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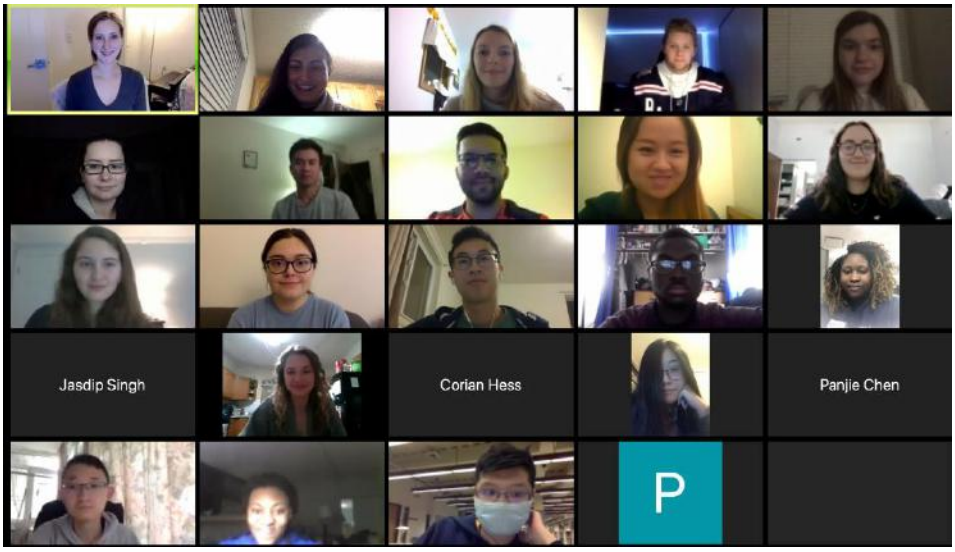
NYS-ACCP Insider

University at Buffalo School of Pharmacy and Pharmaceutical Sciences

Special Points of Interest:

University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS)-ACCP Student Chapter Updates



Virtual Dinner & Discussion with Dr. Maya Chilbert, PharmD, BCCP

Being a Pharmacy Student During a Pandemic:

The COVID-19 pandemic has greatly affected the nation as a whole and as pharmacy students we have seen our world flip upside down. Our curriculum has shifted to mostly remote learning, presenting us with new challenges to overcome. Continuing to hold events and provide programming for our members has been challenging in the virtual world, but feasible with video conferencing tools like Zoom.

As things slowly return to normal with COVID-19 vaccines rolling out, we can now reflect on the difficulties of the past year and see all the growth that we have made. Our goal at UB SCCP has always been to provide students with the tools to develop the clinical skills they will use throughout their

pharmacy careers. We have been able to do that by hosting various events like Journal Clubs, "Dinner & Discussions", alumni panels, as well as ACCP national competitions, in the virtual setting.

UB SCCP Updates:

Last spring, when things went fully remote, we invited several P4 students to come in and do a Q&A over Zoom, discussing their experiences with midyear, residency applications, and the interview process. This was a great opportunity for P1, P2, and P3 students to gain insight into what they may experience in the future. This past Fall semester we held our annual Journal Club primer where upperclassmen taught new P1 and P2 students how to read and evaluate scientific literature. This year we discussed the Jupiter Trial and the use of statins in the primary prevention of cardiovascular disease. Following our primer, we chose to have a Journal Club on the VICTORY trial, which evaluated the recently FDA approved drug Verquvo (vericiguat), indicated for reducing mortality and hospitalizations in patients with HFrEF.

In addition to Journal Clubs, we continued to host "Dinner & Discussions", where guest speakers discuss clinical topics that go beyond our regular coursework. This allows students to discover various areas of pharmacy and treatments that they otherwise wouldn't be exposed to in the classroom or as an intern. This past Fall semester we invited one of UB's Clinical Assistant Professors, Maya R. Chilbert, PharmD BCCP. Dr. Chilbert completed a PGY-2 in cardiology and is a Board-Certified Cardiology pharmacist. In addition to her teaching appointment, she currently works as a clinical pharmacist in the Cardiac ICU at Buffalo General Medical Center. She discussed her experience with left ventricular assistance devices (LVAD) from her residency training. LVADs are heart pumps used by those patients who have reached end-stage heart failure and whose hearts require additional assistance to pump blood throughout the body.

In October, members virtually attended the ACCP Annual Meeting. Students were able to learn about residency and given tips to help them stand out as an applicant, such as interview skills and ways to improve their application. There were a variety of seminars where students learned how to make themselves standout residency candidates through honing application and letter of intent skills. The ACCP meeting was a great opportunity for students to network as well as meet current pharmacists and future colleagues across the nation.

We also held our local exam for the ACCP Clinical Research Challenge and Clinical Pharmacy Challenge virtually. Both competitions serve to give students an opportunity to test their drug literature evaluation and pharmacotherapeutic knowledge base. Earlier this Spring our team of 3 for the Clinical Research Challenge moved onto the 2nd round of competition, where they were tasked with creating a research protocol.

Going Forward:

Later this semester we will be joined by Clinical Associate Professor, Dr. Raymond Cha, who will conduct our annual Professionalism 101 talk. Typically, we host this event every year and let upperclassmen share tips and tricks that they have used to further develop their careers, but this year we are inviting Dr. Cha, a former residency program director, who will be able to give students a unique insight into what it takes to become a residency trained clinical pharmacist.

The UB SCCP chapter is also continuing the "Clinical Topic Discussion" event that was implemented last year, where students create a presentation on a clinical topic of their choosing. Students will then

receive feedback from other students and faculty. This event allows students to gain experience and confidence in presenting various clinical topics and will prepare them for postgraduate training programs including fellowships and residencies.

We at UB SCCP are proud of the work we are doing to prepare the next generation of clinical pharmacists. Our pillar events like Journal Clubs and Dinner & Discussion continue to be well received by students. We hope you enjoy reading the remaining articles in this newsletter and learn some things along the way!

– Samantha Mei, PharmD Candidate, UBSPPS Class of 2023
– Ali Zahid, PharmD Candidate, UBSPPS Class of 2022

FDA Grants EUA to J&J's COVID-19 Vaccine

Introduction to EUA:

When it comes to public health crises such as COVID-19 pandemic, the FDA's emergency use authorization (EUA) comes into play. An FDA EUA is a means to provide a treatment or therapy in a situation where no other adequate products are approved or available for use. Although the process to receive an EUA is rigorous, it is not equivalent to that undertaken by fully FDA approved products. Because of the time sensitivity related to getting these treatments available to the public, there just isn't enough time to gather extensive safety data. In order for a product to be approved for emergency use, a pharmaceutical manufacturer must prove to the FDA that its effectiveness outweighs any potential risks that it may carry. When applying for an EUA a company must submit all scientific information that it has available (i.e., all relevant clinical trial data). The FDA then conducts a risk-benefit analysis to determine whether or not to bring the product to market. Once the declared emergency has ended the EUAs also expire.[1]

Background on viral vector vaccines:

Viral vector vaccines are different from traditional vaccines in regards to how they work. Traditional vaccines use a weakened or inactivated form of the target pathogen to mount an immune response. However, viral vector vaccines use a modified version of a different virus as a vector. The vector then delivers instructions in the form of genes to our cells in order to build an immune response. Viral vector technology dates back to the 1970's and has been studied for use not only in vaccines, but also for gene therapy, treating cancer, and molecular biology research. Moreover, some vaccines that used viral vector technology have been recently used in Ebola outbreaks, and ongoing studies are focused on using viral vector vaccines against other infectious diseases such as Influenza and Human immunodeficiency virus (HIV).[2]

In the case of Johnson & Johnson's COVID-19 vaccine, virus DNA is delivered by a modified, harmless, adenovirus which instructs our cells to make a SARS-CoV-2 antigen called a "spike" protein. This spike protein is then displayed on the surface of the cell which triggers detection by helper T cells. Other immune cells, called B cells, latch onto the spike proteins, and start the production of antibodies. Antibodies then latch onto the spike proteins, preventing further infection and marking them for

destruction by killer T cells. These antibodies are then available to provide a similar immune response in case of future infection by COVID-19.[2]

EUA Approval:

Johnson & Johnson's COVID-19, the third to be given EUA by the FDA, was held to the same safety, efficacy, and quality standards as its predecessors from Pfizer/BioNTech and Moderna. Analysis of an ongoing randomized, placebo-controlled study including 43,783 participants was conducted to determine if the vaccine was appropriate for an EUA. The trial was held in the United States, Mexico, South Africa, and parts of South America.[3] Participants were broken down into two groups, with one receiving the vaccine (n = 21,895) and the other receiving a saline placebo (n = 21,888).[3] Included participants were those who had no evidence of SARS-CoV-2 infection prior to receiving treatment. Participants were followed for a median of eight weeks after vaccination, in compliance with FDA guidance.[4] After at least 14 days following vaccination, there were 116 cases of COVID-19 occurring in the treatment group versus 348 cases in the placebo group.[1] Of these, 14 cases were classified as severe in the treatment group versus 60 cases in the placebo group. After 28 days following vaccination, there were 66 cases of COVID-19 in the treatment group and 193 cases of COVID-19 in the placebo group. Of these, 5 cases were classified as severe in the treated group versus 34 cases in the placebo group. Data analysis showed that the vaccine was approximately 67% effective in preventing moderate to severe/critical COVID-19 occurring 14 days after vaccination, and around 66% percent effective in preventing moderate to severe/critical COVID-19 at 28 days following vaccination. The vaccine was also shown to be approximately 77% effective in preventing severe COVID-19 at 14 days following vaccination and 85% effective at 28 days following vaccination.[1] Common side effects to the vaccine are similar to the other two EUA vaccines and may consist of fever or chills, cough, headache, and muscle or body aches.[3]

Conclusion:

The third EUA for a COVID-19 vaccine should help overcome supply chain issues that are being faced by the healthcare system today. Multi-dose vials of the vaccine are shipped frozen, but can be stored at 2°C to 8°C (36°F to 46°F). J&Js vaccine requires no reconstitution and is the first FDA authorized COVID-19 vaccine that consists of a single-dose regimen. It is still to be determined if the vaccine provides long-term protection against COVID-19 or if it prevents those who are asymptomatic from transmitting the disease to other individuals. Although numerically the efficacy of J&Js vaccine may seem lower than those seen from the current FDA EUA COVID-19 vaccines, it is important to consider the different primary endpoints that were evaluated in each study. While Moderna and Pfizer/BioNTech looked for overall incidence of COVID-19, J&J looked for occurrence of moderate to severe/critical cases of COVID-19.[1,5] J&J also conducted their trials in several different countries, which could mean there was a higher prevalence of newer variants of COVID-19 in their trials. While it's not possible to directly compare the vaccines since they were tested in different settings, what can be said is that the FDA has determined that all three vaccines are appropriate for emergency use. Additionally, it's important to remember that Influenza vaccines, which have been proven to lower infection rates, typically only have an efficacy of approximately 40-60%.[6] Public health experts continue to stress that it is important to vaccinate as much of the population as possible to achieve "herd immunity". Those individuals who are eligible and able to receive vaccination should do so as soon as possible, without waiting until they have access to a particular vaccine.

– Ali Zahid, PharmD Candidate, UBSPPS Class of 2022
– Bashar Othman, PharmD Candidate, UBSPPS Class of 2024

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Multisystem Inflammatory Syndrome in Children

When the COVID-19 pandemic reached the Western hemisphere, many people thought it to be a virus that only targeted the old and those with comorbidities. In the early days, children were mainly asymptomatic or mildly symptomatic.[1] These points still hold true as the pandemic continues to unfold across the globe; the disease is more likely to affect older adults than the younger population and children tend to present as asymptomatic or mildly symptomatic.[1,2] However, after surges in COVID-19 cases, school-aged children who previously tested positive for the virus would report to the hospital with symptoms of fever, hypotension, abdominal pain and cardiac dysfunction.[3] There was uncertainty among the Infectious Disease community on whether these children had manifestations of previously known diseases such as toxic shock syndrome(TSS) or Kawasaki disease(KD) or a new temporally related phenomenon.[1,4] The latter proved to be true, as children were thought to have a novel inflammatory syndrome now referred to as multisystem inflammatory syndrome in children(MIS-C) by the WHO and CDC.[5] Though data remains scarce, epidemiological and immunological studies over the past year have broadened our understanding of the disease, and could help in treatment of MIS-C and shed light on the etiology of long known inflammatory syndromes such as KD.

Although there is uncertainty around the incidence of MIS-C due to its rapidly evolving nature during a pandemic, it can be determined that MIS-C is a rare complication of SARS-CoV-2 infections in children. The initial reports of MIS-C occurred out of South East England in mid-April 2020 where 8 children were diagnosed with hyperinflammatory shock during a period of 10 days, all presenting with similar features to atypical KD or TSS.[6,7] Since then, larger studies started to emerge out of England (58 cases), across the United States (218 cases), France/Switzerland (35 cases), and South Africa (23 cases).[7,8] Notably, there have not been any reports in neither China, nor other Asian countries with significant cases of COVID-19. It's been found that most of the MIS-C cases have occurred in older children and adolescents, and of those cases more than 70% of the affected individuals were previously healthy. With their most common pre-existing comorbidities being obesity (> 95th percentile) and asthma.[9, 2] In most of these studies it was clear to see that majority of cases had positive IgG serology (75% - 90%) along with negative PCR assays for COVID (53% - 80%). This in combination with findings showing that there was a lag of about 3-4 weeks between the peak of the COVID cases and the rise of MIS-C cases indicates that MIS-C may possibly represent a form of post-infection complication associated with the COVID-19 virus.[9]

As of today, the precise pathophysiology of MIS-C isn't well understood. From what can be perceived from the most current literature; MIS-C is thought to be caused by a hyperimmune response to the COVID-19 virus in a child genetically predisposed to susceptibility. The symptoms of MIS-C are similar to that of KD, TSS, bacterial sepsis, and cytokine release syndrome.[11] Although there seems to be immune dysregulation causality in response to the virus that presents similarly to KD, based on the available studies, MIS-C has a particularly distinct immunophenotype.[10,11] The exact mechanisms for which COVID-19 triggers this abnormal immune response is currently unknown; the post-infectious process is suggested through the timing of the rise of these cases relative to the peak COVID-19 cases, as discussed above. The cytokine storm is marked mostly by a persistent fever with significant elevations in proinflammatory cytokines and inflammatory markers such as interleukin-6. With increased data showing cardiovascular involvement and microvascular dysfunction for viral invasion of cardiomyocytes resulting in both cellular damage and ischemic injury.[12] In addition, COVID-19 infections have also been associated with endothelial injury with the activation of the coagulation cascade, resulting in the consequent elevation of D-dimer, which has also been associated with MIS-C.[6] D-dimer is a lab value that is used to indicate degradation of fibrin and reduced thrombin generation. This is normally associated with the severity of the disease in adults diagnosed with COVD-19 and can possibly increase the future risk for both venous and arterial thrombosis.[13]

Given the novelty of MIS-C and the pathophysiology not being well understood, current treatment options are extrapolations of treatment guidelines from similar syndromes such as KD.[1]

Initial management for both conditions is the same: 2g/kg IVIG and high dose aspirin.[1,3] If symptoms do not resolve with the first treatment of IVIG, a 2nd dose of IVIG can be considered after 2-3 days.[1] Corticosteroids are a cornerstone anti-inflammatory therapy, and can also be considered for treatment of patients with MIS-C.[1] Methylprednisolone has been used in the cytokine storm phase of MIS-C, followed by a switch to oral prednisone and conclusion with a taper.[1,5] Biologicals have also been known to be used in treatment of KD and MIS-C. The preferred first line biological is anakinra, an IL-1 receptor antagonist that downregulates the downstream proinflammatory cascade.[1] The safety profile of anakinra and its ability to reduce incidences of coronary artery aneurysms and myocarditis in KD make it an appealing option for treatment of MIS-C.[1] No large-scale clinical trials have looked at outcomes of MIS-C patients treated with any of the above therapies; further research is needed before definitive guidelines are available for treatment of MIS-C.

COVID-19 related MIS-C is a serious and life-threatening phenomenon that has become more prominent since April 2020. The diagnosis of MIS-C has proven to be challenging given the variability in presentation and similar signs and symptoms to other inflammatory syndromes such as KD and TSS.[1,3] A multi-specialty and interdisciplinary approach to the treatment of MIS-C is essential to improve outcomes for patients. Data continues to be scarce one year after the start of the pandemic; progress continues to be made in all areas of the disease ranging from diagnosis, pathophysiology, treatment and clinical outcomes.

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– Jasdip Singh, PharmD Candidate, UBSPPS Class of 2022

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New Drug Review: Lupkynis (voclosporin), First oral treatment for lupus nephritis

What is it and how it works:

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that affects the skin, joints, kidneys, and other organs. In about 50% of SLE patients, the kidney is targeted by autoantibodies which can lead to Lupus Nephritis. Lupus Nephritis increases the risk of morbidity and mortality, and even with current therapies many patients still develop chronic kidney disease (CKD) or end stage renal disease (ESRD) which greatly impacts their quality of life[1]. The current treatment strategies in the management of lupus nephritis consist of an “induction phase” which attempts to reduce the auto inflammatory processes causing injury to the kidneys, followed by a maintenance phase to help prevent exacerbations. The main goal of treatment is to be in complete remission. The current “induction phase” medication regimen consists of corticosteroids and immunosuppressants (mycophenolate mofetil (MMF), cyclophosphamide, azathioprine).

Lupkynis (voclosporin) is a drug developed to treat active lupus nephritis, a lupus-related kidney disease caused by inflammation. It is taken as a pill in combination with standard care therapies and the main mechanism of action is that the voclosporin is a calcineurin inhibitor used as an immunosuppressant medication to suppress the immune system. The mechanism of voclosporin suppression of calcineurin has not been fully understood. Activation of lymphocytes participates in an increase in intracellular calcium concentrations that bind to the calcineurin regulatory site. The immunosuppressant activity results in inhibition of lymphocytes proliferation, T cell cytokine production and expression of T cell activation surface antigens.

Who does it treat:

Voclosporin was approved January 22,2021 for the treatment of active lupus nephritis patients. Voclosporin is available as 7.9 mg capsules. The recommended starting dose is 23.7 mg orally (PO), twice a day. Voclosporin is recommended to be used in combination with mycophenolate mofetil and corticosteroids. Dosage adjustment needs to be made for severe renal impairment and mild to moderate hepatic impairment. Voclosporin is contraindicated with any concomitant use of strong Cytochrome P450 3A4 (CYP3A4) inhibitors and providers should proceed with caution if the patient has hypertension, hyperkalemia, at risk for QT prolongation, or pure red cell aplasia. It is also recommended to avoid any live vaccines in any patient taking voclosporin.

Dosing:

Voclosporin is available as 7.9mg capsules. Normal oral dosage for adults is 23.7 mg PO twice daily initially. Used in combination with mycophenolate mofetil and steroids. When taking the medication, an empty stomach is needed for every 12 hours, with a minimum of 8 hours between two doses. The continued dosage is dependent on the patients' estimated glomerular filtration rate (eGFR). Adjusting the dose based on kidney function is critical for this particular medication and voclosporin discontinuation should be considered if there is no shown benefit by 24 weeks for patients' safety and drug efficacy. The common medication cyclophosphamide taken by many lupus nephritis patients, has not been studied well when taken with voclosporin. So, cyclophosphamide is not recommended while the patient is taking voclosporin.

Side effects:

Nephrotoxicity may occur with using voclosporin therapy, as with other calcineurin inhibitors. The most commonly reported side effect in clinical trials was a reduction in the glomerular filtration rate, which was reported in 70 patients (37.1 per 100 patient-years) treated with voclosporin 23.7 mg twice daily, 27 patients (48.7 per 100 patient-years) treated with voclosporin 39.5 mg twice daily, and 25 patients (11.3 per 100 patient-years) treated with placebo.[2]Some other side effects are hyperkalemia, hypertension, QT prolongation and gastrointestinal adverse reactions such as diarrhea and abdominal pain. More severe side effects include increased risk of developing malignancies for patients taking voclosporin. In clinical trials malignancies were reported in 4 patients (1.7 per 100 patient-years) treated with voclosporin 23.7 mg twice daily; there were no reported malignancies in patients treated with voclosporin 39.5 mg twice daily or in patients treated with placebo. The reported malignancies were single occurrences of stage 0 cervical cancer (cervical carcinoma), skin cancer (skin neoplasm), pyoderma gangrenosum, and breast tumor excision. [2]

Study results:

The AURORA study is a global, double-blind, placebo-controlled (RCT) Phase 3 trial which enrolled 357 patients with active lupus nephritis to evaluate the efficacy and safety of voclosporin vs placebo in combination with using MMF, 2g/day, and rapidly tapered oral steroids. The AURORA demonstrates that voclosporin statistical superiority over standard of care in lupus nephritis. The study's primary point was renal response (RR) at 52 weeks, the AURORA met primary endpoint of RR rates of 40.8% for voclosporin vs. 22.5% for the control group (OR 2.65, 95% CI; $p < 0.001$) [3]. Additionally, all secondary endpoints achieved statistically significance in favor of voclosporin, which included renal response at 24 weeks.

Partial renal response at week 24 and 52, time to achieve UPCR (Urine protein/creatinine ratio) ≤ 0.5, and time to 50% reduction in UPCR.

As a result, voclosporin was well tolerated with no unexpected safety issues. Side effects were reported in 20.8% of voclosporin patients vs. 21.3% in the control group. [3] Overall mortality in the study was low with six deaths observed and voclosporin showed no significant decrease at week 52 in eGFR or increase in blood pressure, lipids profile or glucose level. These results indicate that the addition of voclosporin to standard care by MMF and low dose steroids in active lupus nephritis patents results in a statistically superior and faster renal response rates compared to standard of care for lupus nephritis patients. The study was a multi-ethic global cohort study, which truly showed the benefits of voclopsorin, but there still is a need for more studies due to the percentage of African Americans and Hispanic patients. This study analyzed a total of 14 African American patients and 35 Hispanic patients which only represents 18.5% of the total patients in the study (N=265).

Conclusion:

Overall, based on the studies provided, voclosporin seems like a feasible medication to utilize in combination with mycophenolate mofetil and corticosteroids. In the randomized controlled trials, it showed superiority over mycophenolate mofetil and corticosteroids alone in terms of a faster renal response. voclosporin provides an additional therapeutic option in the treatment of lupus nephritis. However, more studies are needed in the future to determine the relationship between races and efficacy or side effect profiles.

– Alan Cheung, PharmD Candidate, UBSPPS Class of 2022
– Qing Liu, PharmD Candidate, UBSPPS Class of 2022

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Drug Indication Expansion: Entresto (sacubitril/valsartan), Approved for HFpEF

What is it:

The U.S. Food and Drug Administration approved Entresto (sacubitril/valsartan) in July 2015, for the treatment of heart failure with reduced ejection fraction (HFrEF). Approved for use in individuals with HFrEF NYHA class II, III, or IV, sacubitril/valsartan has been shown to reduce morbidity and mortality associated with heart failure (HF).[3] In February 2021, sacubitril/valsartan was granted FDA approval for

the treatment in patients with heart failure with preserved ejection fraction (HFpEF). With no currently approved therapies for HFpEF, sacubitril/valsartan became the first treatment for the condition and the only medication indicated for both HFpEF andHFrEF.[1]

What does it treat:

HF affects approximately 26 million people around the world diagnosed with HF. Of the 26 million people diagnosed, around half have HFrEF and the others diagnosed with HFpEF.[6] HF is a chronic condition caused by cardiac remodeling in which the cardiac output (CO), the amount of blood the heart pumps into circulation, is decreased. In HFrEF, also known as known as systolic HF, the heart muscles are weakened and cannot efficiently pump out the same volume of blood that it would in a healthy heart. This results in a reduced left ventricular ejection fraction (LVEF).[6] HFpEF, also known as diastolic heart failure, occurs when the left ventricular walls hypertrophy, reducing the volume of blood that can enter in to the space during the diastolic phase. Because there is less volume of blood in the heart for it to pump, the reduced CO results in a preserved LVEF.[6] Previously, there have been no FDA approved treatments that showed a mortality or morbidity benefit for HFpEF. Due to the lack of available treatments for this population, HFpEF is associated with high rates of HF exacerbations requiring recurrent hospitalizations and worsen long-term prognosis.[5]

Current first line therapies for patients with HFrEF include a beta blocker and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARBs). These medications have shown to decrease morbidity and mortality in individuals with HF.[7] Other treatments for HF include diuretics. Although no data have shown that they reduce mortality or hospital readmission, diuretics are the only agents that can adequately control the fluid retention associated with HF exacerbations.[7]

Mechanism of Action:

Sacubitril/valsartan is the first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that works to prevent the progression of HF. A large component of the pathophysiology of HF responsible for some of the cardiac remodeling involved in the renin-angiotensin-aldosterone system (RAAS). RAAS activation leads to vasoconstriction, hypertension, increased aldosterone levels, increased sympathetic tone, and eventually, cardiac remodeling, all of which are detrimental to the progression of the disease. Current mainstays of therapy including ACE inhibitors and ARBs block these maladaptive elements caused by RAAS, by blocking the conversion angiotensin I to angiotensin II, as is with ACE inhibitors, or blocking angiotensin II receptor type 1 (AT1 receptor), as is with ARBs. [9] Sacubitril/valsartan contains two active components, sacubitril, a neprilysin inhibitor and valsartan, an ARB. Neprilysin is an enzyme that breaks down proteins such as natriuretic peptides, bradykinin, and substance P into their inactive metabolites. Inhibition of neprilysin increases the levels of these substances that promote vasodilation, natriuresis, abnormal growth, and remodeling[7]. Valsartan inhibits the effects of angiotensin II by blocking the AT1 receptor and inhibiting the release of angiotensin II-dependent aldosterone[3]. Since neprilysin is also responsible for breaking down angiotensin II, inhibition of neprilysin requires the addition of an ARB to

combat the accumulation of angiotensin II. For this reason, a neprilysin inhibitor cannot be used alone; it must always be combined with an ARB to block the effect of the excess angiotensin II.[9]

Dosing:

Sacubitril/valsartan film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg and 97/103 mg (sacubitril/valsartan). In adult patients, the target maintenance dose of sacubitril/valsartan is 97/103 mg twice daily as tolerated by the patient.[5] Sacubitril/valsartan is contraindicated in patients with a history of angioedema related to previous ACE inhibition or ARB therapy. Severe drug interactions include concomitant use of sacubitril/valsartan with another RAAS inhibitor including, ACE inhibitors, ARBs, and direct renin inhibitors, as this raises the risk for life threatening adverse reactions such as angioedema.[2] If switching between an ACE inhibitor and sacubitril/valsartan, a patient must undergo a 36-hour washout period to reduce the risk of angioedema. For individuals with an estimated glomerular filtration rate (eGFR) less than 30 or moderate hepatic impairment (Child-Pugh class B) the lowest dose of sacubitril/valsartan is recommended. Sacubitril/valsartan is not recommended for those with severe hepatic impairment (Child-Pugh class C) [9]

Adverse events:

The most common side effects include low blood pressure, hyperkalemia, cough, dizziness, and kidney dysfunction. Other, more serious side effects include angioedema which can present as swelling of the face, lips, tongue and throat that may cause trouble breathing. If symptoms of angioedema or trouble breathing occur, get emergency medical help right away and discontinue the medication.[2]**.** Use of sacubitril/valsartan in combination with an ACE inhibitor or ARB raises the risk of these adverse effects. Sacubitril/valsartan can cause severe harm or death to the developing fetus when administered during pregnancy and should be discontinued as soon as pregnancy is detected.[7]

Studies Involved in Approval:

The largest clinical trial in HFpEF patients was the PARAGON-HF. The double-blind, randomized, active-controlled parallel-group, phase three, two-arm trial compared sacubitril/valsartan's long-term effectiveness and safety to valsartan in 4,822 HFpEF patients. After a median follow-up of 35 months, the primary endpoint of cardiovascular death and cardiac failure was reduced by 13% in the sacubitril/valsartan group compared to the valsartan group (relative risk (RR): 0.87, 95 % IC: 0.753-1.005, p = 0.058), which missed statistical significance. Despite this, Novartis decided to move forward with the indication expansion due to the other benefits displayed in the trial.[5]The secondary outcomes showed that patients on sacubitril/valsartan reported a reduced decline in quality of life compared to the valsartan group. Hospitalizations for heart failure were also reduced (RR 0.85, 95 % CI: 0.72-1.00), especially in women diagnosed with HFpEF. While a treatment-by-sex interaction was not seen in other HFpEF trials, these studies did show that women derived a benefit to a higher LVEF than men.[3,4,5]
Even though this study did not meet the primary end point, this trial shows benefit of sacubitril/valsartan with improved quality of life and reduced hospitalizations in a population that otherwise does not have many treatment options.

– Samantha Mei, PharmD Candidate, UBSPPS Class of 2023
– Melissa Stein, PharmD Candidate, UBSPPS Class of 2023

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New Drug Review: Verquvo (vericiguat), Indicated for patients with HfrEF to reduce mortality and hospitalizations

What is it:

Verquvo (vericiguat) is used in patients with chronic heart failure with reduced ejection fraction (HFrEF) to reduce mortality and hospitalizations.[1] It is used in those who have had a recent hospitalization for heart failure or for symptomatic patients who needed to receive intravenous diuretics as an outpatient[2].

What does it treat:

Heart failure with reduced ejection fraction affects almost 11.5 million people worldwide.[4] HFrEF occurs when there is dilated cardiomyopathy in the left ventricle, causing a reduced ejection fraction, typically of less than 50%**.** Most HFrEF is caused by a myocardial infarction and this can lead to cardiac remodeling. Heart failure has multiple mechanisms causing disease because of the decrease in cardiac output.

Patients often present during acute attacks with signs or symptoms indicating there is congestion and/or hypoperfusion to their organs. Signs or symptoms of congestion include shortness of breath, weight gain, jugular vein distention, and orthopnea. Hypoperfusion signs and symptoms often include fatigue, altered mental status, and the patient feeling cold. Mainstays of guideline-based therapy for HFrEF include beta-blockers, ACE-inhibitors/ARBs/ARNIs, and an aldosterone antagonist. Recently SGLT-2

inhibitors have also been approved for heart failure, showing a reduction in first heart failure hospitalizations and cardiovascular death in the DAPA-HF and EMPEROR-Reduced trials.

Mechanism of action:

Vericiguat is a novel oral soluble guanylate cyclase stimulator that enhances the cyclic guanosine monophosphate (cGMP) pathway at a binding site independent of nitric oxide and sensitizes soluble guanylate cyclase to endogenous nitric oxide via stabilized binding of nitric oxide to its binding site. Overall, increased cGMP levels will cause smooth muscle relaxation and vasodilation.[3]

Dose:

It is recommended to start patients on 2.5mg vericiguat orally, once daily with food and double the dose approximately every 2 weeks until a maintenance dose of 10mg once daily is reached, as tolerated by the patient. If patients are unable to swallow the whole tablets, they may be crushed and mixed with water immediately before administration.[2] Dosage modifications are not necessary in renal impairment (eGFR ≥15 mL/min/1.73m^2 and not on dialysis). An eGFR <15 mL/min/1.73m^2 or on dialysis has not been studied. Hepatic impairment with a Child-Pugh score of A or B does not require a dosage adjustment. Hepatic impairment under Child-Pugh C has not been studied.[1]

Adverse events:

Adverse events were studied from the VICTORIA trial and more than 10% of patients experienced hypotension; 1-10% experienced anemia. Vericiguat is contraindicated in patients taking other soluble guanylate cyclase stimulators or phosphodiesterase type 5 (PDE-5) inhibitors. Pregnancy is also a contraindication due to possible fetal harm and is indicated with a black box warning.[2]

Studies involved in approval:

There were two trials conducted for vericiguat, VICTORIA for reduced ejection fraction and VITALITY for preserved ejection fraction. The VITALITY trial did not meet its primary outcome and showed that vericiguat did not improve the KCCQ score at 24 weeks in patients with heart failure with preserved ejection fraction (HFpEF).[5] The Phase III clinical trial used for drug approval for HFrEF was the VICTORIA trial, sponsored by Merck and Bayer, which assessed the efficacy and safety of vericiguat.[6] This was a multinational, randomized, double-blind, placebo-controlled trial that enrolled a total of 5,050 patients. Patients were randomly assigned in a 1:1 ratio to receive 2.5mg of vericiguat or placebo. Doses were increased to 5mg, then to the target dose of 10mg daily based on evaluation of blood pressure and clinical symptoms at follow-ups conducted at weeks 2, 4 and then every 4 months until the end of the trial. Patients were followed for an average of 10.8 months.

Inclusion criteria included patients at least 18 years old with chronic heart failure (NYHA class II, III, or IV), reduced ejection fraction of less than 45% within 12 months before randomization, and an elevated natriuretic peptide level within 30 days before randomization.[6] Patients also had to have evidence of worsening heart failure and they were categorized into three cohorts based on hospitalization within 3 months of randomization or within 3-6 months, or patients receiving IV diuretic therapy without hospitalization within the previous 3 months. Exclusion criteria included a systolic blood pressures < 100mmHg; concurrent or anticipated use of long-acting nitrates, soluble guanylate cyclase stimulators

or PDE-5 inhibitors; and use of IV inotropes or implantable left ventricular assist devices. The primary outcome was a composite of death from cardiovascular causes of first hospitalization for heart failure.

Hazard ratios (HR) were obtained using Cox regression models to determine the primary outcome.[6]Death from cardiovascular causes or first hospitalization for heart failure occurred in 897 patients (35.5%) in the vericiguat group and in 972 patients (38.5%) in the placebo group (HR, 0.90; 95% confidence interval (CI), 0.82 to 0.98; p= 0.02). Breaking those into two separate analysis, death from cardiovascular causes occurred in 414 patients (16.4%) in the vericiguat group and in 441 patients (17.5%) in the placebo group (HR, 0.93; 95% CI, 0.81 to 1.06) Hospitalization for heart failure occurred in a total of 691 patients (27.4%) in the vericiguat group and in 747 patients (29.6%) in the placebo group (HR, 0.90; 95% CI, 0.81 to 1.00). Overall, this led to an absolute event-rate reduction of 4.2 events per 100 patient-years. Based on this, the number needed to treat is 24 patients.

Overall, this study found that patients with worsening chronic heart failure benefited from vericiguat, as it decreased the incidence of death from cardiovascular causes or first hospitalizations for heart failure, compared to placebo.

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– Emily Diep, PharmD Candidate, UBSPPS Class of 2024

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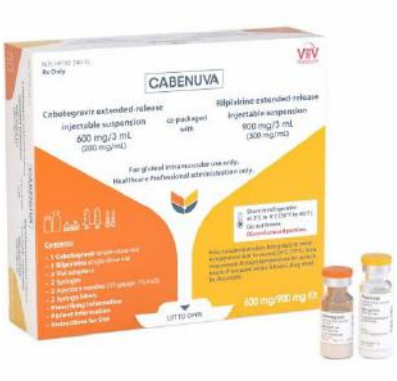
New FDA Approval: Cabenuva® (cabotegravir and rilpivirine) Oral Therapy for HIV

What is it:

Cabenuva is the first FDA-approved injectable that is administered once a month. Consisting of cabotegravir and rilpivirine, Cabenuva is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace a current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either



cabotegravir or rilpivirine.[1] The regimen was developed by ViiV Healthcare and Janssen Pharmaceuticals, and was officially FDA-approved in January 2021.[2]

What does it treat:

Human immunodeficiency virus (HIV) is a condition that affects approximately 1.2 million people in the United States and 38 million people worldwide.[3] HIV is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases.[4,5] It can be spread through various modes of transmission, including contact with certain bodily fluids of a person infected with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV). HIV can also be spread through sharing injection drug equipment such as needles.[5,6]

If HIV goes untreated, it can lead to AIDS (acquired immunodeficiency syndrome). HIV was first identified in 1981, and is the cause of one of humanity's deadliest and most persistent epidemics.[4] There is currently no effective cure for HIV, but with effective medical care, it can be controlled.

Combination antiretroviral therapy for HIV-1 infection provides durable viral suppression, which is associated with improved immunologic function and extended survival.[7] Current guideline-recommended first-line regimens require lifelong daily oral therapy that can be burdensome, potentially affecting adherence and risking treatment failure. Simplified regimens for the treatment of HIV-1 infection may increase patient satisfaction and facilitate adherence.

Mechanism of Action:

Cabotegravir is an integrase strand transfer inhibitor (INSTI) and rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI). INSTIs inhibit the integrase of HIV by binding to the active site which stops the retroviral DNA integration in the essential strand transfer step of the HIV replication cycle.[8] Diarylpyrimidine NNRTIs of HIV-1 block replication using non-competitive inhibition of HIV-1 reverse transcriptase and do not inhibit the human cellular DNA polymerases α, β, and γ.[8] Both of these mechanisms block the replication of the virus and decrease the viral load to be undetectable in the patient.

Dosing and Storage:

Cabotegravir/rilpivirine is injected intramuscularly after at least a 28 day oral lead-in consisting of 30 mg Cabotegravir and 25 mg Rilpivirine.[9] The oral lead-in prior to starting treatment with cabotegravir/rilpivirine is to ensure the medications are well-tolerated before switching to the extended-release injectable formulation.[2] The initial injection is administered on the last day of the oral lead in as a 600 mg LA Cabotegravir injection and 900 mg LA rilpivirine injection at opposite gluteal sites, or at least 2 cm apart.[9] Beginning one month after initiation injections, patients will start a continuous monthly administration of 400 mg LA Cabotegravir injection and 600 mg LA rilpivirine injection with the same administration instructions. Cabotegravir/rilpivirine has a 7-day window before or after target date when the drug can still be administered.[9] If the patient is to unintentionally miss the dose after the 7-day grace period and it has been ≤ 2 months since last injection, the patient should continue normal injections. If it has been >2 months, the patient should reinitiate the initial injection dosing of 600mg/900mg, then continue with normal monthly injections of the 400mg/600mg dosing.[9] There are no dose adjustments

suggested by the manufacturer for patients with CrCl <30 mL/min and patients with severe hepatic impairment because this population has not been studied.[9] Cabotegravir/rilpivirine should be stored in 2°C to 8°C (36°F to 46°F) in original packaging and be brought to room temperature before administration for up to 6 hours. After 6 hours the vials should be discarded. Upon drawing up the doses into syringes, suspension can remain there for 2 hours, and if not used must be discarded.[10]

Adverse Effects:

The most common adverse reaction is at the injection site, reported by 83% of patients with the vast majority being mild to moderate in severity.[11] Other reactions include pyrexia reported in 8% of patients, and fatigue, headache, musculoskeletal pain and nausea reported in ≤5% of patients.[11]The incidence of injection site reactions decreased over time, as reported by patients. Hypersensitivity reactions, including DRESS, have been reported during the phase 4 study and with other integrase inhibitors and could occur. Cabotegravir/rilpivirine should not be used in patients that have a previously recorded hypersensitivity reaction to Cabotegravir or Rilpivirine.[11]

Studies involved in approval:

The approval of cabotegravir/rilpivirine is based on the phase III ATLAS (Antiretroviral Therapy as Long-Acting Suppression) and FLAIR (First Long-Acting Injectable Regimen) studies that included over 1,100 patients from 16 countries. In focusing on the ATLAS trial, it demonstrated noninferiority of the long-acting injectable regimen as compared to daily oral regimens in patients infected with HIV-1.[7] Sponsored by ViiV Healthcare and Janssen Pharmaceuticals (the manufacturers of cabotegravir and rilpivirine; respectively), the study examined whether or not the long-acting injectable regimen of cabotegravir and rilpivirine was noninferior as compared to daily oral regimens in patients infected with HIV-1. The study enrolled HIV-1-infected patients who were 18 years of age or older and had been receiving antiretroviral drugs in an uninterrupted regimen without virologic failure and without a change in medication for at least 6 months before screening.[7]

It was a randomized, open-label, parallel-group, multicenter, noninferiority trial with a total of 616 participants. Patients were randomized in a 1:1 ratio to receive either the long-acting regimen of cabotegravir and rilpivirine (4 week daily oral lead-in cabotegravir 30mg and rilpivirine 25 mg, then at week 4 participants received initial doses of 600 mg of cabotegravir and 900 mg of rilpivirine, followed by injections of 400mg of cabotegravir and 600mg of rilpivirine every 4 weeks), or to continue the daily oral regimen.[7]

Inclusion criteria were: 18 years of age or older; uninterrupted antiretroviral regimen without virologic failure and without a change in medication for at least 6 months before screening; and plasma HIV-1 RNA level of less than 50 copies per milliliter had to have been documented at screening and within 6 and 12 months before screening.[7] Exclusion criteria included the following: evidence of active hepatitis B virus infection, previous virologic failure, INSTI or NNRTI resistance mutations (except K103N mutation); and interruption of the current antiretroviral regimen within 6 months before screening or any interruption exceeding 1 month in duration.[7] The primary endpoint was the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48. The key secondary endpoint was the percentage of participants with plasma HIV-1 RNA levels of less than 50 copies per milliliter at

week 48. Safety outcomes included confirmed virologic failure; graded adverse events; and plasma concentrations of cabotegravir and rilpivirine.[7]

An intention-to-treat exposed population analysis was performed. HIV-1 RNA levels of 50 copies per milliliter or higher at week 48 were found in 5 participants (1.6%) in the long-acting therapy group, and 3 (1.0%) in the oral-therapy group (adjusted difference, 0.6 percentage points; 95% confidence interval [CI], -1.2 to 2.5). These results met the noninferiority criterion for the primary endpoint. Similarly, the long-acting therapy was noninferior to oral therapy with respect to the key secondary endpoint of an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (92.5% and 95.5%, respectively; adjusted difference, -3.0 percentage points; 95% CI, -6.7 to 0.7). Three participants in the long-acting therapy group had confirmed virologic failure, and rilpivirine resistance-associated reverse-transcriptase mutations were detected in HIV-1 RNA samples from all three of these participants. Also of note, plasma concentrations of cabotegravir and rilpivirine at the time of failure in all three were in the lower quartiles of the ranges of observed concentrations. Four participants in the oral-therapy group had confirmed virologic failure, and reverse transcriptase mutations were found in three of these participants. In this trial, 250 participants (81%) in the long-acting therapy group reported an injection-site reaction, and 11 participants (4%) in the long-acting therapy group experienced headache, pyrexia, and fatigue related to the trial regimen.

Overall, the study found that the monthly injectable long-acting regimen was noninferior to standard once daily oral therapy for maintaining HIV-1 suppression. Injection-site reactions were common but generally were of mild or moderate severity and transient, and participant satisfaction was higher with the injectable regimen.

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– Drake Meaney, PharmD Candidate, UBSPPS Class of 2022

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Guest Column: COVID-19 and Telemedicine

COVID-19 and Telemedicine: How Can Pharmacists Help?

With the onset of the COVID-19 pandemic, utilization of telemedicine services has greatly increased. Pharmacist involvement in telemedicine is not new, especially in the clinics at Upstate University Hospital. Here, the ambulatory care pharmacy team supports the Adult Medicine, Rheumatology, Pulmonology, Inclusive Health Services, Endocrinology, and Neurology clinics. In Adult Medicine, pharmacists participate in Collaborative Drug Therapy Management (CDTM) for anticoagulation, diabetes management, and atherosclerotic cardiovascular disease risk reduction. Most of our patient follow-up occurs over the phone, so when the clinics went remote in Spring 2020 a lot of our workflow stayed the same. That being said, increased use of telemedicine has identified additional ways that pharmacists can serve patients.

A (Brief) History of Telemedicine:

The concept of telemedicine has been around for much longer than most people realize. One of the earliest examples is from the Civil War, where telegraphs were used to order medical supplies and provide medical consultations.[1] This may seem strange, but it's important to remember that telemedicine is defined as "the exchange of medical information from one site to another through electronic communication to improve a patient's health".[2] This includes phone calls, video chats and yes, even telegraphs. In the 1920s, radios helped provide medical advice to clinics on ships and in the 1960s closed-circuit television was used to link Nebraska Psychiatric Institute to Norfolk State Hospital for consultation services. The National Aeronautics and Space Administration's Space Technology Applied to Rural Papago Advanced Health Care (STARPAHC) project in the 1970s connected rural patients with Indian Health Services hospitals in Arizona through technology previously only used by astronauts. The American Telemedicine Association was created in 1993, the same year that the Centers for Medicare and Medicaid Services (CMS) began paying for telehealth in underserved rural areas. Under the Obama administration the Health Information Technology for Economic and Clinical Health Act was passed in 2009, which promoted the expansion and adoption of health information technologies, among other things. Through these events, and others, telemedicine evolved into what we know it to be today.

COVID-19's Impact on Telemedicine:

As of March 6th 2020, CMS changed the requirements for telehealth billing, expanding access to these services to keep patients connected with healthcare while also limiting the spread of COVID-19.[3] Three virtual services can be offered and billed for: telehealth visits, virtual check-ins, and e-visits. In New York, Medicaid adopted a similar approach, expanding coverage for telehealth in their fee-for-service and managed care plans.[4] The Office for Civil Rights furthered these efforts by relaxing Health Insurance Portability and Accountability Act enforcement for various communication technologies including (but not limited to) Skype, Whatsapp, iMessage, FaceTime, and Zoom.[5]

Expanding the Pharmacist's Role in Telemedicine:

Although CMS has changed billing requirements for telemedicine, pharmacist compensation for these services, and others, is an ongoing challenge. This is especially true in New York, where pharmacists do not have provider status. Compensation aside, here are some ways that the ambulatory care pharmacists at Upstate have augmented existing telemedicine services:

Refill assessment:

Any patient that has pharmacist involvement, through CDTM or consult, is assessed to ensure they have adequate refills of chronic medications. If needed, pharmacists can refill prescriptions for 90 day supplies with at least one refill. This limits the number of times a patient needs to leave their home and also ensures that they have continued access to medications for their chronic diseases.

Vaccine Screening:

Starting in the Fall of 2020, pharmacists screened patients for the influenza vaccine during phone follow ups. Those who had not already received it were encouraged to do so and educated on the importance of being vaccinated. Pharmacists also booked appointments for patients to come to the clinic and get a flu shot if they expressed interest. This was helpful for our Medicaid patients, who were able to use their covered medical transportation for this visit.
With the increased availability of the COVID-19 vaccine, we are now screening patients again. Many of our patients have chronic conditions which meet New York's vaccine eligibility requirements. For those who meet eligibility criteria, our clinic provides letters to patients documenting their qualifying condition. Patients are able to use these letters to help them sign up for a vaccine.

COVID-19 Support:

Pharmacists help patients get access to COVID-19 testing and identify those who may benefit from outpatient monoclonal antibody therapy. For patients with diabetes and COVID-19, we created a reference document on "sick day rules" that other pharmacists and providers can use for education during remote follow ups. These patients also have more frequent pharmacist follow up, as many experience hyperglycemia secondary to the dexamethasone component of their COVID-19 treatment and may require acute adjustments in their diabetes regimens.

While this is not an exhaustive list, it highlights ways that pharmacists in outpatient clinics can enhance the services they already offer. These actions were easy to assimilate into established workflows and they play an important part in providing comprehensive care. As the role of telemedicine continues to evolve, pharmacists can and should look for ways to further contribute to patient care in this setting.

– Ashley N. Shtoyko, PharmD, BCPS, PGY2 Ambulatory Care Pharmacy Resident

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ACCP interview with Calvin Meaney, PharmD, BCPS, FAPhA, Clinical Associate Professor of Pharmacy Practice; University at Buffalo; School of Pharmacy and Pharmaceutical Sciences

Bio:

Dr. Meaney is a clinical associate professor at the University at Buffalo with expertise in the field of nephrology. He has received various teaching awards throughout his career at UB and also received a New Investigator Award from the American Association of Colleges of Pharmacy. He is a clinical pharmacist at Erie County Medical Center, where he precepts students and residents, and serves on the Nephrology Consultation Service and the Internal Medicine acute care medical teams. Along with teaching and engaging students inside the classroom, Dr. Meaney serves as a mentor for pharmacy students through UB's Clinical Research program for which he serves as a co-chair. He was recently appointed Vice-Chair for Research in the Department of Pharmacy Practice at UB and is the current President-elect of the NYS-ACCP chapter.

Interview:

1. As you're the current NYS-ACCP president-elect, can you speak to the steps you took both personally and professionally to lead you to this point? How do you see this affecting your career as a clinical pharmacist in the short and long term?

Dr. Calvin Meaney, PharmD, BCPS

I have been actively involved in the NYS ACCP organization since starting as a faculty member at UB SPPS. Early on I was fortunate to be a member of the annual meeting planning committee and have worked with a number of the President-Elects (who chair that committee) over the past 5 years. Seeing the progress the organization has made over that time has been remarkable and motivated me to pursue the position of President-Elect. It is a great opportunity to help shape the future of clinical pharmacy in NYS and make lasting connections with colleagues.

2. Having received various honors and awards throughout your career, what would you say is your most significant accomplishment??

My biggest accomplishments are when my students achieve their goals, whether that be a desired residency, fellowship, or pharmacist position.

3. What challenges do you anticipate the field of clinical pharmacy facing in the future and what advice would you give to future pharmacists?

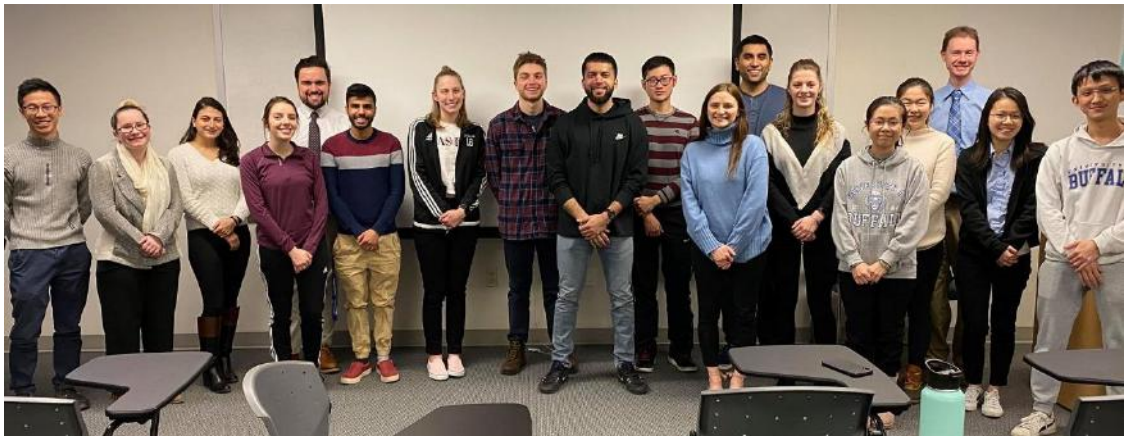
In my opinion, the biggest challenge in clinical pharmacy remains to be value demonstration and systematic clinical pharmacist integration into the healthcare systems. Clinical pharmacists can reduce healthcare costs, improve patient outcomes, and increase provider and patient satisfaction. However, this is not consistently demonstrated across patient care areas and in specialty populations. Pharmacists

need to continue to demonstrate their value in these four domains and publish quantitative results of their interventions/programs to justify further integration. Advice for future pharmacists: get involved in initiatives like Get The Medications Right (GTMRx https://gtmr.org/) and Coalition for the Advancement of Pharmacy practice (CAP https://pharmacistcoalition.com/). These are federal and state level groups that are advocating for advancing the role of clinical pharmacists.

4. **As Co-director for the clinical research program here at UB, you often mentor students, how has mentoring affected your career and what advice do you have for students interested in research*?***

Mentoring is a great opportunity to learn from students and provide wisdom in the research process that has been gained through my experiences. I find that the best mentor-mentee relationships occur when we both learn from each other. Students interested in research should think about possible research mentors (faculty, practicing pharmacists) and investigate that person's research activity. Then ask to meet to discuss opportunities for research and present information you learned when reading their papers or watching their presentations and how that made you want to work with them. This sets the stage for a great relationship and ensures the student is interested in the work being performed.

– Melissa Stein, PharmD Candidate, UBSPPS Class of 2023



Spring 2020 In-person General Body Meeting

University at Buffalo
School of Pharmacy and Pharmaceutical Sciences

Questions or Contributions?
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