under the name Emgality® by Eli Lilly and Company, is a fully humanized, anti-CGRP monoclonal antibody that directly targets the CGRP ligand.[18] Currently, galcanezumab is FDA approved for the preventive treatment of chronic and episodic migraines in adults. In addition to its use in migraine therapy, galcanezumab is the only anti-CGRP medication approved for the treatment of episodic cluster headaches.

When patients begin therapy with galcanezumab, they first receive a 240 mg loading dose of the medication administered as two 120 mg subcutaneous injections in the thigh, upper arm, or buttocks.[18] At present, there is only one strength, 120 mg, of galcanezumab approved by the FDA. The loading dose is then followed by monthly injections of 120 mg.

Since its approval in September 2018, galcanezumab has shown promising results for chronic and episodic migraine headache prevention.[19] In its initial 12 week phase II trial for the prevention of episodic migraine, patients were randomized to either receive a subcutaneous placebo or galcanezumab 120 mg injection every 2 weeks for 12 weeks. The mean change in the number of migraine headache days from baseline measurements in the galcanezumab group was 4.2 days while the placebo group only experienced a 3-day reduction in monthly migraine headache days (least-squares mean difference -1·2, 90% CI -1.9 to -0.6; p=0.0030).

In a 3-month, phase III double-blind placebo controlled study evaluating galcanezumab's effect on episodic migraine on North American patients, EVOLVE-1, patients enrolled saw an average reduction of 4.83 and 4.62 migraine headache days from baseline for 120 mg and 240 mg injections of galcanezumab respectively, versus the placebo group, which only saw a reduction of 2.74 migraine headache days (p < .001 for both doses vs placebo).[20] Additionally, in a 6-month, phase III double blind follow-up study that included patients on a more globalized scale, EVOLVE-2, patients included in the galcanezumab group experienced reductions in monthly migraine headache days by 2.02 and 1.90 days for 120 mg and 240 mg injection, respectively relative to placebo.[21]

Currently, galcanezumab is the only CGRP antibody that is FDA approved for the treatment of episodic cluster headache in adults. Approved in June 2019, galcanezumab has shown benefit in reducing the number of weekly cluster headaches for patients with this condition.[22] In an 8-week double-blind placebo-controlled study in adult patients, the REGAIN study, galcanezumab 300 mg reduced the number of weekly cluster headaches in patients by 8.69 days while patients receiving placebo only saw a reduction of 5.22 days.

No serious adverse effects have been noted from trials of galcanezumab for both migraine and episodic cluster headache trials, but patients in the treatment groups were more likely to experience injection site reactions (8.16% of patients in treatment groups versus 0% of participants in the placebo group).[18]

Galcanezumab is contraindicated in patients with serious hypersensitivity to galcanezumab or any of its excipients; anaphylaxis, angioedema, dyspnea, rash, and urticaria have been reported. If these or any similar symptoms are reported, galcanezumab should be discontinued and appropriate therapy for hypersensitivity reactions should be initiated.

Eptinezumab

Eptinezumab-jjmr (Vyepti™) is a new treatment for migraines that is an anti-CGRP monoclonal antibody and classifies as a migraine prevention treatment for chronic and episodic migraines.[23] Eptinezumab is the latest medication on the market for migraine prevention, being approved in February 2020. Of note, eptinezumab is the only infusion therapy on the market for migraine prevention treatment, and the administration is based on a quarterly schedule and is to be administered in a healthcare facility.[24]

Two major studies that were conducted for eptinezumab were PROMISE 1 and PROMISE 2. PROMISE 1 centered on episodic migraines characterized by subjects having 14 headaches in a month, four of which needing to be migraines.[25] There were over 800 subjects who received either a placebo, or a variety of different dosing options of eptinezumab (30 mg, 100 mg or 300 mg). PROMISE 1 results revealed that subjects who received eptinezumab (100 mg and 300 mg treatment groups) had a >50% reduction in migraines on day 1 after dosing compared to baseline and the reduction was sustained through day 28. In addition, subjects receiving eptinezumab 300 mg experienced significant reductions in their average monthly migraine days over weeks 1-12. Notable statistics include: ≥75% reduction in monthly migraine days over weeks 1– 4 in 32% of subjects and 37% of subjects over weeks 1-12 for the 300 mg dose group. Furthermore, there was a >50% reduction in monthly migraine days over weeks 1-12 in 61% of subjects for the 300 mg dosage group. With more infusions of the 300 mg dose, the number of migraine days per month significantly improved. These results showed that ≥75% reduction in monthly migraine days presented in over 51% of the subjects and ≥50% reduction in monthly migraine days presented in over 70% of the subjects.

PROMISE 2 focused on chronic migraines, which is defined as more than fifteen headaches per month, eight of which needed to be classified as migraines.[26,27] There were 1,072 subjects who received either 100 mg or 300 mg of eptinezumab. The subjects that received 300 mg of eptinezumab after the first quarterly injection had 8.2 fewer monthly migraine days compared to the baseline of 16 monthly migraine days. The placebo group had 5.6 fewer monthly migraine days. After the second infusion, the results were 8.8 fewer monthly migraine days for the 300 mg dose compared with 6.2 fewer monthly

migraine days for the placebo. Another significant finding was that 21% of subjects had a 100% reduction from baseline in monthly migraine days compared to the 9% of placebo subjects with two quarterly infusions of 300 mg eptinezumab. Overall, after two quarterly infusions were administered, 64% of subjects had a ≥50% reduction in monthly migraine days from baseline, 44% were from the placebo and 43% of subjects had ≥75% reduction of monthly migraine days compared to 24% for the placebo. These results suggest that eptinezumab has the potential to offer migraine patients rapid and sustained suppression of migraines.

In terms of safety, PROMISE 1 had similar results of adverse event rates compared to previous eptinezumab studies.[25] Subjects who received either dosage form of eptinezumab (30 mg, 100 mg or 300 mg) or the placebo had very similar percentage rates of adverse events. The most common events were upper respiratory tract infections, nasopharyngitis, and sinusitis. The percentages for the aforementioned side effects from a 300 mg dose of eptinezumab were 10%, 6% and 5%, respectively, while the placebo results were 7%, 5% and 6%, respectively. The results from PROMISE 2 remained consistent with previous studies on eptinezumab as well.[26,27] Comparing the placebo group and participants who received eptinezumab, both had similar adverse event rates. A few common reported adverse events for eptinezumab were: nasopharyngitis (7.4%), urinary tract infection (2.8%), nausea (2.5%), arthralgia (2.3%), dizziness (2.0%), and fatigue (2.0%).

General Administration, Storage Requirements, and Common Side Effects for CGRP Inhibitors

If a subcutaneous maintenance dose of a CGRP inhibitor is missed, it should be administered as soon as remembered.[28-31] Erenumab, galcanezumab, and fremanezumab should be stored in the refrigerator, between 2 to 8°C (36 to 46°F) but should not be frozen.[28-30] Advise patients to remove the product from the fridge 30 minutes before injection to allow the product to reach room temperature before injection (no heat sources should be used to warm the product upon removal from the refrigerator). These products should not be shaken. If necessary, galcanezumab and erenumab may be stored at room temperature up to 30°C (86°F) and 25°C (77°F) respectively in their original packaging for up to 7 days.[28,29] Fremanezumab may be stored at room temperature up to 25°C (77°F) in its packaging for up to 24 hours.[30] If these products are left at room temperature for longer than these designated time periods, advise patients to discard them.[28-30]

For the intravenous administration of eptinezumab, it must first be diluted.[31] A 100 mg dose will require 1 mL of VYEPTI™ from a single-dose vial. A 300 mg dose will require 1 mL of VYEPTI™ to come from 3 separate single-dose vials. After the proper amount of VYEPTI™ is obtained it must be diluted in 100 mL 0.9% sodium chloride injection, USP. In addition, the infusion bags have to be made from polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO). It is necessary to prepare VYEPTI™ using proper aseptic technique since it will be administered through intravenous infusion. The solution can be gently mixed by inverting the solution to mix completely. Furthermore, it is recommended to not shake the solution bag. The infusion must take place within 8 hours of preparation and the solution should be properly stored at room temperature, 20°C to 25°C (68°F - 77°F). After administration, the remaining unused solution should be disposed of. An unprepared injection can be stored in its original carton to protect the product from light in the refrigerator at 2 to 8°C (36 to 46°F) until the time of use. Lastly, the unprepared injection should not

TABLE 2. Migraine Medications Compared[28-33]

Generic Name	Brand Name	Pharmacologic Category	Half-life Elimination[2]	Time to Peak[2]	Route of Administration	Starting Dose	Frequency
Generic							
Erenumab	Aimovig®	CGRP[1] Inhibitors; Monoclonal Antibody	28 days	6 days	SC[3] prefilled single-dose auto-injector	70 or 140 mg	Monthly
Galcanezumab	Emgality®		27 days	5 days	SC[3] via single-use prefilled pen or syringe	240 mg 120 mg	Loading dose Monthly
Fremanezumab	Ajovy®		31 days	5 to 7 days	SC[3] single-dose prefilled syringe or SC autoinjector	Oral 225 mg 675 mg	Monthly Quarterly
Eptinezumab	Vyepti™		27 days	Immediately following infusion	30-min IV[4] infusion in 100mL NS[5]	100 mg or 300 mg	Quarterly
Short Acting							
Urbrogepant	Ubrelvy®	CGRP[1] Receptor Antagonist	5-7 hours	15 hours	Oral tablet	50 mg 100 mg	As needed
Rimegepant	Nurtec™		11 hours	1.5 hours	SL[6] Oral tablet	75 mg	As needed

1, Calcitonin Gene-Related Peptide. 2, Actual response may vary. 3, Subcutaneous. 4, Intravenous. 5, Normal saline. 6, Sublingual.

TABLE 3. Adverse Effects and Contraindications[28-33]

Generic Name	Common Adverse Effects	Contraindications
Erenumab	Irritation at injection site, Constipation, antibody development	Serious hypersensitivity to erenumab or any part of the formulation
Galcanezumab	Irritation at injection site, antibody development	Serious hypersensitivity to galcanezumab or any part of the formulation
Fremanezumab	Irritation at injection site, antibody development	Serious hypersensitivity to fremanezumab or any part of the formulation
Eptinezumab	Antibody development, Nausea, fatigue, nasopharyngitis	Serious hypersensitivity to eptinezumab or any part of the formulations
Urbrogepant	Nausea, somnolence, dry mouth	Concomitant use of strong CYP3A4 inhibitors
Rimegepant	Nausea	Hypersensitivity to rimegepant or any part of the formulation

be frozen or shaken.

Overall, the most frequently reported side effects include upper respiratory tract infection/nasopharyngitis, injection site pain, pruritus, and erythema (Table 3). A risk of contribution to inflammatory bowel disease, diarrhea, or constipation is hypothesized due to the role of CGRP in maintaining the mucosal integrity of the gastrointestinal tract. As an inherent risk of using mAbs as treatment, the body has the potential to develop antibodies against the drug. In trials, efficacy seemed unaffected by the antidrug antibodies detected, although this may not be the case long-term.

At present, clinical trial data for the CGRP inhibitors does not contain a sufficient population of individuals over the age of 65 or under the age of 18 to verify the safety of these medications for geriatric or pediatric use.[28-32] No adequate data are available for these medications in pregnant or lactating women. It is prudent to have women tell their healthcare provider about plans to become pregnant and consider having optimal contraception in place before trialing these medicines since their effects can last months due to their extended half-lives.

Acute Treatment for Migraine

The Institute for Clinical and Economic Review (ICER) published an evidence report comparing the effectiveness of the newer agents for acute migraine treatment, including the "gepants."[34] The primary endpoint in all CGRP antagonist trials was pain freedom two hours after treatment. Pain relief, a secondary outcome, was defined as a decrease in headache pain from moderate or severe at baseline to mild or no pain two hours after treatment; thus, a patient with moderate or severe pain who achieved pain freedom was also counted as having pain relief. Phase III trials also measured absence of the most bothersome migraine associated symptom (i.e. photophobia, phonophobia, or nausea) two hours after treatment as a co-primary endpoint. Rimegepant (1.58, 95% credible interval (CrI): 1.29, 1.94), and ubrogepant (1.64, 95% CrI: 1.28, 2.12) all had higher odds of achieving freedom from bothersome symptoms at two hours post dose compared to placebo.

Because the primary outcomes of the trials were based on a single dose of each drug compared to placebo at two hours after initial treatment, the ability to evaluate benefit of these therapies at four hours post-dose, over time for repeated attacks, and long-term efficacy (reduced disability and improved quality of life) is limited.[34] However, for those who have not responded to triptans or have contraindications or intolerabilities to triptans, the evidence is "incremental or better" for ubrogepant and rimegepant, with "at least a small net health benefit."

Ubrogepant

Ubrogepant, brand name Ubrelvy®, is an oral tablet CGRP receptor antagonist made by Allergan.[32] Ubrogepant was approved in December 2019 and is indicated to treat acute migraine with or without aura in adults. This migraine treatment is recommended to be dosed at 50 mg or 100 mg and can be taken without food. Additionally, a second dose can be taken after 2 hours from the first dose.[32] The maximum dose or ubrogepant in a 24-hour period should not exceed 200 mg. Reported side effects included nausea (most common), somnolence (sedation and fatigue) and dry mouth. Ubrelvy® is also contraindicated with the use of strong CYP3A4 inhibitors. A meta-analysis by Yang et al. looked at relevant randomized clinical trials consisting of 3326 patients in terms of efficacy and safety of short-term use.[35] Their research collection began from the earliest available date to November 10, 2019. From the research that was conducted it was determined that ubrogepant versus placebo did lead to a greater percentage of freedom from pain (20.8% vs 12.6%, relative risk [RR] 1.65, 95% confidence interval [CI] 1.38-1.98) and absence of the most migraine-associated bothersome symptoms (37.3% vs 27.6%, RR 1.35, 95% CI 1.20-1.53) at 2 hours post dose. Other significant data that was found was when dosed at 25 mg, 50 mg, and 100 mg, there was increased pain relief when compared to the placebo. What's more, is when ubrogepant was dosed at a higher range of 50 mg and 100 mg the more bothersome symptoms were treated. More long-term research needs to be conducted to truly determine the safety, efficacy, and tolerability of ubrogepant. There is currently no established data on the safety of treating more than 8 migraines in a 30-day period.[32] Additionally, long term data is also necessary to gain more insight on usage in specific populations (pregnancy, lactation, pediatric, and geriatric use).

Rimegepant

Rimegepant, brand name Nurtec® ODT, is an orally disintegrating tablet CGRP receptor antagonist made by Biohaven Pharmaceuticals.[36] It was approved in February 2020 for the treatment of acute migraine with or without aura in adults.

The current dosing recommendations are a maximum of one 75 mg dose in 24 hours. A meta-analysis by Gao et al.[37] from January 2020 looked at evidence from the randomized controlled trials of rimegepant. Their results concluded that rimegepant was significant versus placebo in the outcomes of freedom from pain 2 hours post dose (20.6% vs 12.5%, relative risk [RR]= 1.70, 95% confidence interval [CI]: 1.39-2.08, p<0.001), freedom from most bothersome symptoms (36.0% vs 25.1%, RR= 1.44, 95% CI: 1.23-1.68, p<0.001), and pain relief at 2 hours post dose (58.6% vs 44.6%, RR= 1.34, 95% CI: 1.25-1.44, p<0.001). The manufacturer states the possible side effects as nausea and hypersensitivity reactions.[36] Notably, chest tightness or pressure was absent, as compared to the triptan class of medications. Rimegepant is also a substrate of CYP3A4, CYP2C9, P-gp transporters, and BCRP transporters, increasing the likelihood of drug-drug interactions with strong CYP, P-gp, and BCRP inhibitors.

Conclusion

While anti-CGRP migraine treatments continue to show promise for migraine prevention and acute treatment, they are still relatively new on the market, and post-market surveillance is necessary to determine long-term effects and collect evidence that will guide their use in specific populations.[38] A potential limitation of mAbs is that they are expensive (about $6000 annually, depending upon insurance coverage); however, the socioeconomic burden from migraines on patients' daily lives can be costly as well. These new treatments must be administered intravenously or subcutaneously, as compared to approved oral prevention therapies, and thus patient preference is an important consideration. And because mAbs for migraine prevention have a relatively long half-life (around 1 month) treatment adherence can be improved since they are administered much less frequently than other treatments, often taken daily.[38] Additionally, clinical benefits from the mAbs can be seen within one month, while traditional oral prevention therapies can take at least three months at therapeutic doses to see effectiveness. In most cases, CGRP antagonists have been well tolerated, including no reported cardiovascular concerns within erenumab multiyear trials.[39,40]

The oral CGRP receptor antagonists, or gepants, for acute treatment of migraine offer another alternative for patients who have experienced side effects from the other specific treatment used, namely triptans, or have health conditions worsened by vasoconstriction, precluding triptan use. Overall, these agents have about a 20% effectiveness for pain freedom at 2 hours post-dose. And while these new oral agents have only been approved for a single dose treatment regimen for acute migraine, worsening migraines with increased use of the gepants (known as medication overuse headache) have not been seen so far. The drug-interaction with CYP3A4 medications requires thoughtful consideration and monitoring. Most importantly, at present, the benefits and advantages of having another migraine-specific treatment strategy for patients suffering from debilitating headaches is a welcome option.

Melissa Smith is a 3rd Year Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Alexandra Falk and Ashley Alter are 2021 Doctor of Pharmacy Graduates from the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Maddie Wiarek is a 4th Year Doctor of Pharmacy Candidate and Kelsey Kapinus is a 3rd Year Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Beth Martin is a Professor at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

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Assessment Questions

1. Characteristics that can classify a migraine without aura may include:
   a. Moderate to severe pain
   b. Pulsating or throbbing
   c. Unilateral location
   d. All of the above

2. Which CGRP inhibitor was the first to be released on the market?
   a. Eptinezumab
   b. Erenumab
   c. Fremanezumab
   d. Galcanezumab

3. Which of the below statements regarding CGRP pathophysiology is FALSE?
   a. CGRP can be located in the peripheral and the central nervous system
   b. CGRP can be released during spontaneous and triggered migraine attacks
   c. CGRP is a vasodilator
   d. Targeting the CGRP ligand and receptor with monoclonal antibodies does not add specificity and produces more side effects

4. Which pair contains only acute migraine medications?
   a. Eptinezumab, Fremanezumab
   b. Galcanezumab, Rimegepant
   c. Ubrogepant, Erenumab
   d. Ubrogepant, Rimegapant

5. **True or False:** CGRP Inhibitor Monoclonal antibodies have a half-life of around one month
   a. True
   b. False

6. Which of the following below is TRUE regarding Ubrogepant?
   a. The maximum dose of Ubrogepant in a 24-hour period should not exceed 300 mg.
   b. The most common reported side effects included: Dry mouth, increased heart rate, and constipation
   c. There is plenty of established data on long term use
   d. Ubrogepant is indicated to treat acute migraine with or without aura

7. Which of the following migraine medications would most likely contribute to improved adherence rates based on a quarterly dosing frequency?
   a. Eptinezumab
   b. Erenumab
   c. Fremanezumab
   d. A and C

8. What is a common adverse effect of Fremanezumab
   a. dysphoria
   b. Irritation at injection site
   c. nausea
   d. No adverse effects were reported

9. Galcanezumab is the only FDA approved CGRP monoclonal antibody to effectively treat:
   a. Acute migraine headaches
   b. Chronic migraine headaches
   c. Episodic cluster headaches
   d. Episodic migraine headaches

10. What are the benefits of using CGRP parenteral inhibitors as migraine prevention therapy?
    a. Relatively long half-life
    b. Administration performed on a month or more regimen
    c. Well tolerated with minimal/less severe adverse effects
    d. All of the above

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

12. 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.

13. 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.

14. 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.

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

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

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

18. Were the authors free from bias?
    a. Yes
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20. Please indicate the amount of time it took you to read the article and complete the assessment questions.

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Remdesivir in the Treatment of Hospitalized Patients with COVID-19: Evolution of Use Over the Course of the Pandemic

by Lauren N. Nevinski, PharmD, Lynne Fehrenbacher, PharmD, BCPS-AQ ID, Thomas J Dilworth, PharmD, BCPS-AQ ID

Since the beginning of the COVID-19 pandemic, significant effort has been directed towards optimizing pharmacologic treatment for patients hospitalized with SARS-CoV-2. Over the course of the past year, several drug classes have been used with limited success in an attempt to treat COVID-19. The World Health Organization (WHO) treatment guidelines have evolved based on ongoing clinical trials with various agents, including, but not limited to, remdesivir (Veklury®, Gilead). A continued debate about using remdesivir has been defining which group of hospitalized patients, as categorized by the WHO COVID-19 disease severity ordinals (Table 1), are likely to benefit the most given the varying results published from clinical evidence.[1] An ordinal, or ordinal number, defines an individual's position or category in a list, to make generalized interpretation easier in clinical studies.

Remdesivir inhibits SARS-CoV-2 ribonucleic acid (RNA)-dependent RNA polymerase, which is vital for viral replication. As an adenosine triphosphate analogue, it competes for integration into the RNA chains, resulting in delayed chain termination during viral RNA replication, thereby reducing the viral load. All medications do come with contraindications and a side effect profile. Currently, remdesivir is not recommended in patients who have a history of significant hypersensitivity reactions to remdesivir or any components within the product. Additional warnings associated with remdesivir include mild to moderate transaminase elevations, which have resolved upon discontinuation. Monitoring of hepatic laboratory testing should occur in each patient, and discontinuation of remdesivir should be considered if alanine transaminase levels increase to >10 times the upper limit of normal.[2] When looking at results from clinical trials with remdesivir, patients are often categorized into ordinals based on presenting symptoms.[3,4]

Clinical Data

The first published trial with remdesivir, released on April 29, 2020, was a randomized, double-blind, placebo-controlled, multicenter trial performed by Wang et al. in Hubei, China.[3] The investigators reviewed approximately 230 hospitalized COVID-19 adults with an onset of symptoms within the prior 12 days, SpO2 ≤94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤300mmHg. Patients were given intravenous (IV) remdesivir (200 mg on day 1 followed by 100 mg daily on days 2-10) or placebo once daily for 10 days; remdesivir was not significantly associated with shorter duration of mechanical ventilation or hospital stay. However, a non-significant numerical reduction in time to clinical improvement was observed with remdesivir compared to placebo, and the authors called for additional larger studies to evaluate this reduction.[3]

Remdesivir's expanded use in the treatment of COVID-19 manifested early in the pandemic when preliminary results from the first stage of the Adaptive COVID-19 Treatment Trial (ACTT-1) were released on April 29, 2020 and signaled that remdesivir was better than placebo in terms of shortening time to recovery (Figure 1).[4] Shortly after this data was released, the Food and Drug Administration (FDA) granted remdesivir Emergency Use Authorization (EUA) on May 1, 2020. The EUA was limited to patients with severe disease who

TABLE 1. WHO Ordinal COVID-19 Disease Severity Ordinals[1]

Patient State	Descriptor	Ordinal Score
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal cannula	4
Hospitalized, severe disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)	7
Dead	Death	8

FIGURE 1. Summary Timeline of Remdesivir for COVID-19

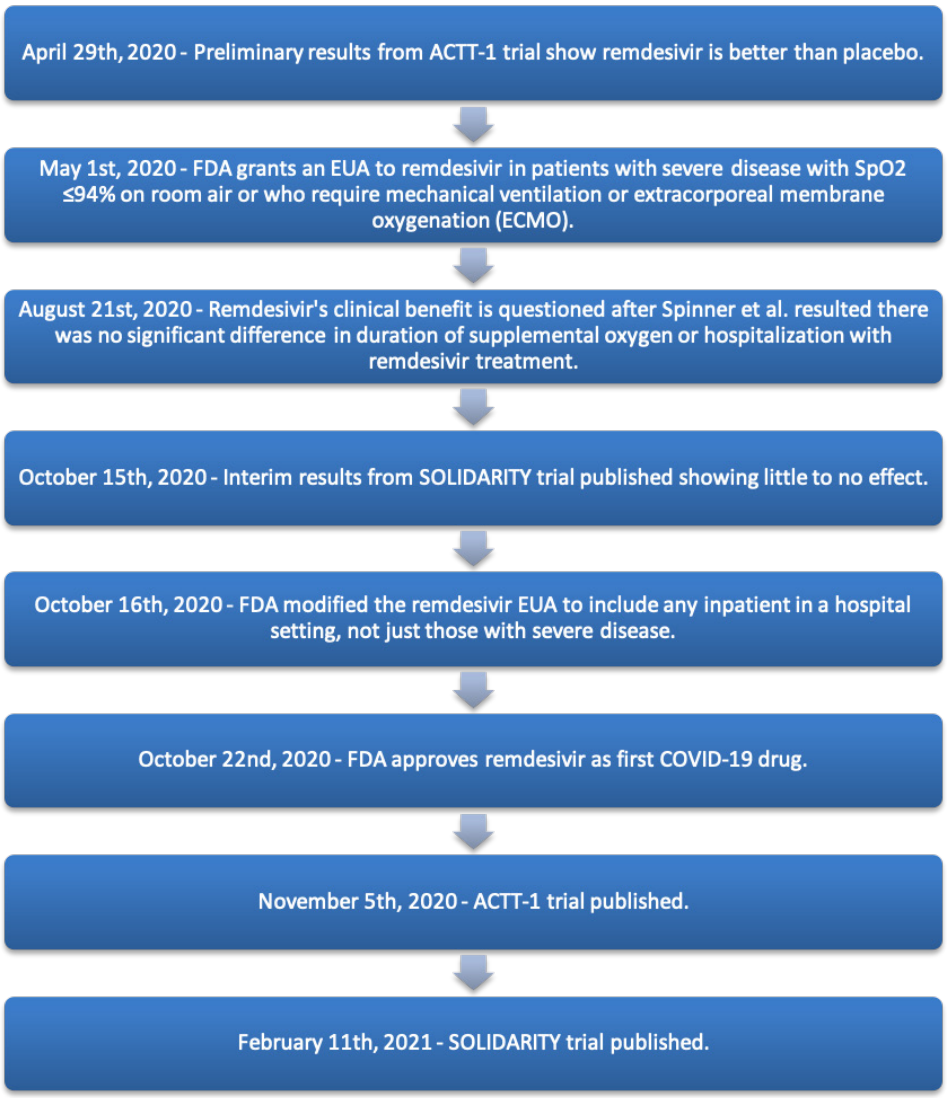


TABLE 2. ACTT-1 Disease Severity Ordinal[4]

Descriptor	*Ordinal Score*
Not hospitalized and no limitations of activities	1
Not hospitalized, with limitation of activities, home oxygen requirement, or both	2
Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons)	3
Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions)	4
Hospitalized, requiring any supplemental oxygen	5
Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices	6
Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	7
Death	8

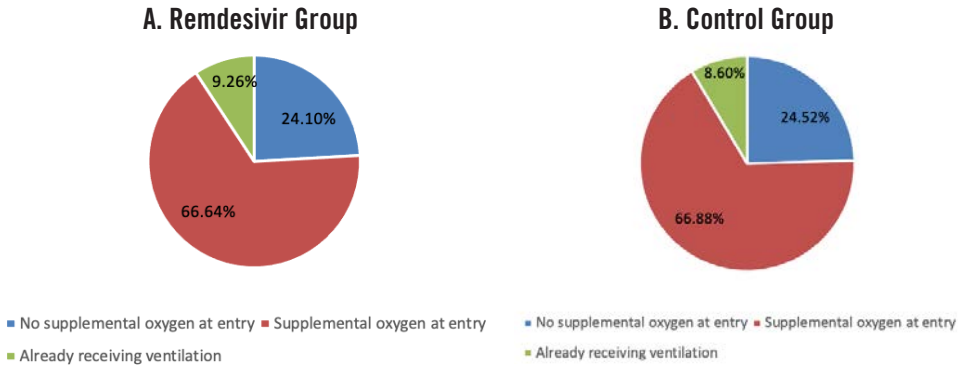
had an oxygen saturation (SpO2) ≤94% on room air, and required mechanical ventilation or extracorporeal membrane oxygenation (ECMO).[5]

On August 21, 2020, results from a Gilead-sponsored trial comparing the effect of remdesivir versus the standard of care on clinical status at 11 days in patients with moderate COVID-19 were published; moderate infection was defined as any radiographic evidence of pulmonary infiltrates and SpO2 >94% on room air.[6] Patients were located in the United States, Europe, and Asia, and were randomized to receive a 10-day course of remdesivir (n=197), 5-day course of remdesivir (n=199), or standard of care (n=200). The trial evaluated clinical status assessed on a 7-point ordinal scale on study day 11. The authors concluded that patients who received a 5-day course of remdesivir had statistically significant odds of a better clinical status than those receiving standard of care (odds ratio, 1.65; 95% confidence interval, 1.09-2.48; P=.02), but had an effect size of uncertain importance. Patients who were randomized to receive a 10-day course of remdesivir had no statistical difference between the standard of care group (P=.18). Overall, the trial demonstrated little benefit for the use of remdesivir in hospitalized patients that required no supplemental oxygenation.

In mid-October 2020, the FDA modified the remdesivir EUA to include any inpatient in a hospital setting, not just those with severe disease as the previous EUA stated. A few weeks later at the end of October 2020, remdesivir was formally FDA approved for the treatment of COVID-19 in hospitalized adult and pediatric patients ≥12 years of age and weighing ≥40 kg.[7] Given the broad category of patients included under FDA approval and new circulating clinical trials, questions again circulated regarding whether the drug was truly beneficial across all WHO COVID-19 disease severity ordinals.

Completed results from ACTT-1 were published in November of 2020.[4] Beigel et al. performed a double-blind, randomized, placebo-controlled trial with 10 days of remdesivir in adult hospitalized patients with confirmed COVID-19 and evidence of lower respiratory tract infection. The trial results demonstrated that patients who received remdesivir had a median

FIGURE 2. WHO Solidarity Trial Entry Characteristics of Respiratory Support for Remdesivir versus Control Group



recovery time of 10 days, compared to 15 days among those who received placebo (recovery rate ratio 1.29; 95% confidence interval 1.12 to 1.49; P<.001). Therefore, the investigators concluded that remdesivir was overall superior to placebo in reducing the time to recovery in hospitalized patients with confirmed COVID-19. When interpreting the results of the ACTT-1 trial, however, it should be noted the median time to randomization for both treatment groups was nine days from symptom onset, which is later than the current recommendation and could explain the higher percentage of patients with severe disease upon randomization. In addition, a few months into the trial, the primary outcome was altered, from comparison of ordinal scale scores on day 15 to a comparison of time to recovery up to day 29. This change was secondary to evolving data on COVID-19 and its concern for a protracted course.

ACTT-1 included subgroup analyses based on presenting disease severity.[4] Of note, the ordinal scale used in the subgroup analysis was slightly different than the current WHO COVID-19 disease severity scale. The ACTT-1 trial used an ordinal scale ranging from 1-8 (Table 2), with ordinal score 7 indicating hospitalized patients with invasive mechanical ventilation or ECMO, and ordinal score 8 indicating death. Results indicated the largest rate ratio for recovery using remdesivir was seen in ordinal score 5 patients, or those hospitalized patients requiring supplement low-flow oxygen (recovery rate ratio 1.45; 95% confidence interval 1.18 to 1.79). Conversely, the subgroup analysis demonstrated the smallest rate ratio for recovery in patients with ordinal score 7.

A large international study published in early December 2020 challenged previous perspectives surrounding remdesivir's benefit in COVID-19 patients. The WHO Solidarity Trial was a randomized, open control trial that included patients receiving remdesivir, hydroxychloroquine, lopinavir, interferon, or no trial drug.[8] When looking specifically at remdesivir, the study found 10.95% (301/2,750) of remdesivir patients died compared to 11.19% (303/2,708) in the control group (rate ratio 0.95; 95% confidence interval 0.81 to 1.11; P=.50) resulting in no statistical significance between the two groups. Overall, it was concluded that no drug definitively reduced mortality, initiation of ventilation, or hospitalization duration for the COVID-19 patients studied. This study did not perform any subgroup analyses to determine a potential clinical benefit or difference with disease severity, but was able to obtain data surrounding respiratory support upon entry into the trial. Baseline respiratory support in the remdesivir group (n=2,743) and control group (n=2,708) (Figure 2) were similar. Approximately two-thirds of remdesivir patients were receiving supplemental oxygen at entry and 9.26% of those patients were already receiving mechanical ventilation at entry. In the control group, approximately two-thirds of patients were receiving supplemental oxygen at entry, but only 8.61% were receiving mechanical ventilation at entry. Limitations should be taken into account while assessing the results, including, as mentioned previously, that there were no subgroup analyses to determine clinical benefit with disease severity, the trial was open labeled, and wide confidence intervals were found.

Of note, the FDA labeling for remdesivir does not align with clinical evidence or national guidelines. The package insert states remdesivir is approved in adults and pediatric patients (≥12 years of age and weighing ≥40 kg) for the treatment of COVID-19 requiring hospitalization.[9] Currently, the Infectious Diseases Society of America's guideline recommends remdesivir use only in hospitalized patients with severe disease defined as SpO2 ≤94% on room air or those who require supplemental oxygen.[10] The National Institutes of Health Therapeutic Management of Adults with COVID-19 recommends remdesivir use in hospitalized patients requiring supplemental oxygen via noninvasive ventilation or high-flow device.[7] Lastly, the Society of Critical Care Medicine (SCCM) recommends remdesivir use in adults with severe COVID-19 who do not require mechanical ventilation, but it should be ideally started within 72 hours of positive SARS-CoV-2 polymerase chain reaction or antigen testing. Furthermore, SCCM recommends against starting remdesivir in adults undergoing mechanical ventilation for critical COVID-19.[11] Both of these recommendations are in line with the findings from both Spinner et al. and ACTT-1 trials, as seen in Table 3.[4,6]

The clinical benefit of remdesivir in hospitalized patients not requiring supplemental oxygen or hospitalized patients requiring any supplemental oxygen (WHO COVID-19 disease severity ordinal 4 and 5) is where opinions are most variable. Although the clinical trials for remdesivir are not directly comparable (e.g. different methods, durations, etc.), they lend evidence to initiate remdesivir treatment early, before patients progress to a severe state and are placed on mechanical ventilation. Based on the ACTT-1 trial results, ordinal 4 in the WHO COVID-19 disease severity ordinal demonstrate the most clinical benefit from remdesivir.[4] It can be concluded that the finding is based on this ordinal group having the largest recovery rate ratio favoring remdesivir, meaning a faster recovery time with the use of remdesivir. In addition, this ordinal group likely received remdesivir early in the viral course of COVID-19 due to their earlier presentation to the hospital, and therefore the virus did not have the

TABLE 3. Summary of Key Clinical Trials with Remdesivir Use in COVID-19

Source	Wang et al.[3]	Spinner et al.[6]	ACTT-1 Study[4]	SOLIDARITY Study[8]
Published	April 29, 2020	August 21, 2020	November 5, 2020	February 11, 2021
Study Design	Randomized, double-blind, placebo-controlled, multicenter trial	Randomized, open-label, Phase 3 trial	Double-blind, randomized, placebo-controlled trial	Multinational, pragmatic, adaptive, open-label trial
Interventions	Randomly assigned in a 2:1 ratio to remdesivir or placebo for 10 days	Randomly assigned in a 1:1:1 ratio to 10-day course of remdesivir versus 5-day course of remdesivir versus standard of care	Randomly assigned in a 1:1 ratio to remdesivir or placebo for up to 10 days or until discharge	Randomly assigned into equal proportions to no trial drug or one of the trial drug regimens that was locally available (remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a)
Primary Outcomes	Time to clinical improvement within 28 days after randomization	Clinical status on day 11 assessed on a 7-point ordinal scale	Time to recovery, defined as the first day on which a patient met criteria for category 1, 2, or 3 on the eight-category ordinal scale	Assess effects on in-hospital mortality
Secondary Outcomes	Proportions of patients in each category of the six-point scale at day 7, 14, and 28 days after randomization	Proportion of patients with adverse events throughout the duration of the study	Clinical status on day 15, time to improvement of one category, mean change in status on the ordinal scale, time to discharge, number of days with supplemental oxygen, incidence and duration of new oxygen use, number of days of hospitalization, and mortality	Initiation of mechanical ventilation and hospitalization duration
Results	Remdesivir was adequately tolerated, but clinically meaningful differences cannot be excluded due to size of trial	Statistical significance between 5-day course of remdesivir and standard of care, but with uncertain clinical importance	Remdesivir was superior to placebo in shortening the time to recovery in adults	Remdesivir had little to no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay

opportunity to progress into requiring ventilation or additional oxygen support prior to admission. As treatments evolve, patient and provider awareness and encouraging earlier patient presentation for treatment will be a paramount to successful outcomes.

Lauren N. Nevinski is a 2021 Doctor of Pharmacy Graduate from Concordia University of Wisconsin School of Pharmacy in Mequon, WI. Lynne Fehrenbacher is a Associate Professor at Concordia University of Wisconsin School of Pharmacy in Mequon, WI. Thomas J Dilworth, is a Pharmacy Coordinator, Infectious Diseases at Advocate Aurora Health in Milwaukee, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

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Original Work

Pharmacists Play Critical Role in State's Hospital SARS CoV-2 (COVID) Response: An Inside Look at the Alternate Care Facility (ACF)

by Nicole Weinfurter, PharmD, Steven Finkenbinder, PharmD, Jeremiah Barnes, PharmD, Justin Guthman, PharmD, Michael Torhorst, RPh, Brook DesRivieres, PharmD, MS, FACHE, Vanessa Freitag, PharmD, MBA

In March 2020, Vanessa Freitag, vice president of operations integration and pharmacy administration for Ascension Wisconsin, was approached by health system leadership to help with the implementation of medication distribution services for a 776-bed alternative care facility (ACF), part of the emergency response efforts for the global pandemic related to coronavirus disease 2019 (COVID-19). The Department of Homeland Security-Federal Emergency Management Agency (FEMA) had pledged to provide the state of Wisconsin Department of Administration (DOA)/Department of Health Services (DHS) the necessary resources to stand up this ACF as a state emergency operations center, to provide medical care to patients in the event of a surge in COVID-19 cases in Wisconsin. The specific designation was a "temporary hospital accommodation" under section 252.02(2), distinct from a licensed care facility, pursuant to an order from the Secretary of DHS. The Army Corps of Engineers was deployed to set up the site within the Exposition Center of the Wisconsin State Fair Park in West Allis. Using the incident command system structure, a number of section chief positions were established to serve as decision makers and ensure delivery on the intended goals. Ascension Wisconsin committed to providing medication management oversight for the ACF, with Freitag acting as the site's chief pharmacy officer.

Within the first 24 hours of assuming responsibility for this project, a small workgroup of Ascension Wisconsin pharmacists was assembled to develop plans for implementing medication distribution services. The workgroup was given eight days to accomplish this task. This article shows the work that pharmacists contributed to prepare and facilitate medication management services at Wisconsin's ACF site, while also serving as a call to action for the further development and standardization of the work completed on this project.

Initial Strategy

Defining Scope, Approach, and Communication Infrastructure

Confirming scope. During the planning period, there were multiple changes to the scope of patient criteria for admission to the ACF. The target population was clarified to be low-acuity, COVID-positive patients with an anticipated length of stay of no longer than five days. The intent of the non-licensed ACF was to be a "pressure relief valve" for area hospitals, allowing for improved focus on higher-acuity COVID patients and other non-COVID patients. This step proved to be an essential component of determining the extent of pharmacy services that would be needed at the facility.

The ACF was to be designed using the simplest strategies, to allow for rapid change implementation. The charge was to build a system independent of the technology and automation commonly used in acute care pharmacy management, to allow rapid deployment of services. The extent of the technology within the ACF was a light version of an electronic health record (EHR) platform, with census and progress note documentation functionality; secure text and video on smartphones; and a printer-copy-fax machine. Medication management was accomplished using a paper system due to the limited pharmacy functionality in the scaled-down EHR use.

Approach. To meet the imminent deadline for implementing services at the ACF, pharmacist workgroup used a "divide and conquer" strategy to create a feasible medication services workflow. The workflow was built with the phases of medication use in mind: selection, procurement, storage, preparation, distribution, administration, monitoring, and disposal (Table 1). Pharmacists in the workgroup were each assigned to a phase to begin research, establish options for execution, and propose a model based on the scope of the deliverable and timeline. Considerations included the source of medication supply (facility- or patient-supplied); security (including handling of controlled substances); and workflow integration with other services at the site (i.e. supply distribution, medical care, nursing practice); all while ensuring the workflows maintained an environment of safety and cleanliness to prevent the spread of COVID-19 within the ACF. It was clear that the team needed to expect the unexpected and readily adapt to this rapidly changing environment by thinking outside of the box.

Stakeholder engagement. When the project launched, engagement with the chief officers (Medical, Nursing, and Operations) for the ACF occurred through daily meetings and via email and text communications throughout the day, so decisions could be made rapidly. "Point people" within the pharmacy planning team were identified, to communicate and coordinate with each of the external stakeholders involved (i.e. wholesalers, Drug Enforcement Administration (DEA) representatives, state agencies, and other vital partners). The medication management planning team also attended multiple touch-point discussions throughout the day to report on completed task items, as well as barriers that needed escalating. A shared file drive (using G-Suite) was established to house all documents related to the project, including reference documents and working drafts. This allowed stakeholders

TABLE 1. Sample Considerations to Define the Medication Use Model

Medication Use Phase	*Sample Considerations*
Selection	Will the formulary be restricted or open? What will be the process for medications not stocked or available at the ACF?
Procurement	Is there a contracted vendor for the ACF for supply ordering? How will account purchasing occur and invoice management? Do accounts need to be established? How will non-formulary medications be obtained? Will controlled substances be ordered by the ACF or only set up to use the patient's own supply?
Storage	Is the space for medication storage secure with limited access? Who will have access if a pharmacist is not present? Is the room intended to serve as a medication room or will the space operate as a licensed pharmacy? Will provisions be available to store controlled substances? What controls need to be in place for refrigerated drug storage?
Ordering	Will a common medication order set be used or will orders fully open to the physician discretion? Are automatic interchanges/substitutions acceptable? Will we use standing orders for select on-demand medications?
Preparation	Will unit dose or bulk dispensing be the primary model? Is a combination of unit dose and bulk medication dispensing be achievable (as patients may be coming with a three-day supply)? Are infusions offered and will sterile compounded products be needed? Coordination with sterile compounding facilities may be necessary if so.
Distribution	Is a med pass model or on-demand model more acceptable for this situation? Will nursing and physicians have access to the medication room or will it be controlled by licensed pharmacists? How will controlled substances be handled when brought by the patient or dispensed from the medication room to ensure security? The distribution model must limit cross contamination of people and products (as ACF has both COVID-positive and COVID-negative areas within the operational structure).
Administration	Who will be doing the med passing? How will medication administration records be maintained? Will this be manual or electronic? Will patients be allowed to manage their own medications?

to make real-time changes, suggestions, and comments to documents, and reduced issues with version control.

Days 2-8

Medication Services Development

The team discussed medication safety, including use of patient identifiers, use of wristbands, space assignments for patients (equivalent to room identifiers), and access to emergency medications at the facility given the unique facility care model.

The team reviewed the following options for medication distribution and ultimately chose Option 1.

- **Option 1:** Full satellite med room. This positions inventory and pharmacy labor on-site to prepare and dispense patient-specific medications. It is the most flexible option, because a pharmacist is on-site to help with situations where reconciliation and adjustments are necessary. The repacking of the patient's own medications into unit-dose packaging would be required, however.
- **Option 2:** Nursing home blister-pack model. This requires a higher level of coordination and multiple distribution models (hospital discharge supplies, and supplies that won't come with the patient).
- **Option 3:** Patient-specific prescriptions, which would facilitate a process for patient-specific prescription vials with retail pharmacy. Medications would be dispensed in prescription bottles, which might be more complex for nursing staff to manage for a medication pass.
- **Option 4:** Patient-managed medications. Patients would bring their home supply of medications and manage their own medication regimen independently. Based on experience with the patients admitted early on, this option proved to be impractical and/or unsafe.

Formulary. Based on other ACF site models around the nation, it was initially proposed that patients admitted to the ACF should be required to have a three-day supply of their outpatient medications provided by their discharging facility for use at the ACF. However, the pharmacists involved in this project recognized that this model would likely not be optimal for hospitals without access to 24-hour pharmacy services or retail pharmacies; therefore, the team developed a medication formulary of just over 100 relatively standard medications. The formulary included one or two drugs in each of the following categories: pain; GI prophylaxis/GI upset/bowel regimens; anticoagulants and antiplatelet agents; fluids and electrolytes; infectious disease; cardiac health; neurology; mental health; and endocrinology. More than 20 items were deemed appropriate for as-needed medication standing orders, and these products were securely stored in the patient care area. Five formulary controlled substances (HYDROcodone 5mg/Acetaminophen 325mg; OxyCODONE 5mg IR; TraMADol 50mg; LORazepam 0.5mg; and Zolpidem 5mg) were also selected for routine stock. This base formulary was supplemented with a model to procure urgent non-formulary medications for patients, leading to the development of two distinct pathways for medication services at the site: formulary medications and non-formulary medications. The site's medication formulary was approved by the medical staff and work was completed to procure the medications from a pharmaceutical distributor, which required a variance by the Pharmacy Examining Board to allow drug distribution from a wholesaler to an address approved by the board (i.e. a "surge site").[1] To mitigate patient safety concerns and further need to supply patients with non-formulary medications, workflows were developed to leverage existing retail pharmacy workflows within the Ascension health system network to have these medications delivered to the ACF for individual patient use.

Above: *ACF Constructed at the Milwaukee State Fair Park Exposition Hall.*

Subsequent development of the standard operating procedures (SOPs) quickly followed to outline the procurement, dispensing, and administration of medications within the ACF. Medication services team members with inpatient and retail pharmacy perspectives were involved in the development of these workflows, along with a pharmacy resident who was pursuing an emergency management rotation. The majority of these processes and procedures were designed to use as little technology as possible, with mostly on-paper tools. A paper order set was developed to mirror the site's entire formulary and serve as a tool to facilitate the admissions process of each patient. A template for a medication administration record (MAR) was created. The pharmacist created an individual paper copy for each patient each day, so nursing staff could document medication administrations. Medication safety was also a top priority in the workflow development process, with many of the medication safety recommendations from the Institute for Safe Medication Practices (ISMP) incorporated into these workflows. Many pharmacist-driven protocols commonly found in acute care facilities (e.g., IV to PO, substitutions per formulary) were modified and adopted as SOPs to fit the ACF patient care model. All protocols and SOPs were approved by the chief medical officer and chief nursing officer for the ACF.

Workspace. Within the Exposition Center used for the ACF, the ticket office was designated as the medication room. To streamline workflows, the medication room was divided into stations for each step of the medication distribution process. An intake and decontamination station allowed staff to sterilize items potentially exposed to COVID, such as paperwork and home medication vials. This was followed by a station for reviewing each patient's admission order set and assembly of the paper MAR. The back of the space housed medication shelving and a workspace for assembling each patient's medication envelope for the day. An additional locked room located within the ticket office was used to store the controlled substances kept at the ACF. A clean space for IV medication preparation was also designated in this area. Intravenous admixture (e.g. remdesivir) was done according to USP's immediate-use compounding guidelines; mixtures were prepared in a clean space within the medication room and given a one-hour beyond-use date. This process required intentional communication between the medication room and nursing staff so as not to waste medication doses. After medications were prepared for delivery, runners delivered the medications to nursing staff using twice-daily medication administration times in patient-specific envelopes to avoid having pharmacists enter the COVID-19-positive patient environment.

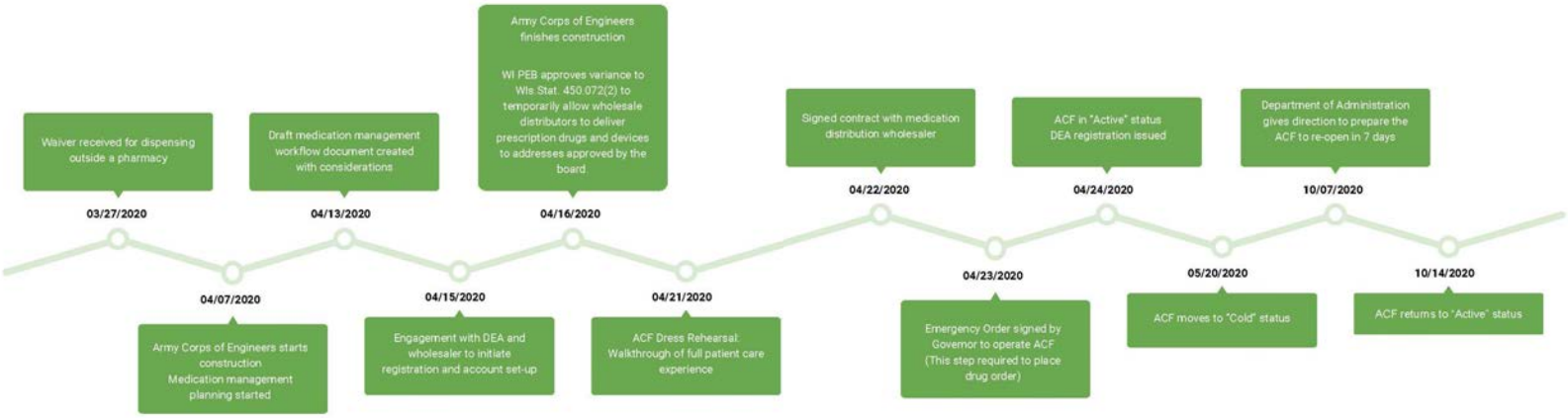
Preparing for Go-Live

Process Refinement and Staff Readiness

After the initial medication use framework had been set up and processes were approaching the go-live date, additional pharmacist help was requested to support workflow optimization and daily operations. At that time, FEMA quickly deployed two additional staff pharmacists from the Department of Veterans Affairs (VA) hospital in Milwaukee. These pharmacists' main duties included creating orientation materials specific to medication management services; reviewing and updating standard operating procedures; inventory maintenance; and short-term staffing of the ACF medication room.

It was immediately recognized that comprehensive training for medication management workflows would be essential to the success of these services. This was especially crucial as the ACF workforce was to be composed of many different pharmacists from a variety of backgrounds, with staff changing on a daily basis. To meet this charge, the VA pharmacists started by evaluating the medication services

FIGURE 1. ACF Timeline (top and bottom of page)



workflows and procedures for efficiency, clarity, and simplicity. After a procedure was finalized, a step-by-step video tutorial was created to visually walk pharmacists through the process. The pharmacists also created workflow checklists, a frequently-asked-questions document, and directions for entry for pharmacists reporting to the ACF. This information was also uploaded to the G-Suite platform to provide easily accessible off-site training to future ACF pharmacists.

A clinical review of medications on formulary was also performed specific to the target population's needs, and adjustments to the base formulary were made. Receiving, returning, and reordering of medications was clearly defined in a checklist for future pharmacist use. A medication safety review was then performed, and Institute for Safe Medication Practices initiatives, such as look-alike-sound-alike (LASA) and hazardous labels and tall-man lettering were implemented. Security measures were added to support controlled substance dispensing, including placing a drug storage lock box at the nursing station with shift-to-shift count reconciliation, and perpetual inventory logs. A compilation of clinical resources pertinent to the treatment of COVID-19 was developed to foster information sharing and strengthen the site-specific knowledge base of pharmacists working at the site.

In retrospect, the lesson is clear: To actualize medication use procedures, collaboration between foundational and operational liaisons is crucial. Through hands-on process testing, strategic simplification, and early initiation of training material development, SOPs can be refined to be ready for application to patient care.

Ready When Needed

While the facility was ready to accept patients by April 24, 2020, area hospitals had pivoted to internally manage patient surges through patient transfers and critical bed management. As a result, the ACF did not receive immediate requests for admissions, which subsequently placed the ACF into cold status (hibernation) from May 20, 2020 to October 14, 2020 (Figure 1). During this hibernation period, all medications were returned to the wholesaler and the facility was locked down. The fall of 2020 saw an additional surge in hospital admissions due to COVID-19 that greatly exceeded the spring surge and strained area healthcare systems. The order to re-activate the ACF came on October 7, 2020, proposing a return to active status on October 14, 2020.[2] This prompted the pharmacy leadership team to once again prepare the ACF for medication distribution services and work with FEMA to contract with the VA to provide pharmacist staffing. Initially, one pharmacist was scheduled per day to cover from 7:00 AM to 7:00 PM, with the intent to complete the morning medication pass and other activities from 7:00 AM to 11:00 AM, break from 11:00 AM to 3:00 PM, then complete the evening med pass from 3:00 PM to 7:00 PM. During the time block from 7:00 AM to 7:00 PM, these pharmacists were on call in case of overnight admissions. By 3:00 PM each day, the pharmacy administrator would receive a notification about how many admissions were planned for the next day and communicate this information to the staffing pharmacists.

The first patient was admitted to the ACF on October 21, 2020. The admission process for the first patients was a bit

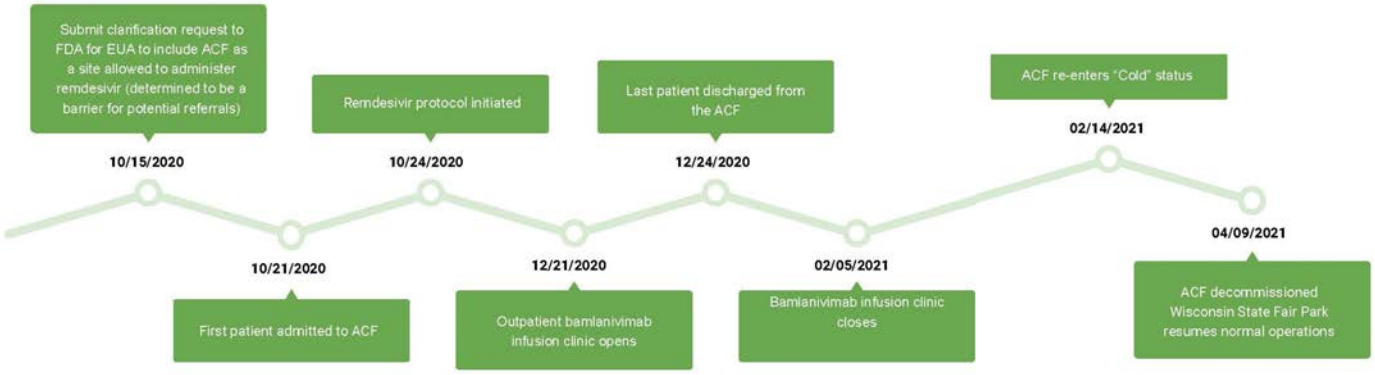


TABLE 2. Patient Requirements for Admission at the ACF

Initial	*Final*
Currently hospitalized for at least 24 hours	• Same day transfers for patients currently hospitalized **OR** • ED for at least 4 hours (pending physician-to-physician review)
Patients age between 18 and 70	Patients 18 and older
Orders for IV fluid hydration and limited antibiotics	Orders for IV fluid hydration, limited antibiotics, and remdesivir
From Floor: oxygen requirement of NC O2 4 Litres per Minute (LPM) or less to maintain pulse ox of greater than 90%	• From ED: oxygen requirement of NC O2 16 LPM or less to maintain pulse ox of greater than 90% • From Floor: oxygen requirement of Optiflow 50 LPM/50% FiO2 or less to maintain pulse ox greater than 90%
Transferring facility must transfer at least 3 days of medication with patient	• Transferring facility should transfer any non-formulary medication with patient • Patients own medications acceptable

cumbersome and ended up taking longer than anticipated. This led to several adjustments to workflow processes.

One of the first changes was streamlining the process for medication reconciliation to ensure patient safety and pharmacy efficiency. Initially, pharmacists were relying on medication lists sent from the admitting hospital as the source of all medication records. This was quickly found to be insufficient and inefficient. As the ACF evolved, the pharmacy team started to reach out to the transferring hospital ahead of time to obtain accurate medication lists, anticipate gaps in medication stock, gather times of last medication administration, and proactively address problems prior to the patient transfer. In the end, the ideal model became a pharmacist-to-pharmacist discussion between the transferring facility and the ACF about the patient's medication list prior to transfer.

A unique aspect of the ACF was that physicians and nursing staff changed daily. Pharmacists at the ACF, on the other hand, were scheduled in week-long blocks, which allowed for process consistency and smoother handoffs of care coordination and medication management. Since pharmacists were proactively reaching out to the transferring facility to perform detailed medication reconciliations prior to admission, the care team quickly determined that pharmacists were best equipped to prepare the medication order template for each patient to be reviewed by the ordering physician. Upon patient arrival to the ACF, the pharmacist would present the reconciled order form to the physician for clinical assessment and modification if necessary, along with the physician signature. This form was then returned to the pharmacist to begin compiling the patient's medication pass envelope. This drastically improved workflow, decreased medication delays, and improved provider satisfaction.

Initial exclusion criteria for the ACF included a negative COVID test; skilled nursing care, nursing home, or assisted living residents; weight over 350 pounds; catheterization requiring assistance; complex wound care; continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP); dialysis; Clinical Institute Withdrawal Assessment for Alcohol (CIWA) score greater than 8; acute mental health issues or drug/alcohol addiction; pregnancy; incarceration or in police custody; severely immunocompromised or contact precautions for acute diarrheal illness, know active Methicillin-Resistant Staphylococcus aureus (MRSA), Clostridium difficile, tuberculosis, Extensively Drug-Resistant Organism (XDRO), Multidrug-Resistant Organism (MDRO), or known Candida auris colonization or infection; or investigational drug regimens. These criteria were established to ensure staff was able to manage patients safely in the unique ACF environment, but were modified as appropriate (such as eliminating a previous age limit).

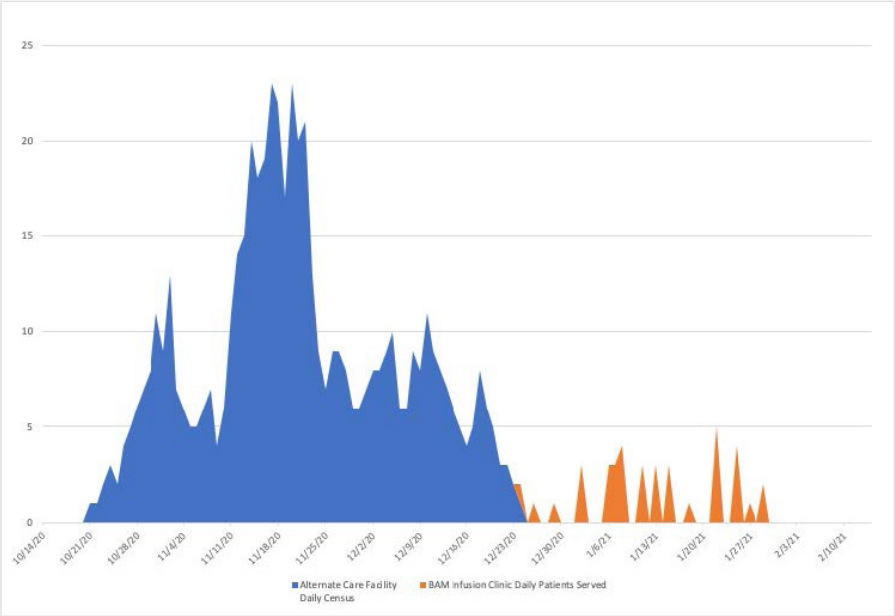
It was recognized early on that the initial acceptance criteria needed to be modified as well to be more inclusive of the COVID patients who were presenting to Wisconsin hospitals (Table 2). This relied on pharmacists, respiratory therapists, and other clinical staff at the ACF for feedback and subsequent integration of these modified criteria. The most prominent modification involved the Wisconsin DOA and DHS submitting a waiver on behalf of the ACF to administer remdesivir. The ACF was the first non-licensed facility in the nation to be granted Food and Drug Administration (FDA) emergency use authorization (EUA) to use remdesivir outside of inpatient acute-care hospitals. This paved the way for other states' COVID response sites, with Wisconsin leading the way. The acceptance criteria were refined using an iterative process with regional health-system chief executive officers, CMOs, CNOs, and care management leaders. Changes were done incrementally to support the state's evolving needs. In the end, the ACF was also able to provide bamlanivumab infusions for the final seven weeks of operations (Figure 1).

Lessons Learned

Staffing

What began as a one-pharmacist operation organically grew into three separate eight-hour pharmacist shifts per day to accommodate an increasing census in a manual medication distribution model. Original staffing models were not sufficient to account for the significant inefficiencies caused by the lack of many of the technological conveniences that acute care facilities are accustomed to. As time went on, the team found that two overlapping pharmacist shifts were ideal to support the ACF care model: one pharmacist to focus on patient intake and medication reconciliation, while the other pharmacist focused on the medication distribution process. At times of very low census, downtime was spent managing medication inventory, coordinating patients' own medication delivery and returns, and performing quality assurance on documentation and records. During the first observed surge at the facility and highest peak of patient admissions, one pharmacist worked an 18-hour day. An on-call system could have been considered for potential unplanned peaks in admissions, but this was never explored. While the intent was

FIGURE 2. Patient Census



to extend the staffing model to include pharmacy technicians, a high reliance on pharmacist credentials to support the clinical staff at the ACF led to using additional pharmacists as cross-coverage instead. Staffing was a combination of FEMA-identified VA pharmacists, ACF-contracted temp agency pharmacists, and Ascension-employed pharmacists.

Common Medications

Remdesivir (if criteria were met), albuterol, dexamethasone, and enoxaparin became inventory staples at the ACF for treating COVID patients. Cough suppressants and guaifenesin were common medications requested for as-needed use and eventually moved to floor stock. Emergency or rapid-response was supported by 24-hour on-site paramedics contracted through an ambulance service, thus eliminating the need for emergency crash carts. A surprising yet understandable need that arose at the ACF was for pharmacologic agents for sleep induction and sleep maintenance, because patient beds were in an area with overhead fluorescent lights that remained partially on at all times.

Scope of Services

As the acuity of patients and the demand for ACF admissions increased, the scope of medication management services did as well. What started as plans to perform only an admission medication reconciliation expanded to daily reconciliation with pharmacist participation in care management and discharge rounds, which were held virtually. In addition to medication reconciliation, daily clinical functions included warfarin and remdesivir lab monitoring. Acceptance criteria changed from requiring inpatient status for admission to allowing direct admittance from an emergency department (ED), which became the most common admission type for the ACF. The medication reconciliation process for a direct admission from an ED often required more time spent on medication reconciliation, as a hospital pharmacist was not typically involved in these patients' care prior to transfer to the ACF.

Communication

Pharmacist-to-pharmacist handoff was crucial at the ACF. Work done by the Pharmacy Society of Wisconsin (PSW) to connect pharmacy leaders from health systems and hospitals throughout Wisconsin proved to be a tremendous resource. A dedicated page within the PSW website shared the ACF formulary, admission criteria, and floor-stock medications, as well as routine conference calls for process refinement and information sharing, which expedited patient handoff between care sites. Prior to or at the time of admission, a pharmacist from the referring facility and an ACF pharmacist would confer on the following:

- Date and time of last known dose of medications given at the referring facility
- Which medications would be transferred with the patient
- Whether the patient would be a candidate for remdesivir, dexamethasone, and/or anticoagulation, and whether these were already started at the referring facility

A complete MAR was then faxed from the referring pharmacist to the ACF to prepare for reconciliation against the formulary. Collaborating with social services and adding a standing placeholder at rounds increased the frequency with which patients discharged with their own home medications. Working closely with the interprofessional care teams was key to effectively serving the COVID-19-positive patients admitted to the ACF.

A total of 170 patients were served by Wisconsin's ACF (Figure 2). As more COVID-19 treatments became available, the ACF saw less demand for acute care services and more demand for outpatient infusion therapy. Having a medication management program that could quickly flex to the changing demand of the public health crisis was important for success.

Leader Reflection and Future Applicability

Developing medication management services for Wisconsin's ACF served as a learning experience for the entire team, especially considering the time constraints. The core medication-use processes set the foundation to build these medication distribution services. The team needed quick action, rapid decision making, and strong collaboration. It was essential that pharmacists were willing to be flexible, to change course when the situation demanded it.

While our project leader was able to reach out to other ACF medication services leaders in other parts of the country, the models and takeaways at each site varied greatly, making it difficult to generalize or adopt a one-size-fits-all model. However, having examples of real operations at other ACF sites did influence some of the decisions and direction for the Wisconsin ACF. Various toolkits and quick reference

guides offered a starting point, but the level of detail needed to bring those processes live, on a tight timeline, was the real challenge. As of this writing, the likelihood of needing to establish another ACF for a global pandemic seems remote, but there would be value in having a toolkit and resources prepared for the implementation of standardized medication services, should other public health emergencies or natural disasters arise in the future. This document could serve as another resource for pharmacy leaders. In fact, the most valuable resource for the ACF medication distribution process success was the contributing pharmacists. Without each pharmacist's contributions and dedication, this ACF site would have not have had the bandwidth to assist state health systems in combating the COVID-19 pandemic.

Nicole Weinfurter is a PGY1 Pharmacy Practice Resident at Ascension St. Clare's Hospital in Weston, WI. Steven Finkenbinder is a Clinical Pharmacist at the Milwaukee VA Medical Center in Milwaukee, WI. Jeremiah Barnes is a PGY2 Internal Medicine Resident at the Milwaukee VA Medical Center in Milwaukee, WI. Justin Guthman is the National Director Pharmacy Operations at Ascension in Marshfield, WI. Michael Torhorst is the Area Director, Pharmacy Continuity of Care - WI at Ascension in Milwaukee, WI. Brook DesRivieres is a Pharmacy Network Executive for Vizient in Waunakee, WI. Vanessa Freitag is the Vice President of Ambulatory Services and Operations Integration at Ascension Wisconsin in Milwaukee, WI.

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Original Work

Impact of Electronic Health Record Alerts on Psychiatric Medication Monitoring in the Ambulatory Setting

by Mickey Hart, PharmD, BCACP, Evan Petrie, PharmD, Alexandra Sklansky, PharmD, BCPP, Lisa Rein, ScM, Thomas Heinrich, MD

Abstract

Introduction: Laboratory monitoring is an important component of the assessment of efficacy, safety, and adherence for many psychiatric medications. Despite the availability of evidence-based guidelines, compliance with recommended monitoring is generally low.

Methods: Targeted clinical decision support for laboratory monitoring recommendations for prescribers of antipsychotics, lithium, and valproic acid/divalproex were incorporated into the electronic health record (EHR). Inclusionary and exclusionary logic was determined based on evidence-based guidelines and clinician preferences.

This retrospective, pre-post quasi-experimental study evaluated the impact of the intervention on compliance with recommended monitoring. The primary study outcome was the difference in the rate of fully compliant medication monitoring pre- and post-intervention for antipsychotic, lithium, and valproic acid/divalproex medications. Secondary outcomes included the difference in mean percentage compliance with antipsychotic, lithium, and valproic acid/divalproex medication monitoring pre- and post-intervention.

Results: The rate of fully compliant antipsychotic, lithium, and valproic acid/divalproex medication monitoring improved from 45.0% in the pre-intervention period to 67.0% in the post-intervention period ($p < 0.001$). The mean percentage compliance with antipsychotic, lithium, and valproic acid/divalproex medication monitoring also improved, from 58.1% to 76.2% (SD 42.4 and 37.4 respectively; $p < 0.001$). This change was driven by improvements in metabolic monitoring for second-generation antipsychotics, whereas changes to lithium and valproic acid/divalproex monitoring were not significant.

Conclusions: Targeted clinical decision support for prescribers, in the form of EHR alerts, can be effective for improving compliance with recommended lab monitoring for psychiatric medications, particularly metabolic monitoring for second-generation antipsychotics, in the ambulatory setting.

Laboratory (lab) monitoring is an important component of the assessment of efficacy, safety, and adherence for many psychiatric medications. Major guidelines from the National Institute for Health and Care Excellence (NICE), American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists (AACE), and North American Association for the Study of Obesity (NAASO) provide recommendations for lab monitoring and frequency for common psychiatric medications, such as antipsychotics, lithium, and valproic acid/divalproex.[1-3]

Despite the availability of these guidelines, data on monitoring after initiation of these medications illustrates that compliance with the recommendations in clinical practice is low.[4-10] A 2011 meta-analysis by Mitchell et. al. evaluated metabolic monitoring for patients prescribed antipsychotics. The meta-analysis included nine studies conducted after the publication of major guidelines, and found that only 56.1% and 37.2% of patients had glucose monitoring and lipid monitoring, respectively.[7] While it had not been formally evaluated, a similarly low rate of compliance to the recommendations had been observed by clinicians at Froedtert & the Medical College of Wisconsin (F&MCW) Center for Consultative Academic Psychiatric Services (CCAPS) clinic, an outpatient behavioral health clinic staffed by post-graduate year 2 (PGY2) psychiatric medical residents and supervising faculty psychiatrists.

Psychiatric medication monitoring support using electronic health record (EHR) alerts has been used as an effective method for improving compliance to psychiatric medication monitoring guidelines since at least 2004, in both the acute and ambulatory care settings.[11-15] Based on this information, clinic leadership in the F&MCW CCAPS clinic requested to be included in creation of clinical decision support, in the form of EHR alerts, for select psychiatric medications that require lab monitoring. This study was completed to determine the impact of these EHR alerts.

Methods

Intervention

A collaborative multidisciplinary team, involving clinical and informatics pharmacists and physicians, created best practice advisories (BPAs) designed to fire for antipsychotic, lithium, and valproic acid/divalproex prescriptions ordered by psychiatry medical residents in the CCACPS clinic. A BPA is a customized, practice-specific alert within the EHR that is programmed to appear for a patient, medication, lab, or other order according to pre-determined triggers, using inclusionary or exclusionary logic.

Inclusionary and exclusionary logic was based on guidelines from NICE, ADA, APA, AACE, and NAASO, with minor modifications to best fit institutional lab practices and clinician preferences.[1-3] Recommended lab monitoring parameters were: for antipsychotics, annual glycohemoglobin and lipid panel; for lithium, semiannual basic or comprehensive metabolic panel, thyroid stimulating hormone, plasma lithium level, and serum calcium; for valproic acid/divalproex, annual liver function tests, complete blood count, and total (with or without free) valproate level.

Upon opening the chart of a patient with incomplete recommended lab monitoring for an included medication, a BPA would fire and display as an alert window within the EHR. From this alert, the prescribing resident could order missing labs or decline to order them. If declining, the resident could select an acknowledgement reason ("labs not appropriate;" "labs already ordered [but not yet completed];" "patient refuses labs;" or "labs completed elsewhere"). The alert could also be deferred temporarily to allow for chart review prior to decision-making. Signing a prescription for an included medication with incomplete recommended lab monitoring would also fire a BPA and display as an alert with similar options. The BPAs were not a hard stop to prescribing or closing the patient's chart (i.e., they could be bypassed).

Study Design

This was a retrospective, pre-post quasi-experimental study. This study was reviewed by the Froedtert Health Pharmacy Research Committee and Medical College of Wisconsin Human Research Protection Program and determined to be a quality improvement project that did not require further review by the Institutional Review Board.

The pre-intervention time period was July 1, 2017 through December 31, 2017, and the post-intervention time period was July 1, 2018 through December 31, 2018. The intervention went live in the EHR on May 1, 2018 after a one-time, in-person education session for all affected psychiatry medical residents and supervising faculty physicians in April 2018.

All prescriptions for antipsychotic, lithium, or valproic acid/divalproex medications ordered by a psychiatry medical resident in the CCAPS clinic were included(medications entered as "historical" or otherwise not sent to a pharmacy were excluded). Medication class, prescription dates, and class-specific recommended lab parameters were collected for included prescriptions. Prescriptions could be considered 100% compliant with recommendations if all recommended labs were complete (with results) or considered partially compliant (recorded as a percentage) if only some of the recommended labs were complete. Labs could be completed up to 28 days after a prescription order and still be considered compliant. This 28-day window was selected to provide adequate time for patients to visit the lab after their office visit or refill request, thus avoiding interruptions to these important pharmacotherapy regimens that could occur if care teams were required to hold prescriptions until after completion of labs.

Outcomes

The primary study outcome was the difference in the rate of fully compliant antipsychotic, lithium, and valproic acid/divalproex medication monitoring pre- and post-intervention. Secondary outcomes were: the difference in mean percentage of compliance with antipsychotic, lithium, and valproic acid/divalproex medication monitoring pre- and post-intervention; the difference in the rate of fully compliant antipsychotic medication monitoring pre- and post-intervention; the difference in the rate of fully compliant lithium medication monitoring pre- and post-intervention; and the difference in the rate of fully compliant valproic acid/divalproex medication monitoring pre- and post-intervention.

Data Analysis

Compliance was recorded as the number and percentage of lab monitoring requirements that were fulfilled for each prescription. Compliance was summarized using the mean, standard deviation, median, and range, and as the frequency and percentage of prescriptions with 100% compliance. The proportion of prescriptions with 100% compliance was compared between the pre- and post-intervention periods using Fisher's exact test. Compliance (continuous) was compared between the pre- and post-intervention periods using the exact Wilcoxon rank-sum test. Comparisons were made for all prescriptions and within the following medication subgroups: antipsychotics, lithium, and valproic acid/divalproex. All statistical analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, r-project.org). All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

The rate of fully compliant antipsychotic, lithium, and valproic acid/divalproex medication monitoring improved from 45.0% in the pre-intervention period to 67.0% in the post-intervention period ($p < 0.001$). The mean percentage compliance with antipsychotic, lithium, and valproic acid/divalproex medication monitoring also improved, from 58.1% to 76.2% (SD 42.4 and 37.4 respectively; $p < 0.001$). Statistically significant improvements were seen in 100% compliance rates and continuous percent compliance for antipsychotic monitoring. No statistically significant differences were observed for lithium or valproic acid/divalproex monitoring. Mean percent compliance for valproic acid/divalproex improved from 72.2% to 86.3%, but this difference was not statistically significant. See Table 1.

The majority of included prescriptions in the pre- and post-intervention periods were for second-generation antipsychotics (86.4% and 81.6%, respectively).

Discussion

The findings of our study demonstrate that targeted clinical decision support, in

TABLE 1. Compliance with Recommended Laboratory Monitoring, Pre- and Post-intervention

	Pre-intervention Prescriptions	*Post-intervention Prescriptions*	*p-value*
Antipsychotics	**n = 168**	**n = 154**	
Fully Compliant	74 (44.0%)	104 (67.5%)	< 0.001
Mean Compliance (SD)	56.5% (42.9)	75.6% (38.0)	< 0.001
Lithium	**n = 11**	**n = 8**	
Fully Compliant	5 (45.5%)	2 (25%)	0.633
Mean Compliance (SD)	65.9% (39.2)	62.5% (35.4)	0.645
Valproic Acid/Divalproex	**n = 12**	**n = 17**	
Fully Compliant	7 (58.3%)	14 (82.4%)	0.218
Mean Compliance (SD)	72.2% (37.2)	86.3% (31.3)	0.239
Overall	**n = 191**	**n = 179**	
Fully Compliant	86 (45.0%)	120 (67.0%)	< 0.001
Mean Compliance (SD)	58.1% (42.4)	76.1% (37.4)	< 0.001

SD = Standard Deviation

the form of EHR alerts for prescribers, can be effective for improving compliance with recommended lab monitoring for psychiatric medications at our institution. These findings are in alignment with and extend the generalizability of similar studies that involved the creation of recommendations on lab monitoring for psychiatric medications and associated electronic reminder tools.[11-15] In our study, the rate of 100% compliant lab monitoring at the time of prescribing antipsychotics, lithium, and valproic acid/divalproex improved from just 45% before the intervention to 67% after the intervention, a relative increase of nearly 50%. This change was driven by improvement in metabolic monitoring for antipsychotic prescriptions, most of which were second-generation antipsychotics (86.4% and 81.6% of prescriptions in the pre- and post-intervention periods, respectively), whereas changes to lithium and valproic acid/divalproex monitoring were insignificant.

Our study had some important limitations. First, because the CCAPS clinic is staffed specifically by PGY2 psychiatry medical residents, the group of prescribers differs in our pre-intervention and post-intervention periods, due to the annual advancement of resident physicians in their program. However, the supervising faculty psychiatrists were consistent in the pre- and post-intervention periods. Second, there were relatively few prescriptions sent for lithium and valproic acid/divalproex, limiting our power to detect a difference in monitoring for those medications. Finally, we were unable to collect data on resident physicians' individual electronic responses to the EHR alerts for the purposes of this study.

Conclusions

Clinical decision support for prescribers, created and implemented by a multidisciplinary team, can improve compliance with evidence-based guidelines for monitoring psychiatric medications, particularly metabolic monitoring for second-generation antipsychotics, in the ambulatory setting.

Mickey Hart is s a Clinical Pharmacist in Primary Care at Froedtert Health in Milwaukee, WI. Evan Petrie is an Informatics Pharmacist at Froedtert Health in Milwaukee, WI. Alexandra Sklansky is a Clinical Pharmacist at UnityPoint Health - Meriter in Madison, WI. Lisa Rein is a Biostatistician at the Medical College of Wisconsin in Milwaukee, WI. Thomas Heinrich is a Professor and Executive Vice-Chair, Department of Psychiatry and Behavioral Medicine at the Medical College of Wisconsin in Milwaukee, WI.

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Original Work

Commercial Member Perception of a Pharmacogenomic Testing Program Led by a Pharmacy Benefits Manager

by Abigail L Deming, PharmD, Marleen K Wickizer, PharmD, Tina A Patel, PharmD, Suzanne Horowitz, MHA, Agata Siwak, PharmD, Julie A Olson, DNP, Robert V Topp, PhD

Abstract

Objective: Pharmacogenomics (PGx) is the study of the role of DNA in an individual's response to a drug. The results can be used proactively to select a personalized medication. Some pharmacy benefit managers (PBMs) offer PGx testing to members, but the member experience is unknown. This study explored the perceptions of two commercial client populations invited to participate in a PGx testing program.

Methods: Members who underwent testing completed an anonymous written survey assessing the test's ease of use, their understanding of PGx, the usefulness of the results, their plans to share the results, and whether they would recommend testing to others. Members who declined testing were surveyed on why they did not participate. Descriptive analyses were calculated for each question.

Results: Most members who completed the test agreed or strongly agreed with each survey question: test directions were easy to follow (96.6%); they understand PGx after meeting with a genetic counselor (70.7%); they plan to discuss the results with their doctor (82.4%); the test can help doctors choose personalized medications (70.7%); and they recommend the test to others (69%). For members who declined PGx testing, common reasons were concerns about personal health information being used (36%) and other unlisted reasons (30%).

Conclusions: Results suggest that most members who complete the test can identify the intended benefits. For members who declined, the survey demonstrated that the test invitation does not adequately address their concerns. Results will be used to improve member education and experience, and highlight best practices for PGx testing programs.

Pharmacogenomics (PGx) is a tool used to predict a member's response to a medication in terms of efficacy and side effects.[1] Pharmacogenomics uses a member's DNA to determine an individualized medication and dose that is likely to be effective with a minimized chance of side effects, based on how their body will process the medication. For example, a pharmacogenomic test can determine that a member has a lower count of an enzyme called CYP2C19, compared to the accepted "normal" amount. CYP2C19 is known to break down and metabolize medications such as sertraline, a drug that treats bipolar disorder, generalized anxiety disorder, panic disorder, and other mental health conditions.[2] In a member with decreased CYP2C19 activity, it will take longer to break down the sertraline, which will cause an increase in exposure to the drug and higher risk for unintended adverse effects. In this scenario, a prescriber could use the member's pharmacogenomic results to guide the prescribing of sertraline at a lower dose, or prescribe a different drug that does not interact with CYP2C19.

Despite pharmacogenomics being an area of study since the 1800s, it is currently an underused prescribing tool.[3-4] Estimates for the number of individuals who have completed PGx testing are not provided in the literature. Throughout 2015 to 2018, 48.6% of Americans were taking at least one prescription drug, 24% were taking at least three prescription drugs, and 12.8% were taking at least five prescription drugs.[5] Despite the widespread use of prescription drugs, studies show that medications are only able to produce the desired effect in 50% to 75% of patients.[6] Additionally, the Food and Drug Administration (FDA) notes that the fourth leading cause of death is adverse drug reactions.[7] Pharmacogenomics is a useful tool to address these concerning statistics by helping minimize drug prescriptions that are not effective or that may cause side effects.

The FDA has shown their support for pharmacogenomics by incorporating it into their drug application evaluations.[8] Currently, the FDA recognizes more than 300 drugs with pharmacogenomic guidance in their labeling.[9] Additionally, various PGx databases have been created to make this information readily available to healthcare professionals. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a group dedicated to increasing the use of pharmacogenomics by offering guidance on the use of PGx results.[10] This resource, and others like PharmGKB and the Dutch Pharmacogenetics Working Group (DPWG), offer information on the most up-to-date drug-gene interactions

available.[11-12] Although the U.S. government and various prestigious research bodies are supportive of pharmacogenomics and the development of comprehensive pharmacogenomic databases, testing is still underused in the healthcare system.

Interest and research in PGx has increased recently. The number of cost-effectiveness studies is increasing, but the primary focus of most studies is to simply identify a gene-drug association.[13-14] And despite moderate evidence of financial benefits, the test might still be considered too expensive for some patients. Pharmacogenomic tests vary widely in price and could cost $250 to over $2,000 in out-of-pocket costs for the member, if not covered by insurance.[15-18] Additionally, healthcare professionals have their own concerns when it comes to pharmacogenomics. Prescribers often feel unfamiliar with pharmacogenomics and therefore are not routinely applying it in their practice.[1] Member and prescriber concerns might stem from a lack of education on the subject. Members might be undecided about the benefits of pharmacogenomics if their prescriber is not confident in applying it in their practice.

Pharmacy benefit managers (PBMs), such as Navitus Health Solutions, have recently begun to offer PGx testing as a benefit to their members. Navitus has partnered with a precision medicine company to allow members to be tested on 27 different genes. The genes correlate to various CYP enzymes and transporters within the body, which are involved in the metabolism of over 100 different pharmacogenomics-testable medications. Pharmacogenomics-testable medications are those with pharmacogenomic prescribing guidance. The test results are made available to the member and their health care provider and can be used immediately to adjust the member's current drug regimen. The results can also be used in the future to choose the best medication and dose, since DNA does not change over time. To initiate the process, the member is mailed a PGx test invitation. If they are interested in participating, they register online and request a cheek swab kit. The cheek swab kit is sent directly to their home and is then mailed back to the precision medicine company. That company processes the sample and offers a genetic counseling session to the member to explain the test results. Lastly, a Navitus pharmacist uses the test results and the member's formulary to determine whether any recommendations can be made to improve the member's drug regimen. Those recommendations are sent to the member's health care provider, who is encouraged to use their clinical judgement and knowledge of the patient's medical history to determine if any changes should be made to the member's medications and treatment plan.

Currently, only a handful of studies are available in the literature that describe the patient or member experience with PGx testing, while the majority of studies focus on the opinions of health care providers.[19-24] Understanding the patient or member experience will help determine the benefits of PGx testing, and the perceived barriers that might keep members from engaging in PGx testing. Prior to this study, only the experience of Navitus PGx pilot program participants were tracked.[25] Those members in the testing pilot reported that 94% were satisfied with the program overall; 83% found the program to be beneficial to their health; and 75% shared the results with a health care provider. The purpose of this study is to continue to collect the opinions of members of two commercial client populations who were involved in a pharmacogenomic testing program led by a pharmacy benefits manager, as well as the opinions of members who declined testing. Results will be used to improve the member experience and highlight best practices for providing a PGx testing program.

Methods

Study Design

This descriptive research survey was approved by the SSM Health Wisconsin Institutional Review Board as well as Navitus population health pharmacists, project management staff and the Navitus compliance and privacy officer. On October 28, 2020, an anonymous survey was mailed to members of two commercial clients who were previously invited to participate in the PGx testing program in the past year. In an effort to increase response rates, the survey was mailed on two additional occasions (November 6 and November 17, 2020). The survey indicated that it should only be completed and mailed back one time per member and to disregard if the member has completed it previously. This anonymous survey was exempt from collecting informed consent, as no identifying information was collected from subjects who participated in the survey. Subjects were not incentivized in any way for their participation.

Survey

The anonymous member survey questions were created based on previous patient-focused surveys in clinical pharmacy literature, but are unique to this study due to the need to assess specific elements of the program offered by Navitus Health Solutions.[19-24] Estimated time to complete the survey was three minutes or less for both members who completed PGx testing and members who declined.

The first question was used to determine if the member completed PGx testing or not. If their answer was yes, the survey instructed members to continue to questions 2 through 6. If their answer was no, the survey instructed members to skip questions 2 through 6 and go straight to question 7. Questions 2 through 6 were used to determine the member's opinion of the cheek swab directions, their understanding of pharmacogenomics, their plan to discuss the results with a health care provider, their understanding that the results should be used by a health care provider for medication prescribing purposes, and if they would recommend this PGx testing program to others. These questions were measured using a 5-point Likert scale (5 – strongly agree; 4 – agree; 3 – neutral; 2 – disagree; 1 – strongly disagree; 0 – not applicable) to measure the degree to which they agreed with each statement.

Question 7 was only answered if the member indicated that they did not complete PGx testing. This final question was used to determine the member's reasons for declining the test.

Members who did not complete PGx testing were asked to select all that applied from a list of potential reasons, including:

- Being unaware of the benefits of the test
- Concerns about personal health information being used
- The cost of the test
- Concerns about the insurance company's use of the results
- The testing process being too difficult
- Their medications are already well-

managed
- Their doctor didn't recommend genetic testing
- They forgot or didn't have time to be tested
- They already completed the test

See Figure 1 for the complete survey

Study Sample

The study included two cohorts: 122 members who completed PGx testing as of September 4, 2020, and 300 members who declined the test as of the same date, for a total of 422 members. All members who completed PGx testing and met the inclusion criteria were invited to participate in the survey study. Inclusion criteria included subjects who were at least 18 years old, a commercially insured member of one of two clients participating in the Navitus PGx testing program, previously invited to participate in PGx testing, and taking a minimum of two or five (depending on client) pharmacogenomics-testable medications in the previous 90 out of 180 days prior to being invited to participate. For members who declined the test, a list of 1,302 alphabetic member names was compiled, from which every fourth member was selected for the study population using block randomization for a total of 300 members.

Exclusion criteria included Medicare members and those not meeting the inclusion criteria.

Statistical Analysis

Descriptive analyses including frequencies of the response categories, means and standard deviations were calculated for survey questions 1 through 6. Qualitative data was collected for question 7 and frequencies were calculated on common themes that were identified. Microsoft Excel was used to graph the outcomes. Additionally, the number of responses received per each of the three mailings was identified.

Results

Of the 422 members who were mailed the survey, responses were received from 59 out of 122 (48.4%) members who completed PGx testing and 50 out of 300 (16.7%) members who declined the test for an overall response rate of 25.8%. No surveys were excluded from the final results.

FIGURE 1. Membership Survey

If you have completed this survey previously, please disregard this mailing.

Navitus Health Solutions Member Survey on Pharmacogenomic Testing

		Yes, go to #2	No, go to #7				
1)	Did you complete genetic testing using the RightMed® test?	O	O				
		strongly agree	agree	neutral	disagree	strongly disagree	N/A
2)	The directions for obtaining a cheek swab were easy to follow.	O	O	O	O	O	
3)	I understand how my genes impact the way my body responds to medications after talking to a genetic counselor.	O	O	O	O	O	O
4)	I have discussed, or plan to discuss, my results with my healthcare provider(s).	O	O	O	O	O	
5)	I believe that the RightMed® test can help my doctor choose the best medication for me.	O	O	O	O	O	
6)	I would recommend the RightMed® test to others.	O	O	O	O	O	

Thank you for completing this survey.

7)	If you DID NOT PARTICIPATE in the RightMed® test, please indicate your reason(s) why by selecting all that apply:	☐	I don't understand the benefits of being tested.
		☐	I have concerns about my personal health information being used.
		☐	The test is too expensive.
		☐	I have concerns about what my insurance company will do with the results.
		☐	The testing process seems too complicated.
		☐	My medications are already well-managed.
		☐	My doctor did not recommend that I complete genetic testing.
		☐	I forgot or didn't have time to get tested.
		☐	I was already tested or plan to be tested using a different genetic test.
		☐	Other

Thank you for completing this survey.

The first mailing yielded 61 responses, while the second and third mailings yielded 35 and 13 responses, respectively.

Most members who completed PGx testing agreed or strongly agreed with each survey statement: test directions were easy to follow (96.6%), they understand PGx after meeting with a genetic counselor (70.7%; 1 member indicated this statement was not applicable), they plan to discuss the results with their doctor (82.4%), the test can help doctors choose medications (70.7%), and they would recommend the test to others (69%).

See Table 1 for specific question response means and standard deviations.

For members who declined PGx testing, the most common reasons were concerns about personal health information being used (36%), other unlisted reasons (30%), concerns about what the insurance company will do with the results (28%), and their medications are already well-managed (28%). See Figure 2 for additional reasons members chose to decline PGx testing.

Discussion

There have been a number of surveys completed by health care professionals related to pharmacogenomics, but not as many have focused on patients, members of an insurance plan, or the general population. This survey was able to demonstrate that members who complete PGx testing have a positive perception of the program and the value it provides. Conversely, members who declined PGx testing have various concerns about sharing

TABLE 1. Survey Responses from Members Who Completed PGx[a] Testing

Question	Mean	Standard Deviation
2) The directions for obtaining a cheek swab were easy to follow.	4.71	0.527
3) I understand how my genes impact the way my body response to medications after taking to a genetic counselor.	3.81	1.131
4) I have discussed, or plan to discuss, my results with my healthcare provider(s).	4.05	0.953
5) I believe that the RightMed® test can help my doctor choose the best medication for me.	3.97	0.898
6) I would recommend the RightMed® test to others.	4.03	0.936

strongly agree = 5, agree = 4, neutral = 3, disagree = 2, strongly disagree = 1, N/A[b] = 0
[a]Pharmacogenomics, [b]Not Applicable

their genetic information, and they don't fully understand the benefits of the test results. Similar results have been seen in previous pharmacogenomics-related studies including subjects who did and did not complete PGx testing.[19-24]

This survey indicated that 41 members (69.5%) reported a better understanding of pharmacogenomics and their results after discussing the test results with a genetic counselor. According to a 2017 survey (Olson et al.) of 1,010 subjects who received their PGx results, 26% said they somewhat understood their results while 7% said they did not understand them at all.[23] These participants were only provided a mailed copy of their test results and educational materials to explain pharmacogenomic testing. The Navitus PGx program excels in this area because of the connection to genetic counselors who can verbally answer pharmacogenomics-related questions for the member.

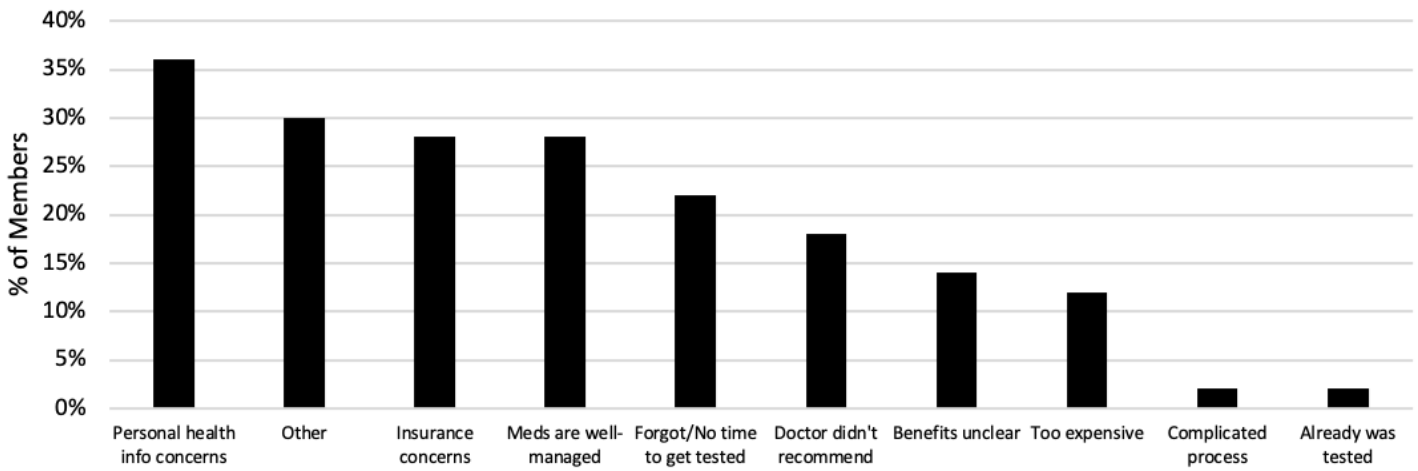
In 2018, another survey (Lemke et al.) was conducted online and included 57 patients, in which most indicated that PGx testing is a helpful tool for their health care providers and they understood what the results meant.[21] Some participants from the same study had concerns about what would be done with their results in terms of privacy and discrimination. These participants, as well as many participants from the Navitus survey, were not familiar with the Genetic Information Nondiscrimination Act, which was put in place in 2008. The act enforces appropriate use of patient genetic information and was specifically aimed at employers and insurance companies.[26]

Another concern that this survey identified was that 6 members (12%) thought the test was too expensive, indicating that they were not aware that the test is offered at no cost to them. In 2017, a small anonymous online survey (Gibson et al.) reported that 81% (27 respondents) said they were interested in pharmacogenomic testing, but would be even more likely to complete the test if they knew their insurance would pay for it.[20] The PGx benefit is offered at no cost to members, but it appears that the Navitus test invitation doesn't highlight this point enough for some members.

The goal of conducting the survey was to use its findings to improve member education and experience. The first step in implementing the feedback was to reconstruct the member PGx testing invitation to address various member concerns identified by the survey. The invitation now includes content about who will be notified of the results, in order to address the concerns about personal health information and what Navitus does with the information. Additionally, a statement was added specifying that insurance copays and coverage will not be adjusted based on genetic results, in accordance with the Genetic Information Nondiscrimination Act. Another piece of information that is now highlighted is the importance of using the test results for future prescribing, since 14 members (28%) indicated that they didn't complete the test because their medications are working well for them at this time. Lastly, a section was created that clearly outlines the benefits of completing the test to address the 7 members (14%) who were unsure of the benefits, including that the test is offered at no cost to the member.

A limitation of this study is that the survey was anonymous; therefore, it is unknown if any member completed the

FIGURE 2. Reason for Declining PGx Testing



survey more than once. Additionally, because all responses were anonymous, it was not possible to compare and contrast the characteristics of respondents, such as the number or types of medications they take. Another limitation is that the survey was sent out in late 2020, but some members were invited to complete PGx testing as far back as late 2019, so they might have forgotten about the invitation to be tested. On the other hand, other members may have received their results and had more time to act on them compared to members who were tested closer to the survey date. Lastly, for members who selected "other" as a reason for declining PGx testing, the member was not instructed to explain; therefore, we were unable to determine what that other reason was.

Further research on pharmacogenomics programs is needed to continue to grow the use of this personalized medicine tool. It would be helpful to determine the provider's perception of pharmacogenomics and how it may have an impact on the member's perception.

Conclusion

Results suggest that most members who completed PGx testing can identify the intended benefits. For members who declined, the survey demonstrated that the test invitation does not adequately address their concerns. Results will be used to continuously improve member education and experience, and highlight best practices for PGx testing programs.

Abigail Deming is a former Clinical Pharmacy Resident at Navitus Health Solutions, LLC in Madison, WI. Marleen Wickizer is a Senior Manager and Clinical Pharmacist in the Population Health Department at Navitus Health Solutions, LLC in Madison, WI. Tina Patel is a Clinical Pharmacist and Supervisor in the Population Health Department at Navitus Health Solutions, LLC in Madison, WI. Suzanne Horowitz is a Senior Product Manager in the Product Development Department at Navitus Health Solutions, LLC in Madison, WI. Agata Siwak is a Clinical Pharmacist in the Population Health Department at Navitus Health Solutions, LLC in Madison, WI. Julie Olson is a Director of Population Health and Product Development at Navitus Health Solutions, LLC in Madison, WI. Robert Topp is a Associate Dean for Research and Scholarship at University of Toledo, College of Nursing in Toledo, OH.

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Original Work

Improving Health Equity through Building COVID-19 Vaccine Confidence with Minority Veterans: A Pharmacist-Led Motivational Interviewing Approach

by Hunter J. Furley, 2023 PharmD Candidate, Emma M. Dreischmeier, 2022 PharmD Candidate, Catherine M. Kuecker, PharmD, BCACP, James A. Gardner, Ellina S. Seckel, PharmD, BCACP, DPLA

Abstract

Objectives:

- Take a proactive approach in addressing vaccine health disparities for minority Veterans.
- Leverage pharmacists who are well-trained in motivational interviewing (MI) to provide a safe environment to discuss COVID-19 vaccination and encourage vaccine acceptance.
- Update the electronic medical record (EMR) to accurately reflect Veteran vaccination rates.

Methods: Minority Veterans without prior documentation of COVID-19 vaccination were identified from a report generated by the EMR. Chart reviews were completed to determine eligibility for telephone outreach by pharmacists during a two-week period in March 2021. Pharmacists discussed COVID-19 vaccination with unvaccinated minority Veterans using MI and education to address their concerns and encourage vaccine acceptance, while also updating the EMR with previous vaccinations.

Results: Upon initial chart review, 297 (23%) of the 1,275 included patients had a previous COVID-19 vaccination or future vaccine appointment, leading to updates in the EMR. A total of 988 Veterans (77%) received unscheduled telephone outreach by pharmacists. Of those, 509 (52%) were successfully reached by telephone on the first attempt and 263 (52%) of them met the primary composite endpoint: 136 (27%) agreed to a vaccine appointment, 114 (22%) reported previous vaccination and had their EMRs updated, and 13 (3%) reported a future vaccine appointment elsewhere.

Conclusion: Pharmacist-driven outreach to minority patients effectively improved their vaccination rates through increasing vaccine acceptance and accurately updating the EMR. While this method is time- and resource-intensive, pharmacists may consider implementing similar programs in their practices to address health inequities more broadly.

COVID-19 disproportionately affects patients of minority racial and ethnic groups in the United States. Black or African American, American Indian or Alaska Native, Hispanic or Latino, and Native Hawaiian or other Pacific Islander patients have died at rates 140% of those of White Americans.[1] This multifactorial health inequity stems from a lack of access to medical services, decreased quality of care, lower rates of health insurance, and linguistic and cultural barriers.[2,3] Despite the staggering discrepancy in mortality, vaccinating America's minority populations proves challenging.

Vaccine hesitancy describes the spectrum, from reluctance to refusal, of a vaccine in the absence of barriers to access.[4] A survey from March 2021 by National Public Radio, Public Broadcasting Service NewsHour, and Marist reported that 25% of Black and 28% of White participants planned to not receive a COVID-19 vaccine.[5] While the two rates are comparable, differences in reasoning exist behind the hesitation.[6] America's traumatic and unethical history of medical malpractice with minority patients, such as in the Tuskegee Syphilis Study, provides some historical basis for the skepticism and distrust.[7]

Proper vaccine education is crucial to countering misinformation; however, education alone is often ineffective. As one of many potential strategies, providers and healthcare institutions may strive for an individualized approach, focused on rebuilding trust to increase vaccination rates and optimize impact among minority

populations.

The Department of Veterans Affairs (VA) recognizes integration and advancement of diversity, equity, and inclusion (DEI) and achievement of health equity for all Veterans as national strategic priorities. Pharmacy and institutional leadership at the William S. Middleton Memorial Veterans Hospital in Madison, WI (Madison VA) are personally and professionally invested in these efforts. Local leadership implements facility-wide goals and initiatives to advance DEI and improve health equity for minority Veterans.

Clinical Pharmacy Practitioners (CPPs) and pharmacy residents at the Madison VA, in partnership with the hospital's Anti-Racism Action Team, led a proactive telephone outreach effort in March 2021 to address COVID-19 vaccine inequities among minority Veterans. CPPs implemented a two-week team initiative to call minority Veterans without prior vaccine documentation and establish supportive conversations, based on motivational interviewing (MI), to build confidence and encourage vaccine acceptance.

Methods

A report was generated from the electronic medical record (EMR) to identify minority Veterans without previous COVID-19 vaccination documentation. CPPs and pharmacy residents performed a chart review and excluded patients if they were deceased, transferred care, or moved out of the service range; if they were already undergoing current discussion with their care team on COVID-19 vaccination; or if the entry was a duplicate. Veterans found to have had previous non-VA COVID-19 vaccination or an upcoming COVID-19 vaccination appointment scheduled at the Madison VA mentioned in their notes but not documented in the EMR had it updated to make the records translatable into broader sharable data systems. The remainder of minority Veterans were eligible for unscheduled telephone contact.

Pharmacy leadership distributed minority-Veteran call lists to CPPs and pharmacy residents based on allotted time for these outreach efforts. CPPs and pharmacy residents performed outreach calls to minority Veterans over a two-week period (March 22 through April 2).

All participating pharmacists received a call guide that included a general call template with guidance for documentation and workload capture. They also received a second document containing motivational interviewing strategies, racial/ethnic historic contextual information, and common COVID-19 vaccine myths/facts facts.

Pharmacists attempted to reach each Veteran with two consecutive calls. A voicemail was left after two attempts, including information about COVID-19 vaccine availability along with callback numbers for vaccine appointments and questions.

For Veterans who answered, calls opened with a greeting, a statement that the COVID-19 vaccine was available to them, acknowledgement of collaboration with the Veteran's primary care provider, and a request for permission to talk about the COVID-19 vaccine. Veterans who accepted the request to discuss were asked if they were interested in receiving a COVID-19 vaccine. Veterans who desired a vaccine were given a warm hand-off transfer to the vaccination appointment scheduling line. For Veterans who declined discussion or expressed ambivalence, patient autonomy was respected, and MI was leveraged as appropriate. Conversations were tailored to each Veteran based on their responses and concerns.

Veterans who reported previously receiving COVID-19 vaccination from a non-VA source had their EMRs updated appropriately. Veterans with a future non-VA vaccine appointment were offered to have it transferred to a VA appointment. Veterans who declined or remained undecided were asked if they would be interested in follow-up with their PCP for further discussion.

The primary composite endpoint was composed of the following based on the telephone outreach: (1) a Veteran newly accepted vaccination and received a scheduled appointment for COVID-19 vaccination at the Madison VA; (2) a Veteran's EMR was updated with a previous historical COVID-19 vaccination; or (3) a Veteran's EMR was updated with a future non-VA COVID-19 vaccination appointment. The success rate was defined as the number of minority Veterans who met the primary composite endpoint divided by the number of eligible minority Veterans reached by telephone.

Reasons for COVID-19 vaccine declination or deferral were compiled, quantified, and summarized into the following categories: clinical concerns, logistical issues, distrust or philosophical reasons, ambivalence, and refusal to elaborate.

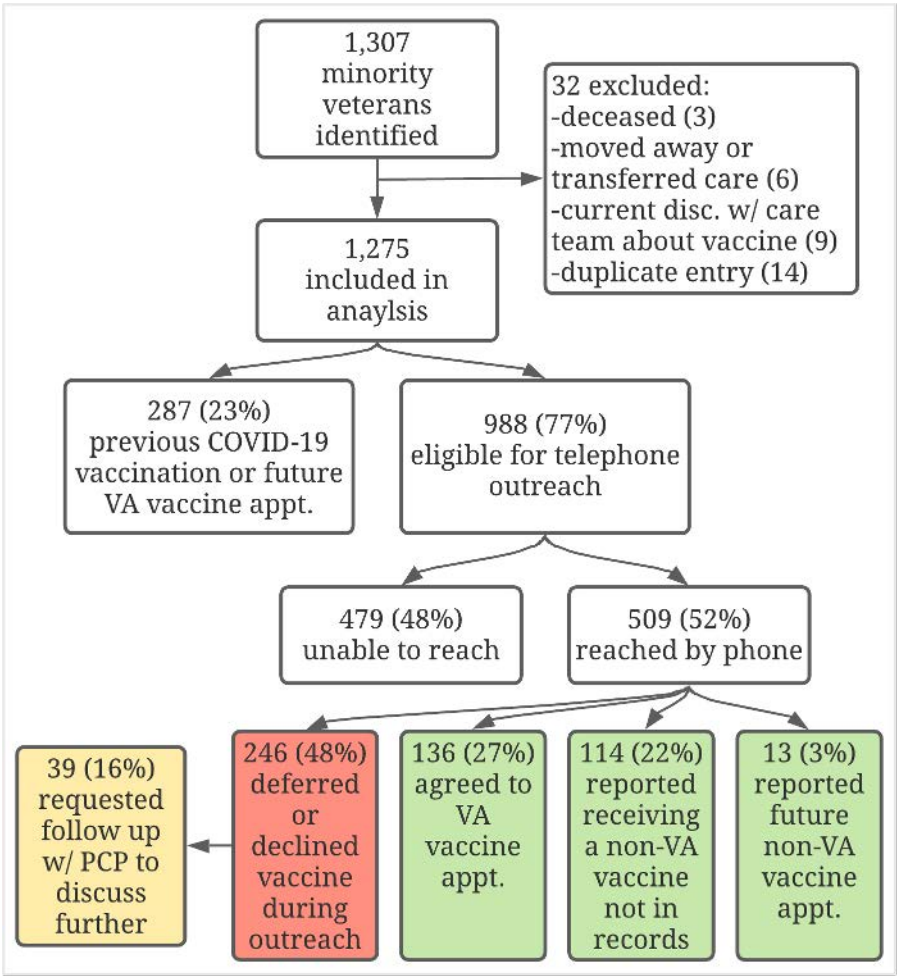
Data were analyzed using descriptive statistics. In a secondary analysis, pre- and post-initiative COVID-19 vaccination levels for all minority Veterans served by the Madison VA were assessed by race. A one-sample test of proportions was used to compare vaccination level changes for each minority racial group between March 18, 2021 and May 4, 2021. Sample size was determined by the March 18, 2021 data set, as it was more conservative with fewer Veterans.

The University of Wisconsin-Madison Sciences Institutional Review Board (IRB) determined this project did not meet the federal definition of research; therefore, IRB

TABLE 1. Veteran Patients without Previous COVID-19 Vaccination

Veterans Identified by Race and/or Ethnicity	*Number Identified*	*Average Age (years)*	*% Male*
American Indian or Alaskan Indian	65	59.5	84.6%
Asian	76	40.6	83.0%
Black or African American	743	56.4	85.3%
Hispanic or Latino	236	46.5	84.3%
Native Hawaiian or Pacific Islander	85	59.5	87.1%
Multiple	102	51.3	82.4%

FIGURE 1. Results of Minority Veteran Outreach.
Identified minority Veterans underwent a chart review to determine eligibility for telephone outreach. Of those reached, 52% of calls successfully met the primary composite endpoint (green). Within the 48% that did not meet the endpoint (red), 16% of them requested follow up to discuss COVID-19 vaccination further with their primary care provider (PCP, yellow).



review was not required.[8]

Results

An initial 1,307 minority Veteran patients without previous COVID-19 vaccination documentation were identified by the EMR. Baseline characteristics are provided in Table 1, with Black or African American Veterans representing the largest group. The majority were males (84.5%) with an average age of 52. A total of 32 veterans were excluded based on the following: deceased (3), moved away or transferred care elsewhere (6), undergoing current discussion with their care team about COVID-19 vaccination (9), and duplicated entry (14). A resulting 1,275 minority Veterans were included in the analysis (Figure 1).

Of those included, 287 (23%) were found to have had either a previous COVID-19 vaccination or a future COVID-19 vaccination appointment scheduled at the Madison VA upon chart review. Of the remaining 988 (77%) eligible for contact by pharmacists, 509 (52%) were successfully reached by telephone for the MI during the two-week initiative. A total of 47 pharmacists (30 ambulatory care CPPs and 17 pharmacy residents) were involved with making calls.

Of those reached, 263 (52%) minority Veterans met the primary composite endpoint. The majority of those meeting the primary endpoint accepted and scheduled a vaccine appointment at the Madison VA (136, 27%). Another 114 (22%) reported receiving a COVID-19 vaccine outside of the VA that was not previously documented in their records, and 13 (3%) preferred to keep a future non-VA COVID-19 vaccination appointment instead of switching to one at the Madison VA. While 246 (48%) affirmed their vaccine declination or deferment during the outreach, 39 (16%) of them requested follow-up to discuss it further with their PCPs. Results of those interactions were not recorded.

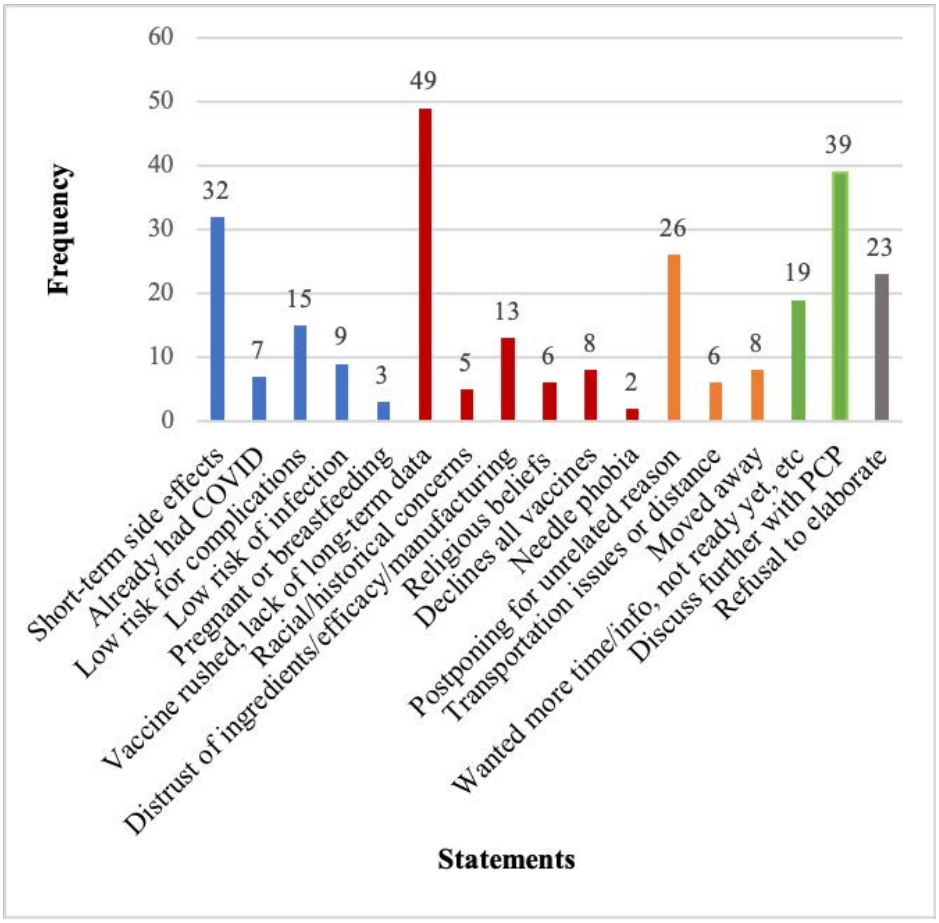
Minority Veterans who declined or deferred the COVID-19 vaccination showed a variety of reasons. Of the five general categories identified, distrust or philosophical reasons was the largest for declining the COVID-19 vaccine (31%). The most common specific concern cited was a feeling that the vaccine was rushed and lacked enough long-term data (49 responses), followed by a request to discuss further with their PCP (39), and concern for short-term side effects (32). Racial/historical concerns were cited 5 times. A detailed analysis of declinations, deferrals, and associated themes is displayed in Table 2.

A comparison of pre- and post-initiative COVID-19 vaccination levels by race is presented in Table 3. Of note, Hispanic or Latino Veterans were not specifically displayed in the table due to their frequent association with other racial groups. COVID-19 vaccination levels between March 18, 2021 and May 4, 2021 increased significantly within all minority Veteran racial groups contacted by the outreach (p-values <0.001). Asian Veterans experienced the largest increase in vaccination of 25%, while Black or African American Veterans' increase of 22% was supported by the largest minority sample size.

Discussion

CPPs and pharmacy residents implemented a proactive telephone outreach initiative that addressed vaccine inequities and significantly increased documented COVID-19 vaccination rates among minority Veterans. Motivational interviewing was fundamental in conducting supportive conversations regarding COVID-19 vaccine decisions, with 52% of Veterans reached meeting the primary composite outcome. Additionally, analysis of responses from participants that deferred or declined vaccination provided greater insight into the reasons behind the

TABLE 2. Reasons for Declining or Deferring the COVID-19 Vaccine in Minority Veterans. Statements were collected from minority Veterans who declined or deferred vaccination during phone contact, then generalized to form the distribution above. Statements are grouped by their corresponding theme.



vaccine hesitancy and highlighted future opportunities to build vaccine confidence. Personalized outreach builds rapport, creates a safe space to share beliefs, and strengthens trust. Leveraging knowledgeable and trusted providers to engage in MI with patients may turn today's ambivalence into tomorrow's vaccine acceptance.

Several limitations were identified during the initiative. Participating CPPs and pharmacy residents had varying degrees of experience and comfort in effectively responding to vaccine misinformation. To address this, a standardized call template and guidance from national VA sources were provided to ensure all Veterans received consistent messaging during COVID-19 vaccine discussions. The use of unscheduled phone calls to conduct outreach also limited results due to the inability to reach many eligible Veterans.

Further, the pre- and post-initiative vaccination-level data included all Veterans at the Madison VA, not just those included or successfully reached in this outreach. Given the wider patient inclusion in that data as well as the extended timeframe between the vaccines' initial approvals from Emergency Use Authorization (EUA) and the pre-initiative data (March 2021) to the post-initiative data (May 2021), some Veterans may have felt more comfortable receiving the vaccine in May regardless of MI efforts. The data is only observational and not solely reflective of the outreach intervention.

Lastly, the leveraging of 47 pharmacists for a two-week initiative, each dedicating two to four hours per week, may be challenging for reproducibility. Rapid addressment of COVID-19 vaccine inequities was a major goal of this outreach. However, future programs may opt for a longer-term focus with fewer providers. Using pharmacy residents, interns, and students, as well as other disciplines trained in MI, such as nurses, may be strategies to expand.

Several opportunities for continued growth were identified and implemented. Based on the success of this initiative, the program was expanded to include nursing staff and primary care teams to provide outreach to all Veterans served by the Madison VA system. Similar methods, including a focus on MI, was replicated. Education on MI was provided to nursing staff prior to implementation of the expanded outreach for use in their patient interactions. Assessing COVID-19 vaccination status and encouraging vaccine acceptance is now standard practice during patient visits. Discussions were also held with two other VA facilities (San Diego and Reno medical centers) for application of this initiative at their sites.

Motivational interviewing techniques and personalized outreach may extend beyond COVID-19 vaccine hesitancy and

TABLE 3. A Comparison of Pre- and Post-Initiative COVID-19 Vaccination Levels

All Veterans by Race	*Total 3/18/21*	*Total 5/4/21*	*% Vaccinated 3/18/21*	*% Vaccinated 5/4/21*	*% Increase in Vaccination*
Native Hawaiian or Pacific Islander	190	195	55.2%	69.2%	14.0%
Black or African American	1,206	1,232	38.4%	60.0%	21.6%
Multiple	162	168	37.0%	57.7%	20.7%
Asian	121	129	37.2%	62.0%	24.8%
American Indian or Alaskan Indian	118	129	44.9%	60.5%	15.6%

provide a framework to address preventative care measures and health inequities more broadly. In their outreach, pharmacists corrected misinformation, provided tailored interventions, and fostered stronger relationships built on trust with minority patients. Barriers of misinformation and distrust are not unique to the COVID-19 vaccine but are prevalent throughout health care in general. Racial and ethnic disparities in contraception access and knowledge[9], chronic disease state management[10], and mental health outcomes[11] have been specifically cited in Veterans; each an opportunity for pharmacists to apply the lessons learned from this initiative and work towards health equity for all.

Minority-specific outreach and personalized education with MI can be an effective approach to encourage engagement with the health care system and reduce health inequities. Pharmacists involved found this initiative rewarding, and calls were well-received by minority Veterans. This outreach exhibits the personal investment and genuine passion for DEI advancement and achievement of health equity at the Madison VA.

Conclusion

Pharmacist-driven motivational interviewing with personalized education effectively reduces vaccine hesitancy and fosters stronger relationships with minority patients. This initiative may serve as a model for future minority-specific outreach efforts aimed at addressing health inequities more broadly. Pharmacists are well-trained in motivational interviewing and well-positioned as the most accessible healthcare providers to lead such efforts. The outreach presented here demonstrates the pharmacy profession's commitment to serving all patients and advancing diversity, equity, and inclusion.

Hunter Furley is a 3rd Year Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Emma Dreischmeier is a 4th Year Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Catherine Kuecker is a Clinical Pharmacist Practitioner, James Gardner is a TCF Data Analyst, and Ellina Seckel is the Associate Chief of Pharmacy, Ambulatory and Specialty Care at the William S. Middleton Memorial Veterans Hospital in Madison, WI.

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ROSALIND FRANKLIN UNIVERSITY OF MEDICINE AND SCIENCE COLLEGE OF PHARMACY STUDENT WRITING CLUB:

The Pharmacist's Role in New Acute Myeloid Leukemia Treatments

by Maximilian Vitas, 2022 PharmD Candidate, Shujie Lin, 2022 PharmD Candidate, Rucha Kulkarni, 2023 PharmD Candidate

Abstract

Newly approved agents such as gemtuzumab, midostaurin, gilteritinib, and venetoclax have created a shift in current treatment practices for acute myeloid leukemia (AML). These agents have evidence for improving AML patient outcomes and act as targeted therapy for specific AML subtypes. Pharmacists hold critical roles in evaluating the safety and use of these new agents as well as the cancer continuum of AML.

Acute myeloid leukemia (AML) is one of four leukemia subtypes that affect myeloid stem cells. This cancer accounts for 1.1% of all new cancer cases in the United States and yields a 28.7% 5-year survival from diagnosis, which is 35% less than the average 5-year survival rate for all leukemia types.[1] Compared to other cancers, AML has the most expensive initial 1-year treatment costs, averaging $182,900 (the next most expensive are cancers of the brain, which average $134,400).[2] With a mean age of 68 at diagnosis, AML is considered a cancer of the elderly; however, it can affect all ages.[1] The death rate of AML has steadily decreased, from 8.36 deaths per 100,000 cases in 1980, to 6.27 in 2016. This decrease is due in part to recent treatment advances and pharmacist intervention in an interdisciplinary team.

In Wisconsin, the most recent census data shows that the state population of individuals aged ≥65 increased by 2.1% over the last 10 years.[3,4] With a growing elderly population, there is cause for concern about growing cancer incidence. Public health data for age-adjusted rates surrounding AML from the Wisconsin Department of Health Services estimated a rate of 4.7 AML cases per 100,000 individuals for 2012 to 2016.[4] With a current state population of 5,822,434, an estimated 274 new AML cases will occur every year.[3] Though the number of cases is numerically low, the expected healthcare burden is an estimated $50,114,600 in direct treatment costs per year.

As part of the interdisciplinary healthcare team, pharmacists hold an important role in both treating patients and addressing the financial burden of treatment. Pharmacists' knowledge of medication use, oversight, and treatment management is paramount in patient health outcomes. With the recent approval of new AML agents such as gemtuzumab ozogamicin, midostaurin, gilteritinib, venetoclax, and more in the pipeline, the pharmacist's expertise serves to guide the cancer continuum team. In this article, the authors attempt to provide a brief overview of AML and discuss both new treatments and the contributions of the pharmacist in AML care.

AML Overview and Mutational Analysis

Acute myeloid leukemia is a hematological malignancy characterized by abnormal differentiation and proliferation of immature myeloid cells.[5] The gold standard for the diagnosis of AML is an examination of peripheral blood smears with confirmation performing a needle aspiration and biopsy of marrow from the iliac crest.[6] The most frequent subtype presentation is M2, accompanied by weakness and bleeding abnormalities.[5] Since AML is a highly variable disease, the clinical presentation may include multiple nonspecific signs and symptoms. These symptoms may include fever, weight loss, and anorexia, and can manifest as sternal discomfort with pancytopenic phenomena.[5,7] In rare cases, leukocytic infiltration resulting in disseminated intravascular coagulation causes risk for intracranial hemorrhaging; this is a common occurrence in the M3 and M5 subtypes, which contributes to the leading cause of death in AML patients.[8-10]

The primary pathogenesis of AML results from chromosomal translocations. Exact mechanisms for chromosomal alterations are not completely understood; however, these abnormalities involve improper or unusual rearrangements of chromosomes resulting in protein alterations that affect myeloid stem cell maturation.[11] The most common translocations, t(15;17), t(8;21), and inv(16), account for 3%-10% of abnormalities found.[12,13] In addition, there are a host of mutations that can alter AML prognosis.

Mutational analysis involves the pharmacogenomic process of determining patient prognostic factors; this is done by examining genetic mutations. By recommending the use of this gene-guided therapy, pharmacists take charge in seeking the best treatment outcomes for their patients through the selection of targeted therapies. For those with AML, cytogenetics play a role in assessing disease progression, prognosis, and therapy. With recently approved agents, mutational analysis is

crucial in assessing the appropriateness of treatment. In 2016, a study conducted by Papaemmanuil and colleagues enrolled 1,540 patients with AML into three prospective trials. The investigators were determined to identify AML genotypes and subsequent treatment outcomes. Upon completion of the study, a total of 5,234 driver mutations were identified across the population, with 96% of patients having at least one mutation and 86% having at least two.[14] One of the most frequent mutations was for FMS-like tyrosine kinase 3 (*FLT3*), which is a target of therapy by both midostaurin and gilteritinib.

The transmembrane tyrosine kinase *FLT3* stimulates cell proliferation by activating multiple signaling pathways. Mutations in *FLT3* genes represent one of the most common mutations found in AML and occur at an approximate frequency of 5-25% of cases.[15,16] There are two main *FLT3* subtype mutations: *FLT3* internal tandem duplication (*FLT3*-ITD) and the *FLT3* tyrosine kinase domain (*FLT3*-TKD).[17] Formally, *FLT3* mutations irregularly activate tyrosine kinase causing the proliferation of malignant cells. Mutations in *FLT3* are also difficult to detect upon diagnosis. Because of these two factors specifically, *FLT3* mutations are shown to have high rates of recurrence and relapse. These factors are also why the National Comprehensive Cancer Network (NCCN) clinical practice guidelines characterize patients with *FLT3* mutations as having poor-risk disease due to reduced overall survival and increased risk of relapse.[18] Despite this risk assessment, both midostaurin and gilteritinib have shown promising results in practice, and there is evidence that both venetoclax and gemtuzumab positively affect patients with *FLT3* mutations.

Supportive Care

Comprehensive leukemia treatment is intense and can greatly affect quality of life. Treatment is not as simple as receiving induction and consolidation therapy; it requires a full examination of current and potential adverse events, drug interactions, and efficacy monitoring by pharmacists. With new agents, both neutropenia and tumor lysis syndrome (TLS) are adverse reactions of high concern. As a result, the management of these adverse reactions by a pharmacist is extremely important.

Neutropenia is the first major concern, due to a high risk for infection following neutrophil depletion resulting from treatment. While the nadir period following induction is an expectation for treatment, many newer and more poorly understood agents, such as gilteritinib and venetoclax, must be strictly monitored for tolerability. In clinical practice, the American Society of Clinical Oncology and the Infectious Diseases Society of America both recommend prophylactic regimens for patients predicted to experience profound neutropenia while in nadir, in order to reduce treatment complications.[19] This regimen consists of fluoroquinolones, triazoles, or echinocandins, and a nucleoside analog for bacterial, fungal, and viral prophylaxis, respectively. This regimen is complicated, so the pharmacist must assess patient data to offer the best options for treatment. Managing the patient's medications and preventing drug interactions becomes key for patient survival during neutropenic events.

The second major concern in treatment is TLS. During chemotherapy, cytotoxic agents cause large-scale malignant cell lysis, prompting a torrent of cellular component release into the bloodstream, leading to hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia.[20, 21] This imbalance causes significant damage, via nephropathy, acute renal failure, and cardiac arrhythmias.[21] According to a retrospective analysis conducted by Ejaz and colleagues, the incidence rate of TLS was found to be 26.4% among a cohort of 183 study participants and presented in 32.6% of patients deemed high-risk.[20] Other studies yielded a broader range of an aggregated 5% and 42% between all hematologic malignancies.[21,22] As the risk for TLS is high among this patient population, pharmacists can intervene by guiding treatment based on lab values related to TLS. To prevent renal complications, pharmacists can offer recommendations for regimens to the interdisciplinary team. Renal prophylaxis for TLS involves adequate intravenous hydration that starts 1-2 days prior to chemotherapy and extends up to 3 days after.[23] Hydration is not the finite management, however; the pharmacist might further advocate for the use of allopurinol or rasburicase to help prevent urate nephropathy.[21,23]

Treatment

The ultimate goal for treating patients with AML is to achieve complete remission and restore normal hematopoiesis. This involves eradicating all residual leukemia cells following the initial induction therapy. Complete remission is defined by the absence of evidence of residual leukemia in the marrow, in addition to an absolute neutrophil count >1000 cells/mm^3; a platelet count >100,000 cells/mm^3; having <5% blasts in the marrow; and transfusion independence.[11] Not every patient will achieve complete remission and may become classified as having reached partial remission (50% reduction in blasts with 5% to 25% remaining).[11,24]

Newer FDA-approved agents, such as gemtuzumab, midostaurin, gilteritinib, and venetoclax, have shown selectively improved efficacy in the treatment landscape of AML. As each of these medications has a different mechanism, there are special monitoring parameters and adverse events to take note of during treatment. From a regimen standpoint, adherence is the greatest challenge. It is well known that pharmacist intervention in medication management significantly improves adherence and therefore health outcomes.[25-27] Monitoring for adverse events is especially important for new agents, because they may impact treatment outcomes. With close follow-up, education, and monitoring practices, however, repeated and targeted interventions will continue to greatly improve adherence over time.[28-30]

Standard of Care Chemotherapy

Induction and consolidation therapy is the primary regimen for patients with AML.[18,31] The regimen consists of a 7-day continuous infusion of cytarabine and a 3-day bolus infusion of an anthracycline, followed by differing amounts of cycles of high-dose cytarabine (HiDAC) dependent on the AML subtype.[11,18] The regimen functions to block DNA synthesis with cytarabine while simultaneously inhibiting topoisomerase II with the anthracycline, after which HiDAC eliminates residual leukemic cells. For induction therapy, young and clinically stable patients with good performance status are considered the most ideal candidates. Approximately 60%

to 85% of this demographic will achieve complete remission.[7,11] In patients with both favorable and intermediate cytogenetics, the cure rate is approximately 60%-70%.[7] Patients with poor cytogenetics often do not receive the same benefit. For patients at the extremes of age, tolerability to this regimen can also be a limiting factor. In such cases, patients are more likely to achieve better clinical outcomes with targeted therapies.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is an older agent in the timeline of leukemia treatment. It was re-approved by the FDA in June 2020 for the treatment of newly diagnosed CD33+ AML in adults or children ≥1 month old.[32] Gemtuzumab ozogamicin acts as a powerful agent for *FLT3* mutations. It also has an indication for the treatment of relapsed or refractory CD33+ AML in adult and pediatric patients ≥2 years of age. The agent is a humanized antibody-drug conjugate, consisting of a monoclonal antibody linked to a cytotoxic molecule called calicheamicin. Mechanistically speaking, GO binds to the CD33 protein expressed on the leukemic cell surface and releases calicheamicin, causing double-strand DNA breaks and apoptosis. In the phase 3 ALFA-0701 trial, the efficacy for GO in improving event-free survival (EFS) was demonstrated at a low dose (3 mg/m^2 on days 1, 4, and 7, plus 3 mg/m^2 in two consolidation treatments) when combined with the standard of care chemotherapy.[33] In the trial, EFS was defined as the length of time to complete remission (CR) or complete remission with incomplete platelet recovery (CRP). The trial included 280 participants between ages 50 and 70 with newly diagnosed AML who were randomized 1:1 into standard of care chemotherapy vs. standard of care with GO. For participants who had achieved CR or CRP, two consolidation treatments consisting of daunorubicin and cytarabine were given with or without GO. The trial revealed that the EFS at 2 years was significantly higher in the treatment arm compared to the control group (40.8% vs. 17.1%; HR 0.58, p=0.0003). It is worth mentioning that the rate of persistent thrombocytopenia after chemotherapy was significantly higher in the GO group as well (16% vs. 3%, p<0.0001).

In clinical practice, GO is a powerful agent for those with favorable or unfavorable cytogenetics, as described by the trial. While GO does not have any certain contraindications, the product information carries a warning for hepatotoxicity and veno-occlusive liver disease (VOD), which can be fatal.[32] The incidence of VOD-related events was found to be approximately 5% in the ALFA-0701 trial, so this is an important monitoring parameter for GO use.[33] VOD is marked by increases in liver enzymes such as ALT and AST. While there are no drug interactions of note with GO, liver function test abnormalities are a common side effect of many medications, so pharmacists are a powerful resource in determining whether a patient may be suffering from VOD.

Midostaurin

Midostaurin is a first-generation *FLT3* tyrosine kinase inhibitor that was approved in 2017 as an add-on therapy for adult patients with newly diagnosed AML and an *FLT3* mutation.[34] Midostaurin has shown remarkable activity in improving overall survival with a relatively balanced safety profile. In the phase 3 RATIFY trial, patients aged 18 to 59 who had AML and an *FLT3* mutation were randomized to receive midostaurin 50 mg orally twice per day, or placebo, on days 8 through 20 following standard of care cytarabine plus daunorubicin induction, or with high-dose cytarabine consolidation, and from day 1 to 28 as a single agent for maintenance therapy.[17] Upon completion, midostaurin demonstrated significantly improved outcomes compared with placebo for median overall survival (74.7 months vs. 25.6 months) in addition to a significant improvement in median EFS (8.2 months vs. 3.0 months). The trial also showed a significant reduction in the overall risk of death by 22% in the midostaurin arm (HR 0.78, p=0.009). The RATIFY trial showed that midostaurin was equally as tolerable as the standard of care chemotherapy with similar rates of adverse events in most cases. Notably, midostaurin showed higher rates of grade 3+ anemia (92.7% vs. 87.8%, p=0.03) and rash (14.1% vs. 7.6%, p=0.008). Although grade 3+ nausea occurred less frequently with midostaurin, a higher percentage of participants in that treatment arm experienced all-grade nausea and vomiting, compared to placebo.

Pharmacists must monitor midostaurin use very carefully, as the adverse effects are intense and there can be significant consequences. One of the major adverse effects not previously highlighted is the risk of QTc prolongation. In a study conducted separately from RATIFY, patients taking midostaurin were found to experience a higher rate of QTc prolongation compared to those taking placebo (10.1% vs. 5.7% with QTc >480 ms, and 6.2% vs. 2.6% with QTc >500 ms). Based on these results, monitoring the patient's heart is extremely important. In addition, midostaurin is a CYP3A4 substrate, so co-administration of strong inhibitors, such as ketoconazole and voriconazole, or inducers such as rifampicin, can drastically alter the course of therapy.[35] To anticipate therapy-induced nausea and vomiting, the pharmacist might use prophylactic anti-emetics, such as ondansetron, olanzapine, or lorazepam prior to administering midostaurin.[36]

Gilteritinib

Gilteritinib is a tyrosine kinase inhibitor *FLT3* targeted therapy with activity against two subtypes, *FLT3*-ITD and *FLT3*-TKD. It was approved in November 2018 for the treatment of relapsed or refractory *FLT3*-mutated AML. Similar to the other agents, gilteritinib studies have established superiority in improving the overall survival of AML patients. In the phase 3 ADMIRAL trial, patients with relapsed or refractory *FLT3*-mutated AML were randomized 2:1 to receive gilteritinib monotherapy or salvage chemotherapy at the discretion of investigators.[37] Upon conclusion of the trial, the gilteritinib arm showed a significantly longer median overall survival compared to the salvage chemotherapy group (9.3 months vs. 5.6 months; HR 0.64, p<0.001). The investigators also found that the proportion of participants who achieved complete remission with full or partial hematologic recovery was remarkably higher in the gilteritinib group (34% vs. 15.3% salvage chemotherapy; 95% CI [9.8 – 27.4]).

Although gilteritinib has been shown to improve overall survival, it must be noted that the median length of exposure to gilteritinib was only 18 weeks.[37] Therefore, the long-term effects on the improvement of overall survival need to be assessed more thoroughly and the use of gilteritinib in practice should be conducted after weighing

the benefits and risks, some of which can be life threatening. In clinical trials, patients experienced differentiation syndrome, pancreatitis, and prolonged QTc intervals following treatment with gilteritinib.[38] The pertinent drug interaction with gilteritinib involves combination p-glycoprotein-CYP3A inducers which effectively reduce the efficacy of gilteritinib treatment, so it is important to check whether the patient is taking such a medication.

Venetoclax

Venetoclax is an oral oncolytic B-cell lymphoma 2 inhibitor that was approved in October 2020 to treat AML, when used in combination with a hypomethylating agent such as azacitidine, decitabine, or low-dose cytarabine (LDAC). The efficacy for this agent was determined after the completion of the VIALE-A and VIALE-C trials, which included 286 and 145 participants, respectively.[39,40] In VIALE-A, patients were randomized 2:1 to azacitidine with either venetoclax or placebo to measure improvements in overall survival and complete remission.[39] Patients who received azacitidine with venetoclax were found to have a longer median overall survival compared to the placebo counterpart (14.7 months vs. 9.6 months; HR: 0.66; 95% CI [0.52 – 0.85]). For complete remission, the azacitidine with venetoclax group was also found to have a significant improvement (37% vs. 18%; 95% CI [12 – 25]). In VIALE-C, patients were randomized 2:1 to venetoclax with LDAC or placebo with LDAC.[40] Unlike in VIALE-A, this trial's efficacy parameter was to measure the duration and rate of complete remission. The median remission time was found to be 11.1 months with venetoclax compared to 8.3 months with placebo, and the remission rate was significantly greater in the venetoclax group (27% vs. 7.4%; 95% CI [2.4 – 16]). Upon conclusion of the trial, the results from VIALE-C did not show any improvement in overall survival when venetoclax was administered with LDAC compared to placebo (p=0.114).

In clinical practice, the NCCN guidelines recommend initiation following leukocyte depletion with concomitant administration of the hypomethylating agent.[18] Because venetoclax has a high risk of causing TLS, the pharmacist must ensure that the patient is being premedicated with antihyperuricemics if needed and that monitoring is conducted every 6 hours until the risk is gone. In addition to monitoring for TLS, the pharmacist should address potential drug interactions. The dosing of venetoclax requires adjustment if the patient is taking CYP3A or P-glycoprotein inhibitors.[41] For patients with relapsed or refractory AML, antifungal prophylaxis may be necessary, in which case the risk for drug interactions increases.[18]

Waste Stewardship

The cost of treatment for AML is an estimated $50,114,600 per year and will continue to increase as more drugs are approved. In an effort to mitigate as much financial burden as possible, pharmacists hold a unique responsibility as waste stewards. Waste significantly impacts the patient and the healthcare system. A study from 2010 surveyed oncologists on the influence of cost on treatment regimens. Of those surveyed, 84% stated that cost had some effect on regimens, including adherence.[42] Oncolytic waste is present in many forms, but is common among oral agents, such as venetoclax, and patients who experience adverse events.[28,43] Previous investigations into the impact of oncolytic waste in the community setting have shown an increasing trend towards the use of oral agents when available.[28,44] For patients with AML, oral oncolytics such as azacitidine or decitabine are commonly used in the maintenance phase following consolidation.[18] Discontinuation rates of oral oncolytics can be seen up to 41%, which causes significant financial aggravation.[44] In clinical environments, waste manifests through compounding and administering intravenous preparations.[43] In the hospital however, pharmacists have more control over ideal conditions such as storage, preparation, delivery, and management. Pharmacists also are in a unique position to manage reimbursement claims for biologic medications, which significantly impacts waste. In Wisconsin, pharmacists and legislators have previously cooperated to create and operate a drug repository program under Wis. Stat. §255.056 wherein an oncolytic drug may be redistributed from an existing patient provided that the product remains in the original container, labels an expiration date within a specific time frame, and is accurately prescribed to the recipient for a valid indication.[28] Through their expertise, pharmacists are at the forefront of reducing waste both in Wisconsin and nationwide.

Conclusion

The cancer continuum of acute myeloid leukemia is both extensive and expensive. Care requires catering to patient-specific factors in order to maximize treatment outcomes. New agents, including gemtuzumab ozogamicin, midostaurin, gilteritinib, and venetoclax, present new benefits and risks in acute myeloid leukemia treatment and new challenges in therapeutic approaches. With new challenges, adherence is the key to improving health outcomes. As more agents enter the pipeline every year, it is the pharmacist's responsibility to ensure that therapy best suits the needs of the individual while simultaneously optimizing adherence and minimizing waste.

Maximilian Vitas and Shujie Lin are 4th Year Doctor of Pharmacy Candidates and Rucha Kulkarni is a Third Year Doctor of Pharmacy Candidate at Rosalind Franklin University of Medicine and Science College of Pharmacy in North Chicago, IL.

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UNIVERSITY OF WISCONSIN-MADISON SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Spotlight on Mental Health: Pharmacist Roles

by Kelsey K Kapinus, 2023 PharmD Candidate, Ashley M Srb, 2023 PharmD Candidate, Amy N Bowman, 2023 PharmD Candidate, Salma Abdelwahab, 2023 PharmD Candidate, ALexa Bekkerus, 2023 PharmD Candidate

Awareness around mental health concerns is becoming more common in today's society; this is due to both the increase in recognition and the increase in occurrence of mental health disorders.[1] With increased awareness, many people are becoming more comfortable discussing their mental health concerns despite persistent stigma.[2] A person's mental health challenges are as unique to them as their own fingerprint, which means treatment needs to be individualized, and often benefits from a multidisciplinary care approach. In refractory cases, it may take several different therapeutic avenues, including medication and non-medication trials, for a patient to find a treatment regimen that is effective for them. It is essential for treatment team members to be understanding, knowledgeable, and supportive during this process. Pharmacists can use the full range of their training and expertise to improve mental health treatment planning and access to evidence-based care. So, what exactly is the pharmacist's role in mental health?

Pharmacists play a larger role in mental healthcare than people might believe. They can aid a patient who is worried about certain side effects by providing information, discussing what to expect, and sharing how to manage side effects to improve tolerability. Pharmacists can support medication adherence by using population health tools to contact patients when their medications are due. As the most accessible healthcare professionals to the public, pharmacists are in grocery stores, hospitals, and outpatient clinics, and they possess the knowledge to answer health-related questions. Additionally, pharmacists help facilitate the implementation of mental health services by focusing on patient accessibility and addressing mental health treatment stigma within the community.[3] Many sources are available for pharmacists to help raise awareness of suicide risk and prevention, and as accessible healthcare providers, they can have a true impact on reducing suicide rates.[4]

In preparation for this publication, the authors interviewed pharmacists from various practice sites to capture their views on the complexities and importance of mental health, and what they have done to improve mental health care at their sites. These pharmacists provide insight into caring for patients with mental health concerns, how to advocate for awareness in the community, how to get involved in different settings, and how to progress as a profession in contributing to the improvement of mental health care.

Jessica DeVito and Stacy Graham

Genoa Pharmacy, Madison

With experience in long-term care initially, Jessica DeVito, PharmD and Stacy Graham, PharmD transitioned to the community setting with an emphasis on caring for patients with mental health illnesses. The care they deliver to patients at Genoa Pharmacy takes into consideration the patient population demographic and provides services that cater to their needs. The patient population includes individuals with complex mental illnesses, and these patients may need help managing not only their medication, but their lifestyles. DeVito and Graham provide consultations, refer patients to specific programs for individualized psychotherapy, and closely monitor patients for several months to ensure treatment is adequate. Pharmacists are an integral part of the healthcare team and meet a need for both providers and patients.[5] Additionally, DeVito and Graham collaborate with prescribers and nurses to provide high-quality, interdisciplinary care.

DeVito and Graham emphasize the importance of pharmacists enhancing their communication skills on these topics, through training on mental health; providing empathy to patients; and getting comfortable having difficult conversations with patients. They say that many patients do not want to be on medication, solely

RESOURCES TO BECOME MORE INVOLVED, SPECIALIZE, AND LEARN MORE

- College of psychiatric & neurologic pharmacists: https://cpnp.org/
- National Alliance on Mental health: https://www.nami.org/Home

WARNING SIGNS

www.nami.org/About-Mental-Illness/Warning-Signs-and-Symptoms

- Excessive worrying or fear
- Feeling excessively sad or low
- Confused thinking or problems concentrating and learning
- Extreme mood changes, including uncontrollable "highs" or feelings of euphoria
- Prolonged or strong feelings of irritability or anger
- Avoiding friends and social activities
- Difficulties understanding or relating to other people
- Changes in sleeping habits or feeling tired and low energy
- Changes in eating habits such as increased hunger or lack of appetite
- Changes in sex drive
- Difficulty perceiving reality (delusions or hallucinations, in which a person experiences and senses things that don't exist in objective reality)
- Inability to perceive changes in one's own feelings, behavior or personality ("lack of insight" or anosognosia)
- Overuse of substances like alcohol or drugs
- Multiple physical ailments without obvious causes (such as headaches, stomach aches, vague and ongoing "aches and pains")
- Thinking about suicide
- Inability to carry out daily activities or handle daily problems and stress
- An intense fear of weight gain or concern with appearance

because of the stigma associated with it; therefore, pharmacists need to reinforce and normalize treatment, in order to improve adherence and thus overall therapeutic outcomes. Both pharmacists reiterate the need for increased mental health awareness with a focus on ending stigma.

Mark Zwaska

SSM St. Mary's Hospital, Madison

As a hospital staff pharmacist and a previous pharmacy director, Mark Zwaska, B.S., M.S. sees a need for pharmacists to be included on psychiatric units for a variety of reasons. Psychiatrists have a specialized role as experts in behavioral medicine, and often have deep, detailed knowledge of the most commonly used groups of medications. From Zwaska's experience, pharmacists help psychiatrists provide individualized therapies to patients with comorbidities. Zwaska mentions that "patients are not in a vacuum," and pharmacists can help bridge the gap between a patient's treatment for mental health and their treatment for other conditions.

When asked about the impact that COVID-19 has had on his patients, Zwaska highlighted that the pandemic has forced isolation on an already isolated population and has created additional barriers to treatment. With an overall young and diverse patient population, in-person therapy has still been provided at Zwaska's hospital, with individuals following social distancing guidelines. Zwaska practices in an inpatient setting, but he emphasizes the importance of understanding the resources patients will have upon discharge. For example, individuals diagnosed with a serious mental illness experience higher rates of homelessness, incarceration, victimization, and trauma.[6] Ultimately, working in conjunction with community pharmacies and the patient is imperative for continuity of care and success outside the hospital in this population.

In Zwaska's position as an inpatient mental health pharmacist, he first and foremost focuses on getting an accurate picture of a patient's drug history. He recognizes that a patient's medication list can look very different from their current drug regimen, due to outpatient management of therapy, patient nonadherence, or a variety of other reasons. By obtaining an accurate medication list, a team of healthcare professionals including a pharmacist can work to optimize drug therapy for patients. Understanding that patients with psychiatric conditions are a unique population with their own needs is critical to providing individualized care for each patient and situation. Zwaska recommends attending rounds with the medical team if possible, while always working toward discharge for the patient. In mental healthcare, 60.7% of patients experience at least one drug-related problem during their hospitalization.[7] Knowledge of drug-related problems, compliance, drug interactions, and a patient's own understanding of their drug therapy is crucial.

Zwaska wants to encourage current and future pharmacists to consider the behavioral health specialty in their practice and not to be afraid of this field. He mentions that this specialty is "up and coming" and offers "an interesting social dynamic," where patients often value independence and personal choices, while also needing support. For students, Zwaska recommends taking advantage of mental health-specific rotations, especially in the hospital setting. There is a unique added advantage to practicing in inpatient units: pharmacists have increased access to psychiatrists, allowing for collaboration and discussion of patient treatment. Most of all, he reiterates the need for more pharmacists in this specialty, and states that having a foundation in this specialty can be helpful for all pharmacists, as a patient's mental health and wellbeing is central to their overall health.

Marie Moser

William S. Middleton VA Memorial Hospital, Madison

Marie Moser, PharmD is a clinical pharmacy specialist in mental health, pain, and anticoagulation at the William S. Memorial Veterans Hospital in Madison, Wis. She has a unique role within mental health pharmacy, as she developed a new clinic within the facility focusing on the intersection of mental health and chronic pain management. In addition, Moser has a role in the transgender clinic team, developing and expanding services for Veterans who are transgender. Some of the common conditions Moser evaluates are post-traumatic stress disorder (PTSD), major depressive disorder (MDD), anxiety disorders, dementia/Alzheimer's, chronic low back pain, and neuropathic conditions.

As mental health conditions are often more stigmatized than physical conditions, Moser saw the opportunity to use her interpersonal skills to advocate for patients in this area. At the hospital, mental health clinical specialty pharmacists have independent prescriptive authority, which allows them to manage a panel of patients with varying diagnoses. Pharmacists in this position can bridge the gap as medication experts, and improve access to patients through executing therapeutic

TRAINING OPPORTUNITIES

(QPR, Mental health training, difficult conversation)

- APHA: Introduction to Mental first aid for pharmacy: https://elearning.pharmacist.com/products/5709/introduction-to-mental-health-first-aid-for-the-pharmacy (4.0 CE)
- Full Mental Health training: https://www.mentalhealthfirstaid.org
- APHA: Townhall: Start the Conversation to Stop Suicide- https://elearning.pharmacist.com/products/5660/townhall-start-the-conversation-to-stop-suicide (2.0 CE)
- APHA: Community Wellness Through Depression Recovery- https://elearning.pharmacist.com/products/5650/community-wellness-through-depression-recovery
- Pharmacy Network Podcast: Pharmacist's Focused on Mental Health- https://omny.fm/shows/pharmacy-podcast-network/playlists/pharmacists-focused-on-mental-health
- Suicide prevention training: https://qprinstitute.com/
- **Suicide hotline #s**
  - » Walgreen's Work & Life Resource line 24/7 at 855-777-0078 or visit www.workandliferesources.net/walgreens.
  - » National Suicide Prevention Lifeline 24/7 at 800-273-8255 or the online chat at https://suicidepreventionlifeline.org/chat/
  - » LGBTQ+ Crisis line at 866-488-7386
  - » Veterans Crisis Line at 866-488-7386
  - » HOPELINE Text Service, text HOPELINE to 741741
  - » https://www.dhs.wisconsin.gov/prevent-suicide/index.htm

plans; ordering/reviewing laboratory values; prescribing and deprescribing medications; performing physical assessments; identifying drug-related problems; ordering consultations; and referring patients when needed.[8]

Moser describes mental health challenges as "liv[ing] in the grey" and emphasizes the importance of tailoring treatment to the patients' needs. Moser discusses how patient-provider relationships are built on trust, and that in order for patients to disclose trauma and past experiences associated with mental health, it takes strong motivational interviewing skills. Each patient brings new stories and complexities, so it's essential for providers to create a trusting relationship. A study evaluating clinical pharmacy services within primary care found a 60% increase in the number of patients who reached therapeutic goals, and a 32% decrease in patients discharged to a mental health clinic, when specialized pharmacists were involved.[9] Moser emphasizes the importance of providers and the community working together to improve mental health and therapy outcomes. To get involved with patient advocacy, she encourages others to join the National Alliance of Mental Illness (NAMI), as well as local organizations.

Casey Gallimore

Access Community Health Center, Madison

Casey Gallimore, PharmD uses her knowledge of mental health to impact the locally underserved patient population, as well as to mentor the next generation of pharmacists. At Access Community Health Center, Gallimore explains, finding out whether a patient is willing and able to take prescribed medications is one of the challenges the primary care team faces, and a place where pharmacists have an impact. Pharmacists can also play a significant role in supporting appropriate safety and efficacy monitoring when psychotropic medications are prescribed in primary care (for example, pharmacists can help ensure metabolic parameters are checked following an antipsychotic prescription). It is important to acknowledge that there are numerous external social determinants that influence someone's mental health that medications alone cannot fix, such as homelessness, trauma, and lack of access to basic resources. As a member of the wider primary care team, Gallimore collaborates with prescribers, nurses, social workers, and psychologists to address these challenges and decrease barriers to treatment. Although she is only at Access once a week, she hopes to see pharmacists become more involved in primary care teams and be confident discussing mental health with patients. Pharmacists are essential members of the healthcare team who can have significant positive impacts on patients' mental health outcomes. For example, a yearlong retrospective study involving pharmacist-led medication management in a mental healthcare setting showed a mean PHQ-9 score reduction of 10 and an overall medication adherence rate of 82.9%.[10]

Gallimore is doing her part to break the stigma around mental illness by educating future pharmacists at the University of Wisconsin-Madison about mental health disorders and how to communicate effectively with this patient population. A 2020 study involving pharmacy students enrolled in an elective mental health first aid course resulted in improved student attitudes towards mental health and increased student strategies to manage their own mental health.[11] Gallimore's advice to other pharmacists and students is to never stop learning, as the field changes quickly with new medications and therapy. She recommends keeping up with current research by registering for table of contents alert emails through JAMA Psychiatry, Medscape, and other mental health-focused journals. Pharmacists can continue to grow their knowledge in this area by attending mental health conferences and reviewing the College of Psychiatric and Neurologic Pharmacists' website. Mental health can be difficult to talk about, but pharmacists can help break down the barrier by expanding their role within care teams and having conversations with patients.

How Pharmacists Can Get Involved to Improve Patients' Mental Health

As previously mentioned, there are many ways for pharmacists to get involved with mental health in any pharmacy practice. In this article, we've highlighted pharmacists from various settings, showcasing how they are helping to fight the stigma surrounding mental health conditions. To take a more active role in mental health, pharmacists can incorporate various strategies in their everyday workflow. For example, they can look for warning signs their patients may present when they come in to pick up their prescriptions. If the pharmacist is aware of patients with mental health conditions, documenting their behavior and appearance at each visit and comparing them over a few months may be beneficial for patients'

long-term care. Pharmacists can refer to the readings or online resources provided in order to expand their mental health knowledge and be of help to struggling patients. One immediate way to help patients who might be in need is posting the number of the National Suicide Prevention Hotline in a visible location. Pharmacists passionate about mental health and eager to learn more can do so by taking mental health-focused continuing education and, if they wish to specialize, working towards a board certification. By being observant and active in patients' mental health management, pharmacists can help improve patients' symptoms and quality of life.

Kelsey K Kapinus , Ashley M Srb, Amy N Bowman, Salma Abdelwahab, and ALexa Bekkerus are 3rd Year Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

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HANDOUTS FOR PATIENTS AND RESOURCES FOR PHARMACISTS

- https://cpnp.org/guideline/essentials
- https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Provider
- https://www.nami.org/Support-Education/Publications-Reports/Guides
- http://www.ncpa.co/issues/APFEB18-HeadHealth.pdf

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Review Article

Recommendations to Appropriately Dose Medications in Transgender Patients

by Jennifer A. Polenska, PharmD

Clinical Question

How does gender-affirming hormonal therapy affect serum creatinine (SCr), body mass index (BMI), and lean body mass (LBM)? How should creatinine clearance (CrCl) and ideal body weight (IBW) be assessed in order to dose medications appropriately?

According to a study completed in 2016 by University of California, Los Angeles's (UCLA) Williams Institute, approximately 0.6% of people identify as transgender, which amounts to 1.4 million Americans.[1] Transgender patients face a considerable number of health disparities, including an increased risk of HIV infection, a lower likelihood of preventative cancer screenings in men, and generally poor access to quality healthcare.[2] In order to provide the best possible care to this specific patient population, it is important to understand and recognize these patients' needs—for example, understanding medication essentials that may require an adjustment based on a changing SCr or weight. Additionally, it is essential that healthcare providers understand the terminology of the transgender community, which helps with communication and documentation. Providers should work to understand the impact that gender transition can have on medication therapy. As laid out in table 1, there are some important terms that providers should understand to help treat this patient population.[3]

When gender transitions occur, hormonal therapy is usually needed to help with the physical transition; this is usually referred to as gender-affirming therapy. Gender-affirming therapy is the primary medical intervention sought out by transgender patients that will allow acquisition of secondary sex characteristics to become more aligned with an individual's gender identity. It is currently unclear how these hormonal therapies can affect the SCr and LBM, and currently only one recommendation exists for how to calculate CrCl and IBW. It is important for healthcare professionals to know how hormonal therapy could potentially affect CrCl and IBW, since medications that are adjusted for renal function or by weight could end up being under- or over-dosed. This article will review the four main studies that exist for this area of study, and will make suggestions on how gender-affirming hormonal therapy can affect SCr, BMI and LBM, and how CrCl and IBW should be assessed to help with medication dosing.

TABLE 1. Defining Vocabulary of the Transgender Community

Term	Definition
Transgender man	A person who identifies as a man and was born with female sex characteristics
Transgender woman	A person who identifies as a woman and was born with male sex characteristics
Cisgender man or woman	A person whose gender identity matches the sex characteristics they were born with

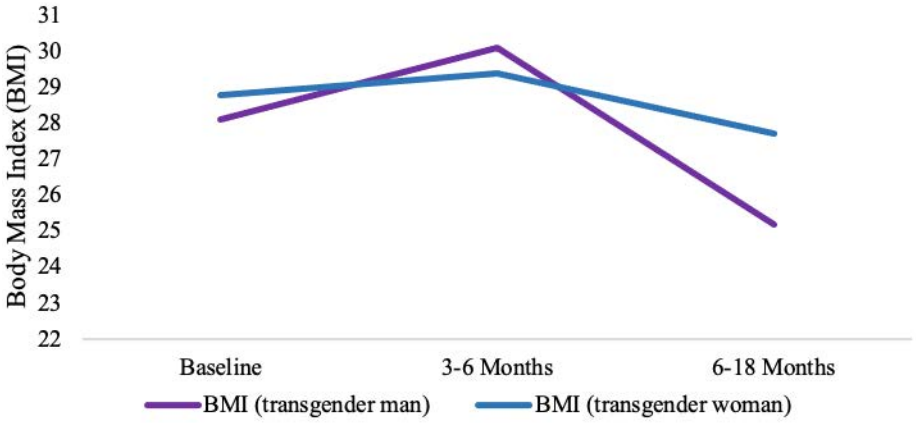
Adapted from GLAAD Media Reference Guide - Transgender. GLAAD. Published March 28, 2021. Accessed January 26, 2021. https://www.glaad.org/reference/transgender

Literature Review

In 2008, an observational cross-sectional study of 23 transgender women was completed to compare bone composition, LBM, BMI, muscle composition, and laboratory values (including SCr).[4] These 23 transgender women were compared to a control group that included 46 cisgender men. The inclusion criteria for this study included transgender women who had completed gender affirmation surgery (GAS) at least 3 years prior to the enrollment and who had taken estrogen therapy for at least 2 years prior to GAS.[4] When looking at LBM, the median LBM was lower in transgender women than in cisgender men (51.2 kg vs 61.8 kg; $P < 0.001$), and the median SCr was found to be lower in transgender women than in cisgender men (0.78 mg/dL vs 0.94 mg/dL; $P < 0.001$).[4] From this study, it was found that long-term treated transgender women with estrogen therapy ended up presenting with a different body composition, smaller bone size, and a lower bone turnover compared to the control group of cisgender men.[4] While this study is one of the first to report volumetric and geometric bone parameters in long-term treated transgender women, it also has some limitations. This study used a cross-sectional design, which did not allow the researchers to draw any causative conclusions from the results.[4] A second limitation is the lack of baseline measurements for the participants, meaning that the differences in body composition, bone metabolism, and size could be attributed to lifestyle factors that might have been present before gender-affirming therapy was started.[4]

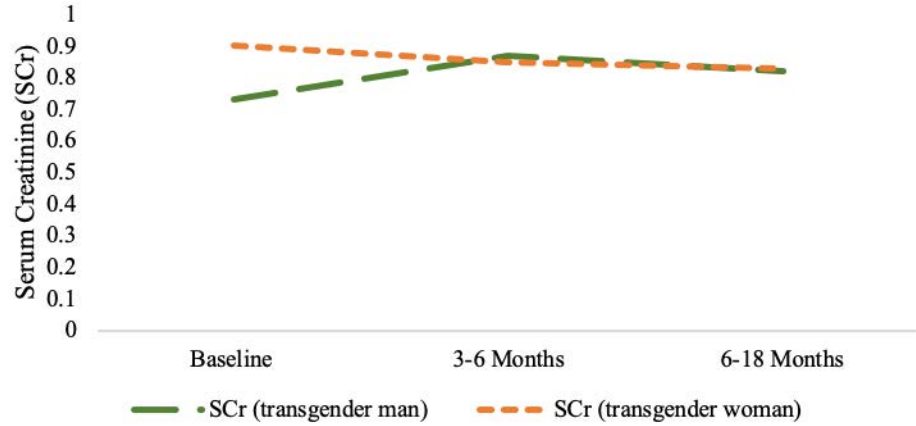
Additionally, in 2016, a retrospective cohort study of transgender women and transgender men who were using gender-affirming hormone therapy was completed to compare their BMIs, blood pressures, and laboratory values (including SCr) at baseline, 3 to 6 months after starting hormone therapy, and 6 to 12 months after starting hormone therapy.[5] This study

FIGURE 1. Effect of Hormonal Therapy on Body Mass Index



Adapted figure 1 from Fernandez JD, Tannock LR. Metabolic effects of hormone therapy in transgender patients. Endocr Pract. 2016;22(4): 383-8. doi: 10.4158/EP15950.OR

FIGURE 2. Effect of Hormonal Therapy on Serum Creatinine (SCr)



Adapted figure 2 from Fernandez JD, Tannock LR. Metabolic effects of hormone therapy in transgender patients. Endocr Pract. 2016;22(4): 383-8. doi: 10.4158/EP15950.OR

included only patients with a baseline and at least one follow-up visit in the study window, which included 33 transgender women and 19 transgender men. These patients were analyzed separately and grouped into two study arms. One study arm was transgender women, and on average they did not experience a significant change in BMI, and their SCr did decrease from a mean baseline of 0.9 mg/dL to a mean of 0.85 mg/dL.[5] The second study arm included transgender men, and on average their BMI did increase from a baseline of 28.1 to 30.1 at follow-up, and their SCr did increase from 0.73 mg/dL at baseline to 0.87 mg/dL at follow-up.[5] Figures 1 and 2 display the data from this study, and the figures represent the effects of hormonal therapy on BMI and SCr in transgender women and men. These figures illustrate how the long-term use of gender-affirming therapy can affect BMI and SCr the longer the hormonal therapy is being used. There are limitations to this study as well. Since this was a retrospective chart review, the data that was available for review was limited.[5] Also, this study experienced a significant drop-out rate that affected the power of the study.[5] Lastly, the timing of follow-up visits after hormone initiation varied among patients, where some had sooner follow-ups, while others had longer intervals between visits.[5] Despite these limitations, it was found that both transgender women and transgender men experienced changes in biomarkers that are used to calculate creatinine clearance and ideal body weight as early as 3 months after starting hormone therapy.

A prospective cohort trial was completed in 1998 that compared LBM, BMI, and laboratory values (including SCr) in 17 transgender women and 17 transgender men, before and after they were on gender-affirming hormone therapy for at least 4 months.[6] The mean SCr baseline values decreased in the transgender women from 0.97 mg/dL to 0.89 mg/dL, but increased in the transgender men from 0.87 mg/dL to 0.96 mg/dL.[6] These findings suggest that after 4 months of hormone therapy, SCr was more closely related to the affirmed gender identity than the patients' sex at birth.

Lastly, a cross-sectional study was completed in 2014 that included 55 transgender women and compared laboratory values (including SCr) to those of 20 cisgender men and 20 cisgender women, to help characterize normal laboratory value ranges in transgender women.[7] For inclusion criteria, the transgender women had to have been receiving estrogen therapy for a least 6 months.[7] The percentile range for SCr values that were reported in transgender women (0.55-1.2 mg/dL) was found to be more like SCr in cisgender men (0.73-1.3

TABLE 2. Recommendations for Pharmacists to Assess Creatinine Clearance and Ideal Body Weight

Duration of Hormonal Therapy	*Recommendation for IBW Dosing*	*Recommendation for Estimating CrCl*
Not taking hormonal therapy or has started taking for less than 1 month prior to admission	Calculate IBW based on sex at birth	Calculate CrCl based on sex at birth
Initiation of hormonal therapy is less than 6 months prior to admission	Consider calculating IBW based on sex at birth	Consider calculating CrCl based on sex at birth
Initiation of hormonal therapy is greater than or equal to 6 months prior to admission	Consider calculating IBW based on gender identity	Consider calculating CrCl based on gender identity

CrCl = Creatinine Clearance; IBW = Ideal Body Weight
Adapted table 2 from Webb AJ, McManus D, Rouse GE, Vonderheyde R, Topal JE. Implications for medication dosing for transgender patients: A review of the literature and recommendations for pharmacists. American Journal of Health-System Pharmacy. 2020; 77(6): 427-433. doi:10.1093/ajhp/zxz355

mg/dL) than in cisgender women (0.65-1.0 mg/dL).[7] The findings of this study suggest that the possible range of SCr values for transgender women is more similar to cisgender men, but since cisgender men's and women's SCr ranges already overlap, it is difficult to interpret these results accurately.

Evidence-Based Answer

The literature review above indicates that after transgender patients have taken gender-affirming hormone therapy, their physiology more closely reflects their affirmed gender identity than their sex at birth. Based on the literature review, table 2 demonstrates existing recommendations to help pharmacists assess CrCl and IBW when transgender patients are being seen in the outpatient setting or while they are hospitalized and taking hormonal therapy.[8] While table 2 gives recommendations for assessing CrCl and IBW, there are currently no recommendations for which weight metric to use when calculating CrCl. We believe it would be appropriate to calculate CrCl using the Cockcroft-Gault equation, in which IBW is routinely used, actual body weight is used if a patient's weight is less than their IBW, and adjusted body weight is used when a patient's actual body weight is greater than 130% of their IBW. In addition, we agree that these 4 studies are a good starting point for this specific topic, but that more studies should be conducted to help make these recommendations stronger. Additionally, this review would be beneficial for healthcare providers to help ensure that transgender patients are being treated effectively and safely with their medications, no matter the healthcare setting where they are being seen.

Jennifer Polenska is a PGY1 Pharmacy Practice Resident at SSM Health St. Mary's Hospital in Madison, WI.

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UNIVERSITY OF WISCONSIN-MADISON SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Business Member Spotlight: Dr. Jessica Benjamin, SSM Health St. Mary's Hospital

by Salma E. Abdelwahab, 2023 PharmD Candidate, Rachel A. Hawley, 2023 PharmD Candidate, Emily A. LaMonte, 2023 PharmD Candidate

SSM Health is a Catholic, not-for-profit health system and integrated delivery network that delivers care throughout Illinois, Missouri, Oklahoma, and Wisconsin.[1] SSM Health St. Mary's Hospital (Madison, Wisconsin) is a 400-bed community hospital and one of 23 hospitals in the health system. The mission of SSM Health is, "Through our exceptional health care services, we reveal the healing presence of God.[2]" SSM Health not only strives to provide optimal care to its patients, but it also aims to give back to the community. At St. Mary's Hospital, Dr. Jessica Benjamin, PharmD, the regional manager of quality and safety, is playing an important role in providing quality patient care and advancing the pharmacy profession.

Benjamin graduated with a bachelor's degree in biomedical engineering from Washington University in St. Louis and worked at Epic as a Willow implementation manager. After several years of working closely with pharmacist informaticists and clinical pharmacists, Benjamin decided to embark on a career change and applied to pharmacy school.

Benjamin attended the University of Wisconsin-Madison. After pharmacy school, she worked at the Pharmacy Society of Wisconsin (PSW) as the Wisconsin Pharmacy Quality Collaborative (WPQC) operations manager, where she helped community pharmacies expand their WPQC medication therapy management (MTM) programs. Benjamin enjoyed her experience working at PSW and partnering with community pharmacies, because she observed community pharmacists practicing at the top of their license and providing clinical services. Importantly, WPQC is a reimbursement model that pays pharmacies for clinical/cognitive services and is not tied to dispensing medication.

In the fall of 2015, Benjamin joined SSM Health St. Mary's Madison as the medication safety pharmacist. Her role evolved over time, and she now is the regional manager of quality and safety for the Wisconsin region (which includes seven SSM Health hospitals). In her new role, she works with the vice president of pharmacy services and pharmacy directors to advance the pharmacy practice model and promote medication safety. She believes that pharmacists are valuable members of the healthcare team and improve the quality of care for patients every single day.

Day-to-Day Practice & Raising the Bar

As the regional manager of quality and safety, Benjamin strives to advance and improve patient care every day. Benjamin facilitates monthly Pharmacy and Therapeutics Committee meetings to determine which medications should be on formulary based on their clinical effectiveness, safety, and cost. Much effort is spent aligning pharmacy clinical practice across the Wisconsin hospitals within SSM Health. She also leads medication safety meetings and collaborates on interdisciplinary process improvement projects to continually assess and improve the medication-use process to advance safety.

Benjamin continuously drafts protocols to optimize patient care and increase pharmacy involvement in the patient care process. She works with the regional clinical coordinator and the regional antimicrobial stewardship (AMS) pharmacist at St. Mary's to standardize protocols and procedures. For example, Benjamin worked with the AMS pharmacist and AMS medical director to develop a community acquired pneumonia (CAP) protocol to have pharmacists more involved in monitoring CAP patients to reduce antimicrobial resistance.

Medication safety is another important aspect of Benjamin's role. She analyzes medication-related events and presents the findings to the medication safety committee. When a safety incident arises, Benjamin frequently questions whether an underlying systemic cause exists, and considers retrospective solutions to prevent the event from occurring again. For example, Benjamin's implementation of barcode scanning of IV products in central pharmacy significantly reduced dispensing errors that were sent to the nursing units. One of the most important aspects of Benjamin's safety role is to create an environment that allows other healthcare professionals to voice their input regarding safe medication practices and ensure that their concerns and ideas are heard.

A key part of Benjamin's job is change management. Whenever the pharmacy department initiates a clinical or operational change, it's crucial to engage key

Below: *Dr. Jessica Benjamin, PharmD*

stakeholders prior to and during the change to solicit feedback and communicate about relevant changes to their respective teams.

Bumps in the Road

All professionals encounter bumps in the road at some point in their career. Dr. Benjamin acknowledges that one of the challenges she faces working within an extremely large health system is that most changes involve obtaining buy-in from multiple hospitals and departments (especially when it involves Epic or other technology-related changes). Thus, change timelines are often long and there are frequently individuals who resist change. Benjamin says she overcomes these challenges by having "a lot of tenacity." She emphasizes that perseverance and tenacity are key to implementing change.

Benjamin demonstrated these key skills in response to a serious medication event that happened in operating suites. The medication packaging included some design flaws that allowed it to be given via the wrong route. After learning the details of the event, Benjamin discussed the design flaw with the manufacturer and wrote an article for the Institute of Safe Medication Practices. She is working to remove the medication from formulary for all of SSM Health until the design flaw is fixed. By doing so, Benjamin advocates not only for the safety of SSM patients, but also for patients across the country. Benjamin put the hospital's mission front and center, where safety methods and best practices for optimal patient care are the main focus. Despite fear of pushback, there was an established culture of safety at her place of work, where she felt valued, safe to speak up, and able to advocate for change.

Moving Forward

Benjamin loves being an integral part of a team. Inspired by strong mentors during her early career at PSW, she is passionate about shaping the next generation of pharmacy leaders. Her advice for aspiring pharmacist leaders includes: Advocate for the profession and the value it provides; tell the story as well as the facts when proposing a change; and model optimism. To help manage negativity in the workplace, she uses empathetic listening (i.e., maybe the negative person in question is just not heard, or is being dismissed); being resilient (e.g., "Don't let others get you down"); and tying in to people's intrinsic motivation (that will usually get them on board).

Above: *Outside SSM Health St. Mary's Hospital in Madison, WI.*

Benjamin also shares her thoughts about being a woman and a leader in pharmacy. She says that, "as [women], we face unique challenges, but it's important to be confident in the knowledge that [we] have and the talent that [we] bring." She encourages everyone who aspires to become a leader in pharmacy to "be in touch with [their] inner voice" in order to advocate for positive change.

A piece of advice that shaped how Benjamin got to where she is today is to "be open-minded, and [not] say no." Benjamin says she "tried to be open-minded during all of [her] rotations to see different things," and "was always one of the first to volunteer." The most translatable skill Benjamin learned in pharmacy school is critical thinking. Being open-minded and adaptable has transformed Benjamin's role at St. Mary's Hospital. She started her career with SSM as a medication safety pharmacist. Next, Benjamin was facilitating P&T committees, aligning services between hospitals within the Wisconsin region, and advancing pharmacy practice every day.

Salma E. Abdelwahab, Rachel A. Hawley, and Emily A. LaMonte are 3rd Year Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

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