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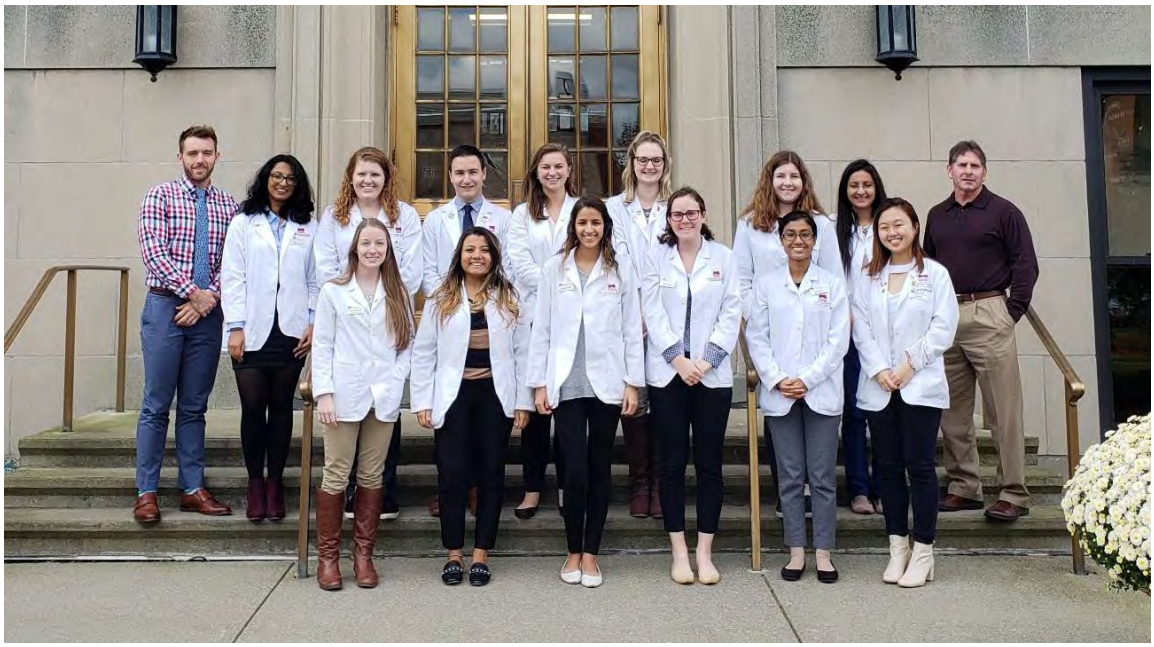
NYS-ACCP Insider

Albany College of Pharmacy and Health Sciences

Special points of Interest:

ACPHS-ACCP Student Chapter Update



Since our SCCP chapter at Albany College of Pharmacy and Health Sciences (ACPHS) was founded our goal has been to uphold the standards and ideals of the ACCP national chapter, while offering students opportunities to be involved on campus throughout their schooling. We aim to offer opportunities where students can grow as professionals and future pharmacists, along with offering networking for students that have an interest in pursuing a career in clinical pharmacy. With the help of our three faculty advisors, Dr. Kate Cabral, Dr. Michael Kane, and Dr. Matthew Stryker our organization has been able to provide great networking, professional development, and clinical experience opportunities to our members. We are continuing to evolve and offer new opportunities for students to get involved on campus and in our community. At the beginning of September our chapter hosted a Professional Runway Show in collaboration with our school's American Society of Health System Pharmacists (ASHP) student chapter. At this event we had student participants show off their best professional attire while strutting down the runway before appearing in front of pharmacy mentors who asked them ethical questions. Questions ranged from owning an independent pharmacy and deciding on whether to ban the sale of tobacco products in your store, to male patients refusing to receive help from any of the females working in the pharmacy.

Our Script Your Future project continues to emphasize medication in a variety of settings, including in an English as a Second Language (ESL) class. This year they will be going to a resource center for patients with HIV/ AIDS and offer tips about remembering to take their medications. Educating these patients on how to remember to take their completed medication regimens is extremely useful.

This year our organization will be participating in a Buddy Program along with numerous professional organizations at our college. The idea of the Buddy program is for undergrad and P1 students, to be able to have an upper-classman as a mentor that can help them as a member of the organization. Our APhA student chapter hosted a "Meet the Professional Organizations Night," where students had the opportunity to come and talk with student leaders from different organizations to see which one, they were most interested in. Once paired with their "buddy" the undergrads will have someone to go to meetings and events with and to ask questions about how to get involved with our organization. This is a great opportunity to get undergrads more involved and excited about our organization before they enter into the professional program.

All of our patient care projects are hard at work planning and organizing events for this year. At SCCP-ACPHS we strive to educate students on the growing world of clinical pharmacy, as well as expose them to different areas of clinical pharmacy before setting up rotations and then ultimately graduating and pursuing their careers. We have a great following of active students that are eager to get involved and participate in all of our events. With the growing interest and new event ideas, we cannot wait to see what our organization will do in the future!

Abigail Healey, BSPS 2018, PharmD Candidate ACPHS Class of 2021

The ASCEND Trial: Would Daily Aspirin use be More Harmful or Beneficial in Diabetes?

By Mariam Gawdat, PharmD Candidate, ACPHS Class of 2019

It is well established that aspirin is highly effective in the secondary prevention of cardiovascular events, however aspirin for primary prevention in the contemporary era is uncertain.[1] Older studies suggest that aspirin may offer a small to moderate cardiovascular benefit in primary prevention, however this was at a time when smoking and suboptimal control of blood pressure and dyslipidemia were more common.[1]

The current USPSTF guidelines recommend initiating a low-dose aspirin for primary prevention of cardiovascular disease (CVD) and colorectal cancers in patients aged 50 to 59 years, who have a 10-year CVD risk score of at least 10% and are not at an increased risk for bleeding. The decision is more individualized for patients aged 60-69, and there is insufficient evidence for ages less than 50 or greater than 70.[7] Over the last few months, there have been several trials published looking at the contemporary use of aspirin for primary prevention. The ASCEND trial was the most recent trial published and studied diabetic patients.[1, 2, 3, 4, 5, 6]

Patients with diabetes have at least double the risk of vascular events than patients without diabetes.[2] The 2016 Circulation guidelines do not recommend aspirin initiation for the sole presence of diabetes, since aspirin offers only a modest benefit in CVD primary prevention, with an increased intracranial and gastrointestinal bleeding.[8] The 2018 ADA guidelines suggest that low dose aspirin may be considered for primary prevention in in men and women, aged at least 50 years, with type 1 or type 2 diabetes and with at least one additional major risk factor (e.g., family history of premature ASCVD, hypertension, dyslipidemia,

smoking, or chronic kidney disease), and who are not at an increased risk of bleeding (e.g., older age, anemia, renal disease).[9] Additionally, ADA guidelines suggest that calculating the 10-year ASCVD risk score for patient with diabetes is unnecessary as diabetes itself confers an increased ASCVD.[9]

The ASCEND trial was conducted to analyze the efficacy and safety of 100 mg enteric coated aspirin compared to placebo in patients with diabetes. A total of 15,480 participants were randomized to one of four groups: active aspirin with either active or placebo omega-3 fatty acid, or placebo aspirin with either active or placebo omega-3 fatty acid. Patients were included if they were at least 40 years old, have diabetes (type 1 or 2), and no known cardiovascular disease. The exclusion criteria were: clear indication for aspirin, aspirin contraindication, or other clinically significant condition that might affect adherence to trial. During a run-in phase of 8 to 10 weeks, participants received placebo aspirin and placebo omega-3. After randomization, every 6 months, participants received the appropriate tablets and follow-up questionnaires regarding side effects, adherence, use of antiplatelet or anticoagulant therapy, and symptomatic bleeding. After 2.5 years, blood samples, urine samples, blood pressure and weight were collected. The trial duration was 7.4 years.[2]

Primary efficacy endpoints included: nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or death from any vascular cause. Primary safety endpoints were major bleeding events, including intracranial hemorrhage, gastrointestinal or eye bleeding, or any other bleeding that resulted in hospitalization. Secondary endpoints included development of gastrointestinal cancer or revascularization procedure. Exploratory analyses were performed by extrapolating the rate ratios in the intention-to-treat analysis to full adherence, assuming similar proportional effects on the incidence of serious vascular events and bleeding.[2]

All baseline characteristics were similar among the groups, with about 75% of participants on statin therapy. Aspirin's benefit in significantly decreasing primary vascular outcomes was shown mainly in the first 5 years. Compared to placebo, aspirin use resulted in 12% lower risk of serious vascular events (658 participants [8.5%] vs. 743 [9.6%]; 95% CI = 0.79 to 0.97; P=0.01), and 29% higher risk of major bleeding events (314 participants [4.1%] vs. 245 [3.2%]; 95% CI = 1.09 to 1.52; P = 0.003). The number needed to treat to avoid a serious vascular event was 91 patients (1.1% absolute reduction). The number needed to treat in order to cause a major bleeding event was 112 patients (0.9% absolute reduction). Exploratory analyses suggested no significant benefit of aspirin in reducing the rate of death form all vascular causes combined, and no attenuated bleeding effect over time. Major bleeding events included, 41.3% gastrointestinal, 32.9% ocular, 17.2% intracranial, and 20.4% bleeding events in other sites. There was no statistical significance in the fatal bleeding, cancer and nonvascular outcomes, compared to placebo. The authors concluded that aspirin's absolute rates of reducing serious vascular events and increasing bleeding risks were similar.[2]

Compared to older trials, more participants in the ASCEND trial were on statin and antihypertensive therapies and were non-smokers, which helps at better assessing aspirin use in a contemporary context. Another strength is that this trial was randomized, double-blinded, had a large sample size of only patients with diabetes and followed them for a long period.

One limitation was that using a 100 mg aspirin in this trial may have increased the rate bleeding without additional benefit, compared to the traditional 81 mg. Additionally, the intent to treat analyses may have underestimated aspirin benefit. The exploratory analyses and patients' questionnaires also carry uncertainty risk due to subjectivity, use of assumptions, and potential bias. Finally, this trial did not offer a comparator group of patients who have no diabetes, but have other CVD risk factors such as older age, race, abnormal lipid levels, high blood pressure, and/or smoking.[7]

In conclusion, it is uncertain whether aspirin's benefit in primary prevention in diabetic patients outweighs its bleeding risks. Specific patient characteristics should be carefully assessed. Alternatively, perhaps a statin would suffice as monotherapy for CVD primary prevention.[1] Statin use in primary prevention showed a 25% decrease major vascular events for every 1mmol/L decrease in LDL-C, without increasing bleeding risk.[1] However, future studies will be needed to further evaluate the necessity of aspirin use for primary prevention in diabetes.

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Clinical Spotlight: Rim Hagdu, PharmD, PGY-2 Nephrology Resident at ACPHS

Interviewed by Merihan Raouf, PharmD Candidate, ACPHS Class of 2020

Tell us about your career as a pharmacist thus far?

I graduated from the 6-year program at St. Louis College of Pharmacy in 2017. I completed my PGY1 residency at Xavier University of Louisiana College of Pharmacy and University Medical Center New Orleans and I am currently a PGY2 Nephrology Pharmacy Resident at Albany College of Pharmacy and Health Sciences. Being a nephrology pharmacy resident is like being an internal medicine pharmacist for patients with kidney dysfunction.

What made you pursue a residency?

I always like to plan five years in advance. As soon as I got into pharmacy school, I started exploring and researching about what I can do with my degree. I got a research job during my first week of school and started attending many residency and fellowship panels. The more I attended, the more I started to be drawn to residency and the kind of career it would provide me. Residency gave me more opportunities to do the things I love such as working side-by-side with other healthcare professionals when making decisions on the floor, talking to patients, and learning new things every single day.

How would you describe what your current typical work day looks like?

I typically arrive to my site at 5-6 am, I work up patients, and discuss cases with the APPE student before rounds. Then, I round with the team and I make my recommendations on pharmacotherapy regimens, as well as provide any clinical education to the team. After rounds, I go with the students to provide discharge education and perform medication reconciliation. In the afternoon, I lead topic discussions with the students and my preceptors and attend meetings. Lastly, I work on my research and other projects. My schedule changes based on my rotation, however, this is what a typical day looks like for me.

Are you involved in any research? If you are, can you briefly tell me about some of your research?

Currently, I am working on four research projects. My main project is a survey-based study assessing blood pressure knowledge and consequences of hypertension among kidney screening program participants at risk for kidney disease. There is literature that shows improved blood pressure control among patients with kidney disease who know their blood pressure goal, however, this study will focus on patients who may or may not have high blood pressure. We will also assess medication adherence and knowledge of normal blood pressure and blood pressure goal in this patient population. Another unique project I am working on is a survey-based study that focuses on tools current or former stay-at-home pharmacist moms utilized for workforce re-entry. We would also like to gain the perspective of pharmacist moms considering becoming stay-at-homes moms and the types of concerns they have prior to making the decision. I decided to pursue this project because, to my knowledge, there is no data out there on pharmacist moms and it is something that I am passionate about.

Have there been any roadblocks in your pharmacy career? And if so, how did you overcome them?

At first, I was interested in specializing in transplant. I applied and interviewed with PGY-2 residencies in transplant but I was not successful in the first match. Through my research, I learned that there was a nephrology residency that I was not aware of when I was going through the first match. After applying and interviewing with the program, I realized this program was perfect for me. The rotations were 50% inpatient and 50% outpatient and it also had an emphasis in academia, research, and public health. This was important to

me because I would like to pursue academia after residency. Even though it might have seemed like a roadblock in the beginning, it actually opened a new door for me and I am really happy with where I am today.

What advice do you have for students in regards to balancing their private life with a vigorously paced career in pharmacy?

Think ahead. Ask yourself, if I am going to be at a job interview 5 years from now and I get asked to explain my involvement in a project, is that something that I am going to be passionate about and will be able to describe my role well? If not, it might be a clue to rethink your decision. Learn to prioritize 2-3 things that you would like to do for each year and pick your projects accordingly. Only say yes to things that will help you reach your goal.

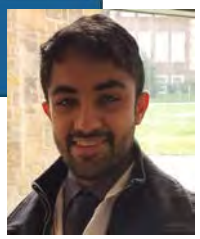
Learn to say no. If you are involved in a project that you are no longer passionate about, move on to something that will diversify your experience and make you a better well-rounded pharmacist.

"I need to do more". Sometimes as a student, you get into the trap of "I need to do more" but you have to look at quality vs. quantity. It is much better to be very involved in 1-2 student organizations and be able to speak for these roles than be involved with 10 different organizations but the substance to your experience is not as robust.

What advice would you give to a student pursuing residency?

Be open-minded to allow yourself the freedom to explore different options so when opportunities present themselves, you will be ready. Take opportunities that take you where you want to be in life. Do your absolute best in your projects so that work can speak for itself and remember to always be true to who you are.

Rescheduling Epidolex and the Clinical Utility of Cannabidiol



By Mit Gandhi, PharmD Candidate, ACPHS Class of 2020

Earlier in June of this year, cannabidiol (Epidiolex) was approved for the treatment of two types of epilepsy, Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS); in addition, on September 27th, it was given a Schedule V designation.[1,2,3] Amid the mainstream media coverage on the legalization of cannabis in several states and neighboring countries, it is important to clarify the potential impact for patients and the regulatory history of cannabinoids in the market.

Approval and Re-scheduling to Schedule V

Historically, cannabis-derived products have been illicit since the institution of the Controlled Substances Act when it was given a Schedule I designation (i.e., no currently accepted medical use within the United States; a lack of accepted safety for use under medical supervision; a high potential for abuse).[4] Prior to the current approval of cannabidiol, cannabinoids had been on the market since 1985 (dronabinol [Marinol] and nabilone [Cesamet]).[4] However, these were produced synthetically, composed of a different cannabinoid (tetrahydrocannabinol, or THC), and have limited use in a clinical setting outside of chemotherapy-induced nausea/vomiting and anorexia in patients with acquired immunodeficiency syndrome (dronabinol only).[4,5,6] The current formulation of cannabidiol is a purified formulation from the cannabis plant itself.[4] Re-scheduling it to Schedule V means evidence supports the medication has limited potential for physical and psychological dependence compared to Schedules I through IV. This re-scheduling only applies to the Epidiolex formulation and continues to render any non-Epidiolex cannabidiol products as Schedule I.[1] GW Pharmaceuticals, the manufacturer of Epidiolex, conducted a study to assess its abuse potential.[7] The single dose, randomized, controlled trial (RCT) assessed recreational polydrug users for the abuse-potential of cannabidiol compared to alprazolam, dronabinol, or placebo. Polydrug users are individuals who have taken multiple drugs together at the same time or sequentially for a specified effect (i.e., taking alcohol and stimulants together for euphoric effects). The primary endpoint, a pharmacodynamic analysis, showed alprazolam and dronabinol having significantly greater Drug-Liking, Overall-Liking, and Take Drug Again visual analog scale E_{max} (maximum effect) values compared to the tested therapeutic doses for cannabidiol ($p \leq 0.004$).[7] The presented evidence

clearly demonstrated cannabidiol carries significantly low abuse potential compared to current medications known for their recreational abuse/misuse.

Lennox-Gastaut Syndrome

LGS is a severe form of epilepsy that frequently begins during childhood and has a high rate of morbidity and mortality. Characterized by multiple types of seizures (i.e., tonic, clonic, or tonic-clonic), it often leads to physical injury and gradually causes intellectual disability. As a chronic disease where 90% of childhood diagnoses continue into adulthood, anti-epileptic drugs (AEDs) are a mainstay in the treatment of LGS.[8] Prior to cannabidiol, there were five medications approved to treat LGS.[9] Valproate, while not indicated for LGS, is a preferred agent due to its broad coverage and efficacy. The figure to the right is the treatment algorithm for patients with LGS.

WPCare3, a double-blind RCT study, assessed the efficacy and safety of cannabidiol at different doses (10 mg per kg or 20 mg per kg, orally) on drop seizures in patients with LGS resistant to multi-AEDs.[10] The primary outcome was percent change from baseline in the frequency of drop seizures (defined as combinations of atonic, tonic, or tonic-clonic seizures). After 14 weeks of treatment, the 20 mg-cannabidiol group demonstrated a 41.9% median reduction in drop seizures from baseline ($p=0.005$). The 10 mg-cannabidiol group yielded a 37.2% median reduction from baseline ($p=0.002$). In comparison, the placebo group showed a 17.2% median reduction. Common dose-related adverse events for the cannabidiol groups together include somnolence (26.2%), decreased appetite (21.5%), and diarrhea (12.8%) compared to 5%, 8%, and 8%, respectively, in the placebo group. In addition, approximately 9% of patients were reported to have elevated serum aminotransferase concentrations (3.2-12.2 times the upper limit of normal) compared to no patients from the placebo group.[10] Monitoring transaminase and bilirubin levels at baseline and monthly after treatment may be recommended.[3] With the addition of this recent evidence and the approval of cannabidiol, clinicians can more confidently treat resistant-LGS with a medication that is relatively safe.

Dravet Syndrome

DS, another complex form of epilepsy during childhood, is associated with medically intractable seizures and is known as one of the most severe forms of status epilepticus.[11] DS is associated with mental disability and behavioral problems, in addition to increased morbidity and mortality. Often, eliminating seizures is not possible and the primary treatment goal is to minimize developmental issues by reducing the frequency and prolongation of seizures. While there were no previous Food and Drug Administration (FDA)-approved medications, valproate and clobazam stand as the preferred first-line medications for prophylaxis based on historical evidence.[11]

A recent double-blind, placebo-controlled RCT assessed the efficacy and safety of adjunctive cannabidiol 20 mg per kg per day compared to placebo in AED-resistant DS.[12] Akin to the GWPCare3 LGS study, the primary outcome was the percent change in frequency of convulsive seizures over a 14-week period compared to a 4-week baseline period. The median percent decrease in seizures was 38.9% for adjunctive cannabidiol treatment versus a 13.3% decrease for placebo (between group difference: 25.6%; $p = 0.01$). However, the safety portion of the study showed cannabidiol as having a significant adverse event profile; patients taking the experimental drug experienced greater rates of fatigue (20%), pyrexia (15%), upper respiratory infections (11%), somnolence (36%) and decreased appetite (28%) compared to placebo (3%, 8%, 8%, 10%, and 5%, respectively).[12] Based on the results from this trial, Epidiolex has become the first approved medication for DS. Further clinical evidence will be needed to support cannabidiol use as monotherapy and monitoring parameters for liver aminotransferases and bilirubin will need to be set. However, clinicians can be confident in utilizing adjunctive cannabidiol in treatment-resistant DS, as evidence shows the benefits outweigh the accompanied adverse event risks.

Discussion

In conclusion, the approval of Epidiolex has extraordinary regulatory implications as it is the first Schedule I drug to gain a Schedule V designation. It signifies that the Drug Enforcement Agency and FDA believe certain plant-derived cannabinoids, if made in a pharmaceutical setting, may have clinical utility with limited potential for abuse. Cannabidiol has the potential to add significant value to clinicians treating LGS and

DS, though monitoring parameters will need to be set for the medication's associated side effects. While other AEDs will continue to remain first-line treatments for LGS and DS, cannabidiol may serve as an important tool in the future for clinicians managing treatment-resistant patients.

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Leaning Toward a Multimodal Approach to Pain Management

By Nardine-Mary Yassa, PharmD Candidate, ACPHS Class of 2020

In response to the nation's current opioid crisis, there have been numerous efforts to decrease the amount of opioids prescribed. It has been shown that utilization of a multimodal pain management regimen is more beneficial to patients as it decreases length of hospital stay and decreases the likelihood for an opioid addiction.[1] A multimodal approach to pain management ideally aims to ease pain by targeting multiple receptors, using a variety of medications that target different pain pathways systemically and locally.[2]

The benefits of prescribing opioids for chronic pain need to be carefully considered in comparison to the potential risks. According to the Centers for Disease Control and Prevention Opioid Data, opioids are associated with increased dose-related risks such as opioid use disorder, overdose and death.[3] Instead of relying on opioids exclusively for pain management, an alternative is a multimodal approach to pain management. A multimodal approach focuses less on opioid use alone, but relies more on the use of other pain management strategies to decrease overall opioid use. According to the American Society of Anesthesiologists, using a multimodal approach to manage pain resulted in decreased opioid use, prescriptions and opioid-related complications in patients undergoing major surgeries.[4] It is imperative to start counseling patients that opioids are not the only pain management option and that there are other therapies available that are not associated with opioid-related complications. It is understandable that opioid use may be warranted, especially directly following surgery. However, there are medications that one can use, in addition to opioids, to decrease dependence on them; alternative therapies may include: acetaminophen, salicylates, non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase-2 (COX-2) inhibitors or ketamine.

In a study evaluating data from 546 hospitals between 2006 and 2016, pain management regimens from 512,393 hip replacements and 1,028,069 knee replacements were analyzed. It was shown that patients undergoing a hip replacement who received multimodal pain management (opioids and one or more pain management modalities [e.g., peripheral nerve block, acetaminophen, COX-2 inhibitors or NSAIDS]) as compared to opioids alone, had 19% less respiratory complications, 26% less gastrointestinal complications and a 12% shorter length of hospital stay.[1] In addition, these patients required 18.5% less opioid prescriptions after surgery.[1]

Patients undergoing total knee replacement who received multimodal pain management as opposed to opioids alone experienced 6% less respiratory complications, 18% less gastrointestinal complications, a 9% shorter length of hospital stay and an 18.5% reduction in post-operative opioid prescriptions.[1] The greatest reduction in opioid-related complications and opioid prescriptions was seen with the use of a multimodal regimen that included NSAIDs and COX-2 inhibitors. More research is required to determine the optimal combination of analgesics for multimodal pain management.

In conclusion, adopting a multimodal pain management approach can decrease length of hospitalization, decrease opioid-related complications and positively impact the national opioid drug crisis. This will likely provide better outcomes for patients, and has a promising prospect in the future of pain management.

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New Drug Update: Braftovi (Encorafenib) and Mekotovi (Binimetinib)

By Dawn Pluckrose, PharmD Candidate, ACPHS Class of 2019

Braftovi™ (encorafenib) and Mektovi® (binimetinib) are oral antineoplastic agents produced by Array BioPharma Inc. and are indicated in combination for the treatment of specific BRAF mutation melanomas.[1] BRAF gene mutations promote the progression of melanoma by displaying greater kinase activity than the wild-type BRAF gene, which stimulates downstream signals in the mitogen-activated protein kinase (MAPK) pathway. Overstimulation of this pathway, which includes BRAF and MEK kinases, promotes the formation of melanoma cells from melanocytes.[2] Encorafenib, a BRAF inhibitor, and binimetinib, a MEK inhibitor, exhibit antineoplastic effects by targeting the MAPK pathway and inhibiting kinase activity.[3]

Clinical trials have demonstrated increased efficacy when combining a BRAF inhibitor with a MEK inhibitor for the treatment of BRAF mutation melanoma and a reduction in toxicities compared to BRAF inhibitor monotherapy. While other BRAF-MEK inhibitor combinations are available for treatment, such as dabrafenib-trametinib and vemurafenib-cobimetinib, their toxic side effect profiles and inability to prevent disease progression beyond 12 months has led to a search for new therapies that are better tolerated and more effective.[3]

The COLUMBUS trial was a two-part multicenter, randomized, open-label phase 3 study that aimed to determine the safety and efficacy of encorafenib and binimetinib. Outcomes were compared between three treatment groups and included progression-free survival and overall survival. The treatment groups consisted of combination therapy with encorafenib 450 mg once daily and binimetinib 45 mg twice daily, monotherapy with encorafenib 300 mg once daily, and monotherapy with vemurafenib 960 mg twice daily, a current guideline recommended BRAF inhibitor. The data show that combination therapy with encorafenib and binimetinib is associated with increased efficacy when compared with encorafenib or vemurafenib monotherapy. Median progression-free survival was 14.9 months (95% CI 11.0-18.5) with encorafenib plus binimetinib, 9.6 months (95% CI 7.5-14.8) with encorafenib and 7.3 months (95% CI 5.6-8.2) with vemurafenib. When comparing encorafenib and binimetinib to vemurafenib the hazard ratio was 0.54 (95% CI 0.41-0.71; two-sided $p<0.0001$).[3] Similarly, combination therapy with encorafenib and binimetinib is associated with increased overall survival when compared with encorafenib or vemurafenib monotherapy. Median overall survival was 33.6 months (95% CI 24.4-39.2) with encorafenib plus binimetinib, 23.5 months (95% CI 19.6-33.6) with encorafenib and 16.9 months (95% CI 14.0-24.5) with vemurafenib. When comparing encorafenib and binimetinib to vemurafenib the hazard ratio was 0.61 (95% CI 0.47-0.79; $p<0.0001$).[6]

In the COLUMBUS trial, treatment with encorafenib and binimetinib was associated with fewer dose modifications and treatment discontinuations due to adverse effects when compared to encorafenib and vemurafenib monotherapy. Additionally, fewer grade 3 or 4 adverse events were reported with encorafenib and binimetinib (111 [58%] of 192), then with encorafenib (127 [66%] of 192) or vemurafenib (118 [63%] of 186).[3] The most common side effects reported with encorafenib and binimetinib were abdominal pain, nausea, vomiting, fatigue and joint pain. The incidence of abdominal pain, nausea, and vomiting were higher with encorafenib and binimetinib than vemurafenib with a difference of 12%, 7% and 14%, respectively. However, the incidence of fatigue and joint pain was decreased compared to vemurafenib with a difference of 3% with fatigue and 20% with joint pain. The most common serious adverse event with encorafenib and binimetinib is a 19% incidence of hemorrhage.[4,5]

Based on the results from the COLUMBUS trial, the US Food and Drug Administration (FDA) approved the combination regimen of encorafenib and binimetinib in June 2018 for the treatment of unresectable or metastatic melanoma that expresses a BRAF V600E or V600K mutation, as detected by an FDA-approved test.[1] The recommend dosing for encorafenib is 450 mg once daily and the recommend dosing for binimetinib is 45 mg twice daily. There are currently no contraindications or boxed warnings for either agent. Encorafenib is not indicated in patients without BRAF mutation melanoma because it can cause tumor promotion or expansion that may lead to tumor progression and increased malignancy .[4,5]

In order to identify patients with BRAF mutations that qualify for treatment the THxID BRAF assay (bioMérieux) is available to test for BRAF mutations.[1] The THxID BRAF assay is an *in vitro* diagnostic device approved by the FDA to identify BRAF mutations in patients with metastatic melanoma. The THxID BRAF assay uses a real-time PCR test to detect the presence of BRAF V600E or V600K mutations in DNA samples extracted from human melanoma tissue.[7] Prior to initiating treatment with encorafenib and binimetinib the presence of a V600E or V600K BRAF mutation must be confirmed using the THxID BRAF assay.[4,5]

Based on the results of the COLUMBUS trial, combination therapy with encorafenib and binimetinib was shown to be more effective than encorafenib or vemurafenib monotherapy and produce a more favorable adverse event profile. This confirms that combination BRAF-MEK inhibitor therapy is more effective and better tolerated than BRAF inhibitor monotherapy for unresectable or metastatic BRAF mutation melanoma. While combination therapy with encorafenib and binimetinib is a promising new therapeutic option for BRAF mutation melanoma it is unclear whether this new regimen is more effective and more readily tolerated than current guideline recommended BRAF-MEK inhibitor combinations without a direct comparison study.

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Smart Glucose Monitoring

By Amy Podesva, PharmD Candidate, ACPHS Class of 2020

Medtronic has developed the Guardian Connect Smart Continuous Glucose Monitoring system which is indicated specifically for patients age 14-75 years taking multiple daily insulin injections and are seeking better glycemic control. This technological advance can be particularly helpful in teenagers and college students who are seeking independence but also need to adapt to changing schedules.

Continuous glucose monitoring (CGM) is a method to track glucose levels 24 hours a day and works through a tiny sensor inserted under the skin, usually on the abdomen or arm. The sensor continuously measures

interstitial fluid glucose levels, the fluid between the cells, every 1 to 5 minutes and wirelessly sends this information via a transmitter to a receiver.

Using Bluetooth technology, the Guardian Sensor transmits the data to the Guardian Connect app on the patient's smart phone (Apple) or watch and alerts him/her of glucose trends. Using the Guardian Connect app, the system can be programmed such that an alarm will sound when glucose levels are changing too quickly or when sugar levels are too low or too high. By monitoring glucose trends, the patient can take the necessary steps to prevent high and low sugar levels before they occur, ultimately allowing better glycemic control and less hypoglycemia. Family members or caregivers can also be notified of the patient's levels via text messages.

Using the Carelink system, the data collected can be shared with healthcare providers in real time. This allows clinicians to observe what type of control the patient has and give recommendations to optimize or adjust therapy if needed. The Guardian Connect system is unique in that it does not require the patient to carry a separate receiving device and it is not associated with an insulin pump. The system decreases the number of finger sticks the patient is required to do to two per day.

After speaking with several parents of teenagers and special needs adults, the general consensus was that this technology gave them peace of mind while they were away from their child. One parent of a special needs child that I spoke with stated that this technology has given the whole family much more freedom. They don't have to rely on a separate receiver (that could frequently not come home from school) and text message alerts can be sent directly to the child's aid or school nurse during the day without disrupting classroom activities. Currently, the Guardian connect app is only compatible with Apple products, however developers at Medtronic are working on a system that is compatible with Android products.

References:

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Carbapenem-Sparing Regimens: Are Beta-Lactamase Inhibitors Enough?

By Kyle Farina, PharmD Candidate, ACPHS Class of 2019

A growing concern in healthcare is the increasing rates of antibacterial resistance against pathogenic bacteria which produce extended-spectrum beta-lactamases (ESBL) causing resistance to penicillin- and cephalosporin-based antimicrobial therapies. As a result, carbapenems are the preferred treatment of infections caused by these bacteria due to their inherent resistance to most beta-lactamases; however, increased carbapenem use raises concern for increasing rates of carbapenamase producing gram negative pathogens. The use of ESBL-inhibitors, such as tazobactam or avibactam, paired with a penicillin or cephalosporin is a potential alternative approach to treating ESBL-producing gram negative bacteria.

The MERINO trial (Harris PNA, Tambyah PA, Lye DC et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: A randomized clinical trial. JAMA. 2018 Sep 11;320(10):984-94.) evaluated the mortality rate of hospitalized patients using piperacillin/tazobactam (Zosyn), a beta lactam/beta-lactamase inhibitor (BLBLI), versus meropenem for definitive treatment of ESBL-producing Escherichia coli or Klebsiella pneumoniae. This trial was an open-label, randomized, non-inferiority, parallel group trial study which took place at 26 sites in 9 countries (Australia, New Zealand, Singapore, Italy, Turkey, Lebanon, South Africa, Saudi Arabia and Canada) from July 2014 to February 2017. Study inclusion criteria included: age>18 (age>21 in Singapore), and at least one positive blood culture for E. coli or K. pneumoniae which was resistant to ceftriaxone and cefotaxime but remained susceptible to piperacillin/tazobactam and meropenem. Exclusion criteria included: allergy to either study drug, expected survival of ≤96 hours, treatment which was not intended to be curative, polymicrobial infection, pregnancy, or the use of concomitant antibiotics outside of the study drugs.

Once a positive blood culture for ESBL-producing E. coli or K. pneumoniae was obtained, patients were assigned to receive either intravenous meropenem 1g every 8 hours or intravenous piperacillin/tazobactam 4.5g

every 6 hours for a minimum of 4 days, and up to a maximal treatment duration of 14 days. Each infusion was given over a total of 30 minutes. Blood cultures were repeated on day 3 post-randomization, as well as on any day the patient was febrile (up to day 5). Patients were followed for 30 days after randomization, either in hospital or via telephone call if discharged.

The primary outcome of this trial was to assess all-cause mortality at 30-days post randomization to either meropenem or piperacillin/tazobactam; a noninferiority margin of 5% was used. Secondary outcomes included time to clinical resolution, time to microbiological resolution, relapsed bloodstream infection, death at day 4 post-randomization, and secondary infection with either a carbapenem-resistant or piperacillin/tazobactam-resistant organism.

A total of 378 subjects were randomized, received at least one dose of study drug and were available for follow-up at 30 days post-randomization; 191 subjects received meropenem and 187 subjects received piperacillin/tazobactam. The baseline demographics were similar between groups. Of note, the median age of the population was 70, 80% of the patients were Caucasian, 85% of the infections were caused by E. coli and most infections were urinary tract infections.

The primary outcome occurred in 12.3% of patients receiving piperacillin/ compared to 3.7% in the meropenem group [confidence interval (CI): -∞ to 14.5, p-value: 0.90] at 30 days post-randomization. Subgroup analysis of the primary outcome, including: income, Pitt bacteremia score, pathogen, hospital versus non-hospital associated infection, appropriate empiric therapy, source of infection and immunocompromised state also showed no significant difference in 30-day mortality between the two groups.

Secondary outcomes, including microbiological and clinical resolution of symptoms, microbiological resolution >4 days post-randomization, relapsed infection – defined as growth of the same organism within 30 days from randomization – and secondary infection with piperacillin/tazobactam or meropenem resistant or clostridium difficile, were not statistically different between the piperacillin/tazobactam and meropenem groups.

There are several limitations regarding this study. There was a significant amount of cross-over treatment between the two groups, with 13.8% of the piperacillin/tazobactam group receiving meropenem as empiric therapy and 26.2% of the meropenem group receiving a BLBLI as empiric therapy. Second, the applicability of trial to the United States is limited, as no sites from the United States were included. The authors acknowledge that management in other countries may differ from those countries included in the trial. Third, this trial does not evaluate the use of a extended-infusion piperacillin/tazobactam and only used 30 minute infusions of both study groups. While an initial bolus infusion of piperacillin/tazobactam could have potentially achieved a desired concentration above MIC, follow-up extended infusion may have kept the concentration of piperacillin/tazobactam above the MIC for longer and may have improved efficacy.

This study was the first randomized trial to assess the non-inferiority of a BLBLI to a carbapenem for treatment of ESBL producing gram negative bacteria. The results from this trial are striking and suggest that piperacillin/tazobactam is not an appropriate alternative to meropenem for treating definitive bloodstream infection caused by E. coli or K. pneumoniae bacteria which are ESBL-producers. Currently, there are no other randomized clinical trials evaluating carbapenems against BLBLI. The MERINO trial was unable to demonstrate non-inferiority of piperacillin/tazobactam to meropenem for treating bloodstream infections caused by ESBL-producing pathogens and suggests that carbapenem therapy, specifically meropenem, should be utilized to treat these infections. The results of this trial should not be extrapolated to other BLBLI combinations (i.e. ceftazidime/avibactam, ceftolazone/tazobactam) and further trials should be conducted to evaluate these potential alternatives to carbapenem therapy. There is also no evaluation of outcomes for the empiric treatment of patients with piperacillin/tazobactam or meropenem; therefore, the results of this trial should not be extrapolated when choosing antimicrobial therapy empirically.

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