Volume 4 | Issue 4
March 2019

NYS-ACCP Insider

University at Buffalo School of Pharmacy and Pharmaceutical Sciences

Special points of Interest:

UBSPPS ACCP Student Chapter Updates

Role of Aimovig™ in Migraine Therapy

New Drug Review: Dupilumab (DupixentTM)

Cannabidiol: Management of Dravet Syndrome

Review of TEC Trial

ACE-Inhibitors and Risk of Lung Cancer?

Clinical Spotlight: Dr. Brian Tsuji

UBSPPS-ACCP Student Chapter Updates

The medical profession is a constantly evolving field. Each year, new findings from research further expand the horizons of medicine. Due to the ever changing field of health care, professionals in this realm of practice continue to push the threshold of learning, having to stay current with the most recent available information. Pharmacists are vital healthcare professionals who possess the ability to analyze the new data, making the best patient-centered decisions based on their findings. It is unrealistic to think that pharmacists know and understand every drug/interaction in the world. In fact, their role on the team is to be aware of where to find the information and to convey the ideas in the literature in a concise manner in order to make therapeutic decisions.

With their knowledge of medication therapy and background as a clinician, a pharmacist plays a vital role within the patient care team. One of SCCP's core values is to promote excellence in patient care, research, and education. The evolving profession demands a student population that grows along with the ever-changing environment. SCCP prides itself on providing students these fundamental principles to navigate them on their educational path. Each year, the University at Buffalo (UB)'s SCCP chapter has been able to educate the student members with these facts in mind.

In the Fall 2018 semester, the SCCP chapter set up a Dinner and Discussion with Dr. Donald Mager, who discussed varying careers in pharmacokinetic and pharmacodynamics research. Dr. Mager is one of the most highly regarded PK/PD researchers of the new era,

He simplified complex topics and gave students a glimpse into what goes on in a typical day of a researcher. Students enjoyed the stress-free learning environment while eating some Wegmans subs. This tradition has always been a student favorite and will continue for semesters to come.

SCCP tries to incorporate as much fun into the learning experience as possible. One event that SCCP has been hosting for the past three years is called "Extra Life." Extra Life is a global event that aims to raise money and awareness for the Children's Miracle Network Hospitals. These hospitals provide treatment to 32 million kids across the United States every year. Extra Lifers came in nationwide on November 3rd and played video games or board games together in order to grow awareness and donate money to the cause. It allowed people to use their video game addiction and to have fun for a good cause. SCCP donated all proceeds from the event, which totaled more than $60, to the cause.

Each year, the state organization holds a conference in which students and pharmacists go to learn and present research that has developed over the past year. In November 2018, over 30 UB students attended the NYS-ACCP Conference in Cooperstown, NY. While the conference is mostly directed toward current pharmacists, students that attended expressed that they greatly benefited from the knowledge accumulated throughout the day. A new addition to the conference schedule was a student "Pharmacy Quiz Bowl." Each school selected a team of three students to play in a jeopardy-like game, where they answer therapeutics questions as quickly as possible. The UB SCCP chapter brought home the first-place trophy with a resounding victory against the other three schools that participated. This was a very exciting portion of the conference that future students will want to be a part of and defend the title in following years.

Omar Marzouk (left), Jean Tian (middle) and Atul Dilawri (right) win 1st place in the "Pharmacy Quiz Bowl" at the 2018 NYS ACCP Conference

In the Spring 2019 semester, the organization held a Journal Club with one of the faculty members, Dr. Edward Bednarczyk. With his help, our members analyzed an article that discussed a Phase III trial about Epidiolex, which is a new FDA-approved medical marijuana treatment for seizures. Students gathered together to discuss the literature, helping each other go through primary literature. As mentioned previously, pharmacists will be called upon by clinicians to analyze the literature in order to help make proper therapeutic decisions for patients. The skills learned from the Journal Club will help make proper therapeutic decisions for patients. The skills learned from the Journal Club will help students practice using skills essential to evidence-based medicine in their careers.

Lastly, the organization is in the process of implementing a new event into the regular yearly agenda. SCCP is starting an event called the "Clinical Topic Discussion." This event is geared towards prompting students to do research on a given topic and to become more comfortable presenting/interviewing. The skills, feedback, and experiences learned through this project will benefit students throughout their pharmacy career. SCCP has made it their goal to prepare students for residency positions, and we believe this event could be a factor that separates UB graduates from other students.

It is important to find a field of pharmacy that interests you; otherwise, you may struggle to find it exciting. School can be extremely difficult for students when they go through it alone. Our organization provides students a glimpse into the exciting clinical side of pharmacy while allowing them to learn alongside friends and mentors. The SCCP chapter at UBSPPS extends itself even further into the student body and aims to get students involved with hands-on learning experiences outside of the classroom. SCCP has been an active organization in UBSPPS for four years thus far and will continue to enable students to grow in their education for years to come.

Christopher Brighton, PharmD Candidate, UBSPPS Class of 2021

-

Dinner & Discussion with Dr. Joshua Sawyer, PharmD, AAHIVP

Role of Aimovig™ in Migraine Therapy

Developed by Novartis and Amgen in May 2018, Aimovig™(erenumab-aooe) was the first FDA approved calcitonin gene-related peptide (CGRP) receptor antagonist indicated for the prevention of migraine attacks in adults. Prior to the advent of this rapidly burgeoning drug class, sodium valproate and topiramate were the only agents available FDA approved for migraine prophylaxis.[1]

Aimovig™ has a unique place in the therapeutic management of migraines due to its high efficacy and mild side effect profile.[2] It is a 100% humanized monoclonal antibody which the patient self-administers by SureClick™ auto-injector technology subcutaneously every four weeks. The dosing is 70mg per injection, although some patients may receive benefit from a 140mg injection.[3] The phase II trial that was pivotal resulted in a decrease of 6.6 migraine days per month (at both doses) in patients that experienced chronic migraines, or 15 or more migraine days per month.[4] The two subsequent phase III trials, STRIVE and ARISE demonstrated a reduction in migraine days per month in patients with episodic or chronic migraines by at least 50% (at both doses) with similar safety as placebo. The phase III trials also demonstrated efficacy in patients refractory to traditional migraine treatment, which is defined as prescription-strength NSAIDs, drugs in the triptan class, and adjunctive options, and/or has failed one trial of migraine prophylaxis. Aimovig™ has been well-tolerated throughout the trials with commonly reported side effects of injection site reactions and constipation.[5,6]

Image of Aimovig™ (erenumab-aooe) SureClick Autoinjector for subcutaneous injection.

As the majority of migraine sufferers are women, prophylaxis measures using sodium valproate and topiramate are not commonly utilized due to significant, known, teratogenic effects. Both are not without other challenging side effects in men and women, such as peripheral neuropathy. Aimovig™ confers another prophylactic option for patients and has demonstrated efficacy and superior safety, even if the effects on pregnancy and lactating women are not yet studied.[4]

Cost is the hurdle that prevents Aimovig™ from benefiting a wider breadth of patients in practice. At $6900 per year of prophylaxis, private insurance companies and public programs prefer to keep it off the formulary and cover oral triptan treatment instead. From the results of the STRIVE and ARISE trials, patients that have chronic migraines refractory to traditional migraine treatment may be the niche group that would benefit the most from Aimovig™, perhaps warranting administrative hoop-jumping for coverage. Cost issues aside, Aimovig™ is a safe and effective option for preventing migraine attacks in adults, adding a new level of protection.

Jean Tian, PharmD Candidate, UBSPPS Class of 2020

References:

1. Buse D, Lipton R, Hallström Y et al. Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with erenumab. Cephalalgia. 2018;38(10):1622-1631. doi:10.1177/0333102418789072
2. AIMOVIGTM [package insert]. Thousand Oaks, CA: Amgen Incorporated and Novartis Pharmaceuticals Corporation; 2018
3. Aimovig. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: http://online.lexi.com. Accessed March 8, 2019.
4. Aimovig (erenumab-aooe). Aimovig for US Health Care Professionals Only website. Available at: https://www.aimovighcp.com/. Accessed March 8, 2019.
5. Dodick D, Ashina M, Brandes J et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018;38(6):1026-1037. doi:10.1177/0333102418759786
6. Goadsby P, Reuter U, Hallström Y et al. A Controlled Trial of Erenumab for Episodic Migraine. New England Journal of Medicine. 2017;377(22):2123-2132. doi:10.1056/nejmoa1705848

New Drug Indication: Dupilumab (DupixentTM)

What is it:

Dupilumab (Dupixent™) was approved in October 2018 as an add-on maintenance treatment for patients at least 12 years of age who have moderate-to-severe asthma with an eosinophilic phenotype, or with oral corticosteroid-dependent asthma. [1] Dupilumab was developed by Regeneron Pharmaceuticals and originally FDA-approved in March 2017 for treatment of moderate-to-severe atopic dermatitis.

What does it treat:

Asthma is a common chronic lung disease that affects 8.4% of the U.S. population and 4.3% of the population worldwide.[2] It is characterized by airflow obstruction, bronchial hyperresponsiveness, and airway inflammation.[3] Type 2 inflammation, which is mediated by interleukin-4 (IL-4) and interleukin-13 (IL-13), has been observed in about 50% of patients with asthma.[4] Studies have also found an association between type 2 inflammation and serum levels of eosinophils, fraction of exhaled nitric oxide, and serum IgE levels.[5,6]

Patients often present with respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity. Of those with asthma, about 20% have uncontrolled, moderate-to-severe disease, and they have multiple exacerbations per year and no relief of symptoms despite being on appropriate inhaler therapy according to the GINA guidelines or NAEPP guidelines.[7] In addition to the short-acting beta-2 agonist that should be used as needed for symptom control, patients with moderate-to-severe asthma should be on maintenance therapy with medium- or high-dose inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA), and oral corticosteroids may also be necessary if their asthma is still not controlled with a high-dose ICS and LABA.[8]

Mechanism of action:

Dupilumab is a human monoclonal IgG4 antibody that binds to the α subunit of the interleukin-4 receptor (IL4Rα), thereby blocking IL-4 and IL-13 signaling.[1] This subsequently inhibits cytokine-induced inflammatory responses, which includes the release of nitric oxide and IgE, that are involved in Type 2 inflammation.

Dosing:

Dupilumab is injected subcutaneously and can be given either with an initial dose of 400 mg followed by 200 mg injected every other week, or with an initial dose of 600 mg followed by 300 mg every other week, which is recommended for patients with oral corticosteroid-dependent asthma.[9] There are no dose adjustments for hepatic or renal impairment provided by the manufacturer, as there was no formal trial to study the effects of dupilumab on renal or hepatic function in patients with hepatic or renal impairment.[1] This medication should be stored in the refrigerator between 2 and 8 degrees Celsius. If a patient misses a dose, they should take it as soon as they can, as long as it is within 7 days from the missed dose.

Adverse events:

The most common side effect includes a reaction at the injection site, which occurs in 10% to 18% of patients.[1] Other side effects include throat pain and increased levels of eosinophils, which occur in 2% of patients. A patient should alert their doctor if they notice they are having an allergic reaction, changes in vision or eye pain or swelling.

Studies involved in approval:

One Phase III clinical trial, known as LIBERTY ASTHMA QUEST, demonstrated benefit in patients with uncontrolled, moderate-to-severe asthma, leading to its approval for that indication and for patients with an eosinophilic phenotype.[10] Sponsored by Sanofi and Regeneron Pharmaceuticals, the manufacturer of Dupixent™ (dupilumab), the study examined the effectiveness and safety of dupilumab in patients age 12 years and older with at least a 1-year history of asthma. It was a randomized, double-blind, placebo-controlled trial with a total of 1902 participants, of which 1638 completed . Patients were randomized in a 2:2:1:1 ratio to receive add-on dupilumab at a dose of 200 mg or 300 mg every 2 weeks or matched-volume placebos. The intervention period was 52 weeks long, and the post-intervention follow-up period was 12 weeks long.

Inclusion criteria were: current treatment with medium-to-high-dose inhaled corticosteroid plus no more than than two additional controllers such as a LABA or leukotriene-receptor antagonist; FEV1 ≤ 80%; FEV1 reversibility ≥ 12% and 200 ml; and worsening of asthma in the previous year that results in hospitalization or treatment with systemic corticosteroids for at least 3 days.[10] Exclusion criteria included the following: patients with weight > 30 kg; patients with COPD or other lung disease; current smoker or cessation

of smoking within the past 6 months; and previous smoker with > 10-year smoking history. There were two primary outcomes assessed: the annualized rate of severe exacerbation events; and the absolute change from baseline in the pre-bronchodilator FEV1 at week 12. The secondary endpoint was percentage change in pre-bronchodilator FEV1 from baseline. A subgroup analysis was also performed with the same primary and secondary outcomes in patients with blood eosinophil count ≥ 300/mm^3.

An intention-to-treat analysis was performed. Compared to placebo, patients treated with dupilumab had lower rates of severe asthma exacerbations; it was 47.7% ($p<0.001$) and 46.0% ($p<0.001$) lower for those on the lower and higher doses of dupilumab, respectively, compared to placebo.[10] The adjusted annualized rate of severe asthma exacerbations was 0.46 in patients on lower-dose dupilumab, versus 0.87 in those on matched placebo (95% CI, 0.39-0.53); for those on higher-dose dupilumab, the rate was 0.52, versus 0.97 in those on matched placebo (95% CI, 0.81-1.16). Additionally, the subgroup analysis showed those with blood eosinophil count ≥ 300/mm^3 benefited more from either dose of dupilumab, compared to those with lower eosinophil counts; it was 65.8% and 67.4% ($p<0.001$) lower for those on the lower and higher doses of dupilumab, respectively, compared to placebo.

Dupilumab also showed improvement in the change in FEV1 before bronchodilator use from baseline. In the overall trial population, patients on the lower-dose dupilumab experienced a change of 0.32 L, compared to 0.18 L with matched placebo (difference, 0.14 L; $p<0.001$); patients on the higher-dose treatment showed a change of 0.34 L, compared to 0.21 L with matched placebo (difference, 0.13 L; $p<0.001$).[10] The greatest benefit was seen in patients with blood eosinophil count ≥ 300/mm^3: 0.43 L with lower-dose dupilumab versus 0.21 L with matched placebo (difference, 0.21 L; 95% CI, 0.13-0.29); 0.47 L with higher-dose dupilumab versus 0.22 L with matched placebo (difference, 0.24 L; 95% CI, 0.16-0.32).

Overall, the study found that patients aged 12 years and older with uncontrolled, moderate-to-severe asthma benefitted from adding on dupilumab to their ICS+LABA therapy, and that patients with asthma of eosinophilic phenotype benefited more compared to those with a lower blood eosinophil count.

Sylvia Ou, PharmD Candidate, UBSPPS Class of 2020
Marissa Saber, PharmD Candidate, UBSPPS Class of 2022

References:

1. Dupixent. Drugs@FDA. Food and Drug Administration website. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf. Accessed March 8, 2019.
2. Loftus PA, Wise SK. Epidemiology of asthma. Curr Opin Otolaryngol Head Neck Surg. 2016;24(3):245-249.
3. Sorkness CA, Blake KV. Asthma. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. New York, NY: McGraw-Hill. Available at: https://hubnet.buffalo.edu:4306/content.aspx?bookid=1861&sectionid=146058008. Accessed March 9, 2019.
4. Fahy JV. Type 2 inflammation in asthma — present in most, absent in many. Nat Rev Immunol. 2015;15:57-65.
5. Robinson D, Humbert M, Buhl R, et al. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. Clin Exp Allergy. 2017;47:161-175.
6. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol. 2017;13:425-437.
7. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. Respir Med. 2006; 100: 1139-51.
8. Global Strategy for Asthma Management and Prevention (2018 Update). Global Initiative for Asthma (GINA). https://ginasthma.org/gina-reports/. Published 2018. Accessed March 8, 2019.
9. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. New England Journal of Medicine. 2018;378(26):2475-2485.
10. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378:2486-2496.

Cannabidiol: Management of Dravet Syndrome

Background:
Dravet syndrome is a form of early childhood epilepsy characterized by episodes of prolonged febrile and afebrile seizures within the first year of a child's life. The prognosis includes progression to other seizure types such as myoclonic, tonic-clonic, atypical, focal, or atonic seizures. The seizures are often insensitive to medications, and all patients are at risk of status epilepticus. Patients often experience developmental delays, and the risk of sudden unexplained death is significantly high.[1] Variants in the SCN1A gene has been found in over 80% of cases of clinically diagnosed Dravet syndrome.[2] Treatment goals for Dravet syndrome are to reduce seizure frequency and to limit drug-related adverse events. First-line therapies for Dravet syndrome include clobazam or valproic acid or in combination if neither one alone allows for adequate control of the seizures. Second-line therapies include stiripentol, topiramate, or a ketogenic diet as add-on therapy if control is still suboptimal. Lastly, should any first or second line agents fail, the addition of clonazepam, levetiracetam, zonisamide, ethosuximide, or phenobarbital may be considered.[2] With these therapies, complete inactivity of seizures is rarely achievable.[1]

Introduction
Previous small randomized studies on the use of cannabidiol in epilepsy have been too small to provide definitive answers on its applications. Nevertheless, there is immense public interest in the use of cannabidiol in the treatment of refractory seizures. In this trial, cannabidiol or placebo was added as adjunct therapy to the current antiepileptic drug regimen of children and young adults with Dravet Syndrome. These patients' seizures were not adequately controlled with their current regimen and were taking a median of 3.0 antiepileptics to control their seizures. This study sought to find clinical applications of cannabidiol in the treatment of drug-resistant epilepsy in Dravet syndrome.[3]

Pharmacology
The exact mechanism of action of how cannabidiol exerts anticonvulsant effects in human is unknown. However, it appears that it does not have any appreciable affinity for the cannabinoid receptors. It also lacks the psychoactivity of tetrahydrocannabinol.[3] Animal studies show that cannabidiol does not produce behavioral changes and does not appear to produce any rewarding effects. Further, 4-week observations following cannabidiol administration have not shown signs or symptoms of dependence on the medication.[4]

Study Participants
177 patients were screened in the United States and Europe, with only 120 meeting criteria to undergo randomization. The average age of participants in the study was 9.8 (range, 2.3-18.5). Patients were eligible for the study if they had established Dravet syndrome, were currently taking at least one medication to treat their seizures, and had four or more convulsive seizures at baseline during the 4-week baseline period. The median convulsive seizures per month was 13.0 at baseline.[3] Some exclusions include having a significant uncontrolled comorbidity other than epilepsy, having significant illness in the 4 weeks prior to screening other than epilepsy, or having significantly impaired liver function.[5]

Trial Design
This trial was a multinational, randomized, double-blind trial. It started with a 4-week baseline period where caregivers recorded daily seizure frequency of participants, and those that satisfied inclusion criteria were randomized 1:1 to receive either placebo or cannabidiol in addition to their stable antiepileptic regimen. All medications and interventions for epilepsy needed to be stable for at least 4 weeks before screening. A 2-week dose escalation period followed where doses were escalated to 20 mg/kg/day given twice daily. Following the 12-week maintenance therapy, doses of cannabidiol were tapered by 10% each day over a period of 10 days. A 4-week follow up was also conducted to measure safety. An open-label study was made available to all patients following completion of trial. [3]

The primary endpoint was a percentage change per 28 days from the 4-week baseline period in convulsive seizure frequency following treatment in those that received cannabidiol compared to those that received placebo. The secondary endpoint included measures of the Caregiver Global Impression of Change assessing disease severity prior to treatment, reduction in seizure frequency and length as reported by the caregiver, frequency of sleep disruptions, quality of life improvement scores, episodes of hospitalization relating to seizures, appearance of new seizure types, and the need for rescue medications.

Statistical Analysis
The sample size was calculated to provide 80% power to detect an absolute difference of 32 percentage points between groups in the primary endpoint with a standard deviation of 56% and a two-sided significance level of 5%.[3] The primary endpoint was analyzed using the non-parametric Wilcoxon rank-sum test. The median and 95% confidence interval were calculated using the Hodges-Lehmann approach. Percentages in reduction of convulsive-type seizures from baseline were analyzed with the Cochran-Mantel-Haenszel test. Change from baseline for the Caregiver Global Impression of Change was analyzed using an ordinal logistic-regression model.[3]

Results

In patients receiving cannabidiol, convulsive seizure frequency in a 28-day time frame saw a median change of -38.9% (interquartile range, -69.5 to -4.6) from baseline. As for placebo, patients saw a reduction of -13.3% (interquartile range, -52.5 to 20.2). There was a significant adjusted median difference between the cannabidiol group and the placebo group of -22.8 percentage points (95% CI -41.1 to -5.4, p=0.01). The potential of cannabidiol was seen as early as in the first month of the maintenance period.

Using the Caregiver Global Impression of Change scale, 37 of 60 caregivers judged that their child's condition significantly improved while on cannabidiol, compared to only 20 of 58 caregivers in the placebo group (difference: -1.0, 95% CI -1.0 to 0, p=0.02). Analysis of the sleep-disruption score and the Epworth Sleepiness Scale found no significant difference in sleep-disruption or negative impact on sleep, respectively, between groups. Quality of Life in Childhood Epilepsy score and Vineland-II score showed no significant difference.[3]

Adverse Events

More patients in the cannabidiol group reported adverse events with greater occurrence during the 2-week dose escalation. The most commonly reported adverse events included vomiting, fatigue, pyrexia, URTIs, decreased appetite, convulsions, lethargy, somnolence, and diarrhea. Somnolence was the most common adverse event in the cannabidiol group. It was found that a majority of patients who experience somnolence were also taking clobazam. This prompted a dose reduction in the cannabidiol group, which then saw eventual improvements in their side effect profile.[3]

Elevated Liver Aminotransferases

Overall, 12 patients in the cannabidiol group and 1 in the placebo group had elevated levels of liver function enzymes, and it was found that these patients were taking a form of valproate. As the study progressed, their aminotransferase levels eventually returned to normal, suggesting a transient stress on the liver.[3]

Critiques

A concern with this study is the unblinding of groups; caregivers in the cannabidiol group might have figured out that their child was receiving the study agent due to increased incidences of diarrhea, vomiting, or other side effects. Further, assessment of caregivers reported the drug agent as bad-tasting compared to the placebo group, and this could have affected blinding in a small number of patients.[3]

Another concern was the inability to determine any significant reduction in seizures of the non-convulsive type. The authors conclude that cannabidiol may only be useful to convulsive-type seizures in the setting of Dravet syndrome or that caregivers cannot be accurately depended upon to account for such seizure types in children with developmental delays.[3] Further studies may be needed to arrive at a definitive answer.

It would be unethical to halt baseline seizure medications, especially for those in the placebo group. Cannabidiol is a moderate to strong CYP3A4 and CYP2C19 inhibitor, which may affect the metabolism of antiepileptic agents. Therefore, it is uncertain whether seizure reduction was due to cannabidiol alone or to cannabidiol increasing the exposure and activity of existing antiepileptic agents.

Conclusions

In patients with Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-type seizure frequency when used in combination with other antiepileptic agents. However, cannabidiol is also associated with higher rates of adverse events such as diarrhea, vomiting, fatigue, pyrexia, somnolence, and elevated liver function tests. The clinical use of cannabidiol in the treatment of Dravet syndrome is promising, but even researchers admit that more data on the long-term efficacy and safety of cannabidiol for Dravet syndrome still need to be gathered.[3]

Ngan Nguyen, PharmD Candidate, UBSPPS Class of 2021

References:

1. Wirrell EC. Treatment of Dravet Syndrome. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2016;43(S3):S13-S18.
2. Wirrell EC, Laux L, Donner E, et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. Pediatric Neurology. 2017;68:18-34.e13.
3. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. New England Journal of Medicine. 2017;377(7):699-700.
4. Epidiolex (Cannabidiol) [package insert]. GW Pharmaceuticals plc., Cambridge, United Kingdom. 2018.
5. A DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-PART STUDY TO INVESTIGATE THE DOSE-RANGING SAFETY AND PHARMACOKINETICS, FOLLOWED BY THE EFFICACY AND SAFETY OF CANNABIDIOL (GWP42003-P) IN CHILDREN AND YOUNG ADULTS WITH DRAVET SYNDROME. [Supplementary Material: Protocol]. GW Pharmaceuticals plc., Cambridge, United Kingdom. 2014.

A Randomized Trial of E-Cigarettes vs. Nicotine Replacement Therapy (TEC Trial)

Background

The number of teen users of e-cigarettes has outnumbered the number of adult users.[1] Recently, they have been scrutinized for the lack of efficacy for their initial use as a method for smoking cessation and for companies' marketing tactics that have been correlated to increase popularity in teen smoking. There are 2 main types of e-cigarettes available on the market: closed and opened systems. Open systems are refillable with nicotine and flavoring solutions, or juices.[2] Closed systems are disposable or use disposable cartridges. These can be further broken down to reusability, which is determined by whether or not the e-cigarettes are rechargeable. According to a publication by AAP, reusable open system e-cigarettes or tanks have been used more often.[2]

E-cigarettes contain vegetable glycerin, propylene glycol, benzoic acid, and a proprietary blend of flavors.[3] Although many studies have been conducted on the dangers of cigarettes, few have studied the effects of chemicals vaporized in e-cigarettes. Additionally, e-cigarette companies are not required to release a list of ingredients in their proprietary blend of flavors. Due to the lack of studies on the vaporization of proprietary blends, researchers do not know what the dangers of e-cigs are. Another danger of e-cigarettes comes from DIY sites. A quick web search would show adolescents how to make their own nicotine solutions. With the exception of nicotine, any adolescent can buy these ingredients online without being of age. These solutions can often introduce chemicals from the environment into their lungs, causing further toxicity. In a published by APP, researchers found that 23.1% of adolescents that regularly smoked e-cigs progressed to exclusively smoking cigarettes.[2,4]

Introduction

The TEC trial, which was published in the NEJM in February 2019, evaluated the effectiveness of e-cigarettes compared to nicotine products approved for smoking cessation. Prior to the study, a Cochrane review showed e-cigs containing nicotine were more effective in smoking cessation compared to e-cigs without nicotine. They were unable to determine if e-cigs with nicotine was more effective than traditional nicotine replacement therapy (NRT), and more data was needed to reach a definitive conclusion. Thus, this study was conducted to compare the effectiveness of smoking cessation with e-cigs with nicotine versus NRT.[4,5]

Pharmacology

NRT is commonly used to help with smoking cessation by alleviating nicotine withdrawal symptoms. A tapering strategy is used to help reduce and wean off the number of cigarettes. Nicotine acts on postganglionic neurons in the SNS and PNS, skeletal muscle, and nicotinic receptors in the CNS system. Nicotine in cigarettes works by acting on the nicotinic acetylcholine receptors expressed on dopamine neurons, causing dopamine release. Chronic stimulation leads to nicotine tolerance and withdrawal symptoms can occur when it's not stimulated.[6,7]

Inclusion/Exclusion Criteria

Inclusion criteria were 18 years and older, current smoker accessing a stop smoking service, and able to read/write/understand English.[5] Exclusion criteria were pregnant or breastfeeding, a strong preference to use or not use NRT or e-cigs in the quit attempt, currently using NRT or e-cigs, and already enrolled in interventional research. Patients who used the non-assigned product for at least 5 consecutive days or if they didn't complete the 52-week follow-up were excluded.[5]

Trial design

This was a two-group, pragmatic, multicenter, individually randomized, controlled trial conducted in the United Kingdom. Patients either received e-cigarettes or NRT of their choice. 886 participants were randomized on the quit date in a 1:1 ratio. Patients in the e-cig group received a starter pack containing the e-cig device and a 30 mL refillable bottle of 18mg/ml nicotine. The NRT group received a 3-month supply of their choice of NRT. They were free to switch between products and the use of combination therapy was encouraged. After 3 months, they were encouraged to buy their own supplies. Smoking status and expired monoxide level were measured at baseline, week 4, and week 52. Other data collected were ratings of trial products, the rating of withdrawal symptoms (week 1-6) and adverse reactions. All patient received multisession behavioral support, which consisted of weekly one-on-one sessions with a clinician. Each patient was followed up by phone on week 26 and week 52.[5] The primary outcome was sustained abstinence for 1 year using e-cigs compared to standard NRT. Secondary outcomes were participant-reported treatment usage, adverse reactions, and respiratory symptoms.[5]

Results

The abstinence rate was 18% in the e-cig group and 9.9% in the NRT group (RR 1.83; 95% CI 1.3 to 2.58; p<0.001). Both e-cig and NRT were reported less satisfaction than cigarettes, but e-cigs provided greater satisfaction than NRT. Participants in the e-cig group had a less severe urge to smoke compared to those in the NRT group (95% CI -0.5 to -0.1). Nausea was more frequently reported in the NRT group compared to the e-cig group (37.9% vs. 31.3%). Throat and mouth irritation were more commonly reported in the e-cig group compared to the NRT group (65.3% vs. 51.2%). Respiratory symptoms of cough and phlegm were commonly reported at baseline, and more patients in the e-cig group had symptom-free by 52 weeks.[5]

.

Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)‖

* Abstinence at 52 weeks was defined as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date, validated biochemically by an expired carbon monoxide level of less than 8 ppm at 52 weeks. Abstinence between week 26 and week 52 was defined as a self-report of smoking no more than five cigarettes between week 26 and week 52, plus an expired carbon monoxide level of less than 8 ppm at 52 weeks. Abstinence at 4 weeks was defined as a self-report of no smoking from 2 weeks after the target quit date, plus an expired carbon monoxide level of less than 8 ppm at 4 weeks. Abstinence at 26 weeks was defined as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date to 26 weeks; there was no validation by expired carbon monoxide level.
† The analysis was adjusted for trial center only.
‡ The analysis was adjusted for trial center, marital status, age at smoking initiation, and score on the Fagerstrom Test for Cigarette Dependence.
§ The analysis was adjusted for trial center, age, score on the Fagerström Test for Cigarette Dependence, and age at smoking initiation.
¶ The analysis was adjusted for trial center, education level, partner who smokes (yes or no), and score on the Fagerstrom Test for Cigarette Dependence.
‖ The analysis was adjusted for trial center, sex, age, and partner who smokes (yes or no).

Critiques

A limitation of this study was that it could not be blinded for the product selection. Because of the nature of this study, there was no way to blind patients on what they were receiving. This can also be viewed as a benefit because it simulates real-world practice. Another limitation is the long-term effects of these products. The use of e-cigs simulates the act of smoking a cigarette; therefore, it may lead the patients to habitual use of e-cigs.

Conclusion

This trial provides more evidence in the use of e-cigs as a form of smoking cessation and nicotine replacement therapy. E-cigs have proved to increase abstinence rates compared to traditional NRT; however, e-cigs also cause more throat and mouth irritation. This pragmatic study, which simulates "real life," demonstrated that they may have a role in smoking cessation in smoking cessation service programs. However, the use of e-cigs could potentially cause habitual use of e-cigs, and further studies need to be conducted to determine if the results of this study could be generalized to outside the UK.

Mason Chan, PharmD Candidate, UBSPPS Class of 2020, UB SCCP President
Anant Shah, PharmD Candidate, UBSPPS Class of 2022

References:

1. The facts on E-cigarette use among youth and young adults. https://e-cigarettes.surgeongeneral.gov/. Accessed March 5, 2019.
2. McMillen R, Tanski S, Wilson K, Klein JD, Winickoff JP. Adolescent Use of Different E-cigarette Products. *Pediatrics*. 2018;142(4):e20180260.
3. JUULpod Basics. https://support.juul.com/home/learn/faqs/juulpod-basics. Accessed March 5th, 2019.
4. E-liquid FAQ. https://www.halocigs.com/faqs/eliquid/. Accessed March 5th, 2019.
5. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2016;9:CD010216.
6. Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med*. 2019;380(7):629-637.
7. Lüscher C. Drugs of Abuse. In: Katzung BG, ed. *Basic & Clinical Pharmacology, 14e*. New York, NY: McGraw-Hill Education; 2017.
8. 8. Pappano AJ. Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs. In: Katzung BG, ed. *Basic & Clinical Pharmacology, 14e*. New York, NY: McGraw-Hill Education; 2017.

- ACE- Inhibitors and Risk for Lung Cancer?

Introduction

This journal explores about the possibility of an association between ACE inhibitors (ACEi) and lung cancer development. ACEi are one of the most commonly used medications to treat hypertension. Every year, around 22 million (32%) of all antihypertensive prescriptions dispensed in the United Kingdom are ACEis. Their main mechanism of action is preventing the conversion of angiotensin I to angiotensin II. In the absence of angiotensin II, the vessels won't vasoconstrict, thus preventing further increases in blood pressure. The major side effects of ACEi are dry cough and angioedema due to the accumulation of bradykinin. Without angiotensin II, bradykinins are not broken down, which can stimulate carcinogenic growth of lung tissue as well as accumulate substance P, a known associate of tumor proliferation and angiogenesis. In past studies, randomized controlled trials that explored the relationship between ACEi and lung cancer have been considered invalid because of the relatively small sample sizes and short duration of follow-up. In this study, 992,061 people were analyzed and followed up for 10 years; the study used angiotensin receptor blockers (ARBs) as the reference.

Methods

The database the study used was the UK Clinical Practice Research Datalink (CPRD). The study cohort required all subjects to be 18 years or older and have at least one year of medical history recorded in the CPRD before initiation of any new antihypertensive drug class between January 1, 1995 and December 31, 2015. Cohort entry was defined by the date of the first prescription. Patients with less than one year of follow up after cohort entry, as well as those with a past diagnosis of any cancer except for non-melanoma skin cancer, were excluded. This would avoid the possibility that the lung cancer could be due to the initial diagnosed cancer. Follow-up was started one year after cohort entry up until whichever occurred first: diagnosis of incident lung cancer, death from any cause, end of registration with general practice, or end of study period (December 31, 2016). Each subject was marked by three exposure categories: ACEi alone or in combination with other antihypertensives barring previous use of ARBs, ARBs alone or in combination with non-ACEi antihypertensives, and other antihypertensives (included those who switched from ACEi to ARB or from ARB to ACEi for reasons like side effects). All the possible relevant confounding variables were adjusted and considered, like history of smoking, alcoholism, use of any statins, etc. To measure general comorbidity, models were adjusted for total number of unique drug classes prescribed the year before cohort entry.

Statistical Analysis

Poisson distribution was used to calculate both crude incidence rates of lung cancer as well as the 95% confidence interval in each exposure group. Standard use of time-dependent Cox proportional hazard models estimated both the hazard ratio and 95% confidence interval for incidence of lung cancer associated with use of ACEi versus ARBs. Five total imputations were combined using Rubin's rules to find variables with missing information; the use of ordinal logistic regression for smoking and linear regression for body mass index, along with explanatory variables, cumulative hazards, and all confounders were utilized.

Secondary Analyses: The first was a time-dependent analysis of cumulative duration of ACEi use and incidence of lung cancer. Three categories of predefined duration were created using estimated hazard ratios: ≤5 years, 5.1-10 years, and >10 years. Secondly was the association between time since initiation of ACEi and risk of lung cancer using the same categories as those in the first. Thirdly, interaction term between smoking status and exposure variables was used to investigate possible effect modifications due to smoking status. Repetition of primary and secondary analyses were done on non-smokers as well. Sensitivity analyses were utilized to further strengthen their findings. These were: use of a 2-3-year exposure lag period, stratifying the model to tenths of disease risk to alternatively control confounding, and repeating the analysis using a marginal structural Cox proportional hazards model instead to adjust for time-dependent confounding with time varying exposures. Inverse probability of treatment and censored weighting were methods of the Cox proportional hazards model.

Results

In comparison to ARBs, ACEis were associated with an overall 14% increased risk of lung cancer. For the secondary analyses, the study showed that the adjusted hazard ratios of cumulative ACEi use of less than or equal to 5 years was not statistically significant (HR: 0.96-1.25; $p<0.001$), while cumulative ACEi use of 5.1-10 years as well as >10 years were statistically significant (HR: 1.06-1.40 & HR: 1.08-1.59 respectively; both with $p<0.001$). Time since starting ACEi showed a similar association, and overall results were consistent with the primary analysis. Because of the large sample size and population, small effects in this study could translate to a large number of patients at risk for lung cancer.

Critiques

Meta-analyses of randomized control trials looking at the same association were not sufficiently powered or designed to assess the same outcomes. This was due to a relatively short median duration follow-up of 3.5 years affecting the ability to properly assess cancerous events. While there are several observational studies looking at the same association as this study, the only one that was sufficiently designed to investigate this study's association had a similar conclusion with respect to cumulative ACEi use of less than or equal to 5 years. While bradykinin's effects were briefly mentioned in the introduction, additional effects such as stimulating release of vascular endothelial growth factor and enhancing vascular permeability through activation of matrix metalloproteinase (thereby facilitating tumor invasion and metastases) add to the biological plausibility that ACEi could be associated with lung cancer. The strengths of this study included: large population size, new user design, varying exposure definition to eliminate immortal time bias, and adjustment of potential important confounders. Limitations of this study were: information on other confounders (exposure to radon/asbestos, family history of lung cancer, etc), precision of smoking status, adherence to treatment regimen, use of ARBs as a comparison, possible misclassification of lung cancer, and the concern of over-detection of lung cancer due to ACEi induced persistent cough.

Conclusion

The association between ACEi use and increased risk of lung cancer is statistically significant, with evidence of a duration-response relation. While the observed estimates are modest, given the number of patients potentially at risk for lung cancer, further studies must replicate these findings in other settings.

Jack Chen, PharmD Candidate, UBSPPS Class of 2021
Fei Li, PharmD Candidate, UBSPPS Class of 2022

References:

1. Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. The BMJ. http://www.bmj.com/content/363/bmj.k4209. Published October 24, 2018. Accessed March 11, 2019.

Clinical Spotlight: Dr. Brian Tsuji

1. **With your recent publication of "International Consensus Guidelines for the Optimal Use of the Polymyxins" what are your future plans or what comes next? What were some of the challenges of writing these guidelines and coordinating with various healthcare professionals?**

   There is considerable confusion on how to optimally use the polymyxin antibiotics. These guidelines represent consensus recommendations from expert clinicians and scientists around the globe. The endorsement from 6 international organizations was amazing and took years.

2. **What advise do you have for students to get involved in research? What skill sets can students learn during their didactics to prepare them for research during practice?**

   I got involved in research to change how we can optimally treat our patients. The biggest piece of advice I would have is find an area that you are passionate about pursue all unanswered questions that may be challenging in treating patients and be practical in your research.

3. **How did your involvement with ACCP help you achieve your goals? What are some recommendations you have for students who would like to pursue a career in infectious disease?**

   I have been involved with ACCP for over a decade as a member, past-president of NYS ACCP, and now co-chair of the polymyxin guidelines. Ask a ton of questions. Be resilient. Be inquisitive. And always love what you do.

Dr. Brian Tsuji, PharmD

"My advice to PharmD students is to Ask a ton of questions. Be resilient. Be inquisitive. And always love what you do."

University at Buffalo
School of Pharmacy and Pharmaceutical Sciences

Questions? Please contact: Amanda Engle, PharmD NYS-ACCP Secretary/Treasurer
Amanda.Winans@bassett.org