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The Annual Review of Changes in Healthcare (ARxCH)

The ARxCH is a student run publication at the University of Findlay College of Pharmacy. The journal reviews various topics that have a clinical impact on pharmacy practice in a variety of specialties. The ARxCH also focuses on key changes in healthcare and specifically incorporates the dynamic role of informatics in pharmacy. Featured content includes review articles, original research, and a special topics section. The goal of the journal is to keep healthcare professionals aware of the changing landscape in healthcare, so that patients receive the best care possible.

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Annual Review of Changes in Healthcare

New Drug Approval for Lasmiditan: A New Approach to Migraine Treatment

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Abstract

Millions of people worldwide suffer from migraines, and current treatment may not be suitable for all patients. Patients who have cardiovascular risk factors as well as migraines are not able to take triptans, which are the mainstay of acute migraine treatment, because triptasns can cause an increase in blood pressure and potentially cause an unwanted cardiovascular event. Lasmiditan (Reyvow™) is a newly FDA-approved drug that is indicated for acute treatment of migraine with or without aura in adults that is safe for patients who have cardiovascular risk factors. This new drug gives hope to many patients who have untreated migraine pain and has the potential to greatly change the current treatment guidelines for migraines.

A migraine is a neurological condition characterized as a very severe headache.[1] It can present with a variety of symptoms, but it is most commonly described as an intense head pounding that lasts from hours to days and can worsen upon movement or activity and exposure to bright light or noise.[1] Pain associated with migraines is normally on only one side of the head but is on both sides in about ⅓ of patients.[2] Nausea, vomiting, irritability, extreme sensitivity to light or sound, and tingling/numbness are commonly experienced with a migraine attack.[2] Classical migraines (also referred to as complicated migraines) start with an aura.[1] An aura usually precedes a migraine but can also follow a migraine. Auras can last from 15 to 30 minutes and are typically characterized by vision changes such as flashes of light, color, or patterns.[1] It could also be associated with loss of vision in an area of the field of vision. Common migraines do not have an aura associated with them.[1] Common migraines may last longer, have a slower onset, and interfere more with daily activities than classical migraines.[1] Common migraines are also more prevalent than classical migraines.[1]

Migraines are an increasingly prevalent neurological disease that affects over 1 billion people worldwide.[2] It is now ranked in the top three most prevalent illnesses worldwide and is considered the sixth most disabling illness.[2] About 85% of people who suffer from migraines are women, and 1 in 4 women experience a migraine in their lifetime.[2] Women are more likely than men to experience migraines because fluctuations in estrogen can cause an onset of a migraine.[2] Migraines due to estrogen fluctuations are usually more severe and more frequent.[2] Before puberty, boys are more likely to experience migraines than girls, but after puberty, girls are more likely to experience migraines.[2] Migraines also tend to be more frequent and severe in girls after puberty compared to boys after puberty.[2] While this neurological condition is more common in women, it does not discriminate as it also affects men and children.[2] Migraines alone are responsible for costing the United States over 157 million lost workdays annually and up to $36 billion in healthcare and lost productivity costs.[2]

Medications for migraine treatment belong in the drug classes of triptans, ergot alkaloids, and analgesics. While all of these classes are options, triptans were specifically designed for treating migraines and therefore, are the mainstay of migraine treatment.[3] Analgesics include ibuprofen, acetaminophen, and opioids and are typically only used for very mild migraines.[3] Although not specifically designed for migraine treatment alone, ergot alkaloids, are only successful in treating headache-related pain when used as pain relievers.[4] However, these medications are typically reserved as last-line for those who are unresponsive to analgesics or triptans for migraine relief.[3] Any kind of acute migraine treatment should not be used longer than 10 days per month because medication-overuse headaches can occur.[3]

Triptans are not only the mainstay of migraine treatment in general, but have also shown to be more effective in treating

moderate to severe migraine episodes than other analgesics.[3] There are 7 FDA-approved triptan medications which include sumatriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, and zolmitriptan. As a class, all triptans work as selective agonists for specific serotonin receptors in cranial arteries in an effort to cause vasoconstriction and alleviate inflammation.[5] Each triptan produces the desired effect by selectively activating the 5-HT_{1B} and 5-HT_{1D} receptors, with the exception of eletriptan which selectively activates 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors.[5]

Although triptans are successful in treating moderate to severe migraines with or without aura, they still have their own limitations. Although they are selective for specific serotonin receptor subtypes, they are not specific for the location of those subtypes. Triptans will activate the 5-HT_{1B} and 5-HT_{1D} receptors at any place those receptors may be located throughout the body.[6] The 5-HT_{1B} and 5-HT_{1D} receptors are found throughout the central nervous system as well as the vascular system; hence, activating these receptors can lead to vasoconstriction.[6,7] As a result of this, triptans are contraindicated in those with uncontrolled hypertension, ischemic heart disease, ischemic bowel disease, or a history of cerebrovascular syndromes such as stroke.[5]

Lasmiditan (Reyvow™) is a new oral drug with the indication of acute treatment of migraine with or without aura in adults that was recently approved in October of 2019.[5] Lasmiditan represents the first drug in a new class of medications for acute migraine treatment (5-HT_{1F} receptor agonists). Lasmiditan is unique because it is specific to 5-HT1F receptors, while triptans are not. Triptans cause vasoconstriction in the brain as well as the rest of the body which means that people with existing hypertension or other cardiovascular risk problems cannot take triptans due to the risk of worsening their cardiovascular health.[7] Lasmiditan does not have the same risk as triptans of worsening patients' cardiovascular health because it does not affect some receptors that cause vasoconstriction, unlike triptans.[7] This makes lasmiditan a novel new option for patients with cardiovascular risk factors who have an unmet need for acute migraine treatment.[7,8]

Lasmiditan's effectiveness has been shown in two double-blind, randomized clinical trials.[9] In these phase-3 studies included in the New Drug Application for lasmiditan, over 3,000 adult patients who suffer from migraines with and without aura received either lasmiditan (100 mg or 200 mg) or placebo. Two hours after taking either placebo or drug, the percentages of migraine pain resolution as well as resolution of the patients' most bothersome symptoms (nausea, light or sound sensitivity) was significantly higher with lasmiditan at any dose than with placebo.[10] These studies also showed that lasmiditan is generally well-tolerated. Adverse effects of lasmiditan in the phase-3 studies were mostly mild to moderate in severity and the most common were dizziness, fatigue, paresthesia, sedation, nausea, vomiting, and muscle weakness.[8]

In one phase 3 study, over 75% of patients had at least one cardiovascular risk factor in addition to migraines which is a strength of the study because it shows that patients with cardiovascular risk factors can take lasmiditan with successful results.[10] However, patients with known coronary artery disease, clinically significant arrhythmias, uncontrolled hypertension, and patients with >15 migraine days per month were excluded from the trial, which is a limitation because it is unclear how these patients would respond to the drug.[10] There are currently no contraindications listed in the manufacturer's labeling for lasmiditan.[5]

While lasmiditan shows a lot of promise as a new acute treatment for migraines, it does have limitations and side effects. 9-17% of patients reported experiencing dizziness with lasmiditan.[5] Other less frequent (<10%) side effects include paresthesia, chest discomfort, drowsiness, nausea, and vomiting.[5] Due to the CNS depressant effects, there is a significant risk of impairment while driving while taking lasmiditan.[9] Patients are advised not to drive within eight hours of taking lasmiditan.[9] Patients are also cautioned not to drink alcohol or use other CNS depressants while taking lasmiditan.[9] Furthermore, clinical trials have resulted in patients having symptoms consistent with serotonin syndrome while taking lasmiditan.[8] The risk of serotonin syndrome increases if patients are on other serotonergic drugs. Patients and providers are advised to discontinue lasmiditan immediately if serotonin syndrome is suspected.[8]

A precaution of lasmiditan that differs from the current mainstay of migraine treatment is its abuse potential. A study on human abuse potential compared lasmiditan to alprazolam 2 mg and placebo in recreational multi-drug users.[8] The lasmiditan doses studied were therapeutic doses of 100 mg and 200 mg as well as a supratherapeutic dose of 400 mg.[8] The study found that with all doses of lasmiditan, subjects reported higher "drug liking" than placebo, but lower "drug liking" than alprazolam.[8] The researches deemed these results statistically significant.[8] These results were attributed to the propensity of lasmiditan to cause euphoric mood when taken as 200 mg and 400 mg doses.[8] This adverse event occurred to a similar extent as alprazolam.[8] Conversely, subjects experienced more relaxed feelings with alprazolam than with lasmiditan, regardless of the lasmiditan dose.[8]

While phase 2 and phase 3 studies demonstrated that lasmiditan causes euphoria and hallucinations more than placebo, the incidence of these adverse events was low, occurring in only 1% of patients.[8] However, because lasmiditan does demonstrate significantly higher "drug liking" than placebo, each patient must be evaluated and observed for signs of drug abuse both prior to and during lasmiditan therapy. Lasmiditan is currently under review by the DEA for its controlled substance classification and is expected to be decided within 90 days of the drug's FDA approval date.[8] Once the classification is determined, lasmiditan will be available in community pharmacies.[8]

Moving forward, lasmiditan has great potential and is expected to positively impact the strategies for treating migraines. As migraines continue to incapacitate millions of people, the addition of new and successful therapies is warranted. Patients with a contraindication to triptans may now be able to effectively treat their migraines and increase the time they are pain-free.

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Leadership Development and Practical Application: A Comparison of Pharmacy Students and Pharmacists

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Abstract

Having leadership characteristics is important for a pharmacist to be successful throughout their career. The primary objective of this study was to analyze how pharmacists and pharmacy students developed their leadership skills by comparing the two groups to determine major differences in leadership development. The second objective was to determine how ready new pharmacist graduates are to hold a leadership position. Two different surveys were made specifically for pharmacy students and pharmacists. Surveys were delivered via email to pharmacy students and staff at the University of Findlay. Paper copies of surveys were given to retail pharmacists. When asked how likely it is for a new pharmacy graduate to obtain a leadership position within a community pharmacy setting, 50% of pharmacists and 28.6% of students said it is somewhat likely or very likely. Pharmacists most commonly cited working in a pharmacy (100%) as the source of their leadership development, while only 66.7% of students said that working in a pharmacy gave them their leadership traits. The majority of pharmacists agreed that new pharmacy graduates are likely to hold a leadership position within the field of pharmacy. Pharmacy students may be unaware of the potential to be selected for a leadership position upon graduation. The leadership traits that pharmacy students receive from college curriculum and extracurricular activities should be supplemented with experience working in a pharmacy to further improve their leadership.

Pharmacy is a field that fits into healthcare in many different ways. From verifying medications to vancomycin dose calculations, there is a broad range of jobs for a pharmacist. One pathway that exists in pharmacy, much like all other careers, is leadership and/or managerial positions. Pharmacists that are placed in these roles usually have significant experience, but at times pharmacists fresh out of school have been put right into leadership positions. For the new graduates that thrive in leadership positions the question has been raised, how do they learn what it takes to lead a pharmacy without having to gain several years of experience? For the new graduates that struggle in their new position, what could they have done differently in the past to improve their chance to excel in a leadership position? This leads to the curiosity of how prepared newly graduated pharmacists are for leadership roles. The objective of this research was to reveal what prepares new and experienced pharmacists the most for a leadership position, and how prepared they are to take on that type of leadership role.

A pharmacist needs to have many different qualities to be effective, but some are more important than others. The top characteristics, according to Thompson, Nuffer, and Brown, include communication, efficiency, professionalism, adaptability, knowledge, and being personable.[1] The development of these traits is an ongoing process, but having a solid foundation can set a pharmacist up for success during their career. Communication can be improved, (both verbal and non-verbal communication), through a combination of curriculum and practice experience in the job field.[1] The majority of pharmacy interns and supervisors believe that being a clinical leader was the most important job for a pharmacist.[2] This majority has been growing, as more and more people see the importance of a pharmacist being viewed as not just an expert of medicine, but a leader among their peers.

With its high level of importance, it is valuable to understand how leadership is developed. Preliminary research pointed to the collegiate institutions as having the duty to make sure their students would graduate with appropriate skills to lead in the pharmacy field. According to Bradley-Baker and Murphy, "Colleges and schools of pharmacy have a responsibility to incorporate leadership development opportunities throughout their curriculum in order to provide future practitioners with the knowledge, attitudes, and skills needed to implement positive change."[3] Schools of pharmacy can present these opportunities in several ways from required classes in the curriculum to Advanced Pharmacy Practice Experiences (APPEs). Existence of various opportunities results in the consideration of which method is most efficient for developing leadership among students. Leadership is a vital quality for a pharmacist to have, so knowing how to enhance this characteristic would impact both current and newly licensed pharmacists.

Methods

This study was conducted in Findlay, Ohio with participants consisting of pharmacists at the University of Findlay and

pharmacists in the retail setting. There were at least nine retail settings used in this research from at least six different companies in the Findlay, Ohio area. Two distinct surveys were created, one for pharmacy students and another for pharmacists, that were approved by The University of Findlay Institutional Review Board. Surveys were designed in Google Forms and were delivered to potential participants via email or in person with paper copies. Participants with paper copies were given one week to fill out the survey before it was collected in person.

The questions on both surveys were all presented as multiple choice questions. For some questions, participants had an option to write in their own answer. This was an option on all of the questions where more than one answer could be chosen (select all that apply). This was done by creating select all that apply style of questions for participants to select as many responses they thought pertained to their leadership development. All other questions consisted of a Likert scale format that gave five options to choose from.

Participant inclusion criteria consisted of pharmacy students in an accredited college of pharmacy program and pharmacists in any stage of their career. The student population that was surveyed was the current pharmacy students at The University of Findlay, while the pharmacist population consisted of both professors of The University of Findlay and registered pharmacists in the community setting of Findlay, Ohio.

Knowledge Check: True or False?
The survey questions used to collect data consisted of extended response style questions.

Answer: False

Results

There were a total of 42 surveys submitted by pharmacy students. The breakdown in the number of participants by class year is listed in Table 1. There were 18 pharmacists that submitted surveys for this research. The breakdown in the years of experience for pharmacist participants is listed in Table 1. For the answers to each question there is a breakdown of how many students and pharmacists selected the specific options presented. Percentages of students and pharmacists that selected each answer choice for each question also accompanies each possible answer in Figures 1, 2, 3 and 4.

Data analysis yielded important statistics that showed differences between student and pharmacist answers. 50% of pharmacists said it is somewhat likely or very likely that a new graduate would get a leadership position in a pharmacy within one year of graduating from pharmacy school. This differed from what current pharmacy students thought about obtaining a leadership position upon graduation. 28.6% of students

said it would be somewhat likely or very likely for a new graduate to get a leadership position in a pharmacy within one year of graduation. Along with this, pharmacists have also seen multiple new graduates get placed in a managerial role in their careers. 66.7% of pharmacists throughout their careers have seen three or more new graduates elevated to a leadership role in a pharmacy.

Other important statistics portray how pharmacists and current students have developed their leadership skills they currently possess. When asked where their leadership skills came from, every pharmacist said working in a pharmacy. While only 7.1% (1 person) of pharmacists selected college curriculum as a source for the majority of leadership development. The students were presented these questions in the exact same format as pharmacists, but had differing numbers in this area of the research. 35.7% of pharmacy students said a majority of their leadership skills have developed from college curriculum. It is worthy to note that 35.7% of pharmacy students that participated did not have a job in a pharmacy. All other data is shown in a chart below for each question and answer.

Table 1. Survey Participants by Career Standing and Experience Level

Survey Responses from Active Pharmacy Student's by Year				
P1: 6 people	**P2:** 5 people	**P3:** 6 people	**P4:** 6 People	**P5:** 19 people
Survey Responses from Active Pharmacists by Experience				
0-5 years: 2 people	**6-10 years:** 3 people	**11-15 years:** 3 people	**16-20 years:** 4 people	**Over 20 years:** 6 people

Figure 1. Leadership Position Likeliness, Pharmacist Perspective

How likely is it for a newly graduated pharmacist to obtain a leadership position in a pharmacy within a year of graduation?

18 responses

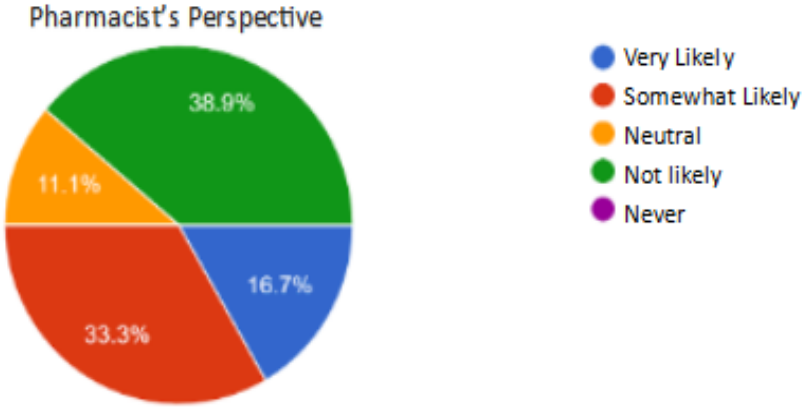


Figure 2. Leadership Position Likeliness, Student Perspective

How likely is it for newly graduated pharmacists to obtain a leadership position in a pharmacy within one year of graduation?

42 responses

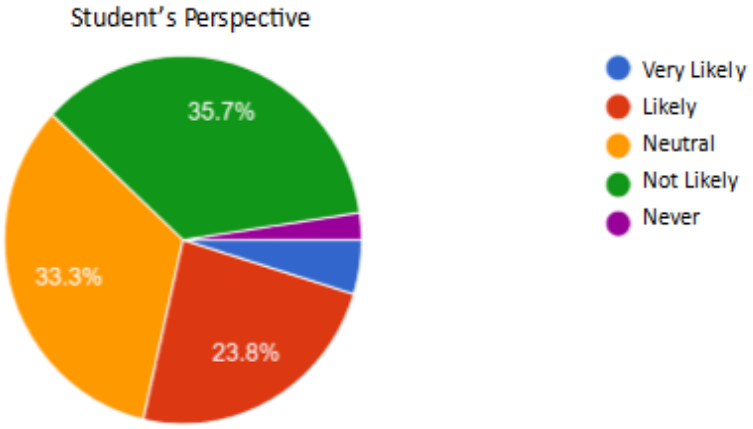


Figure 3. Leadership Skill Development, Pharmacist's Perspective

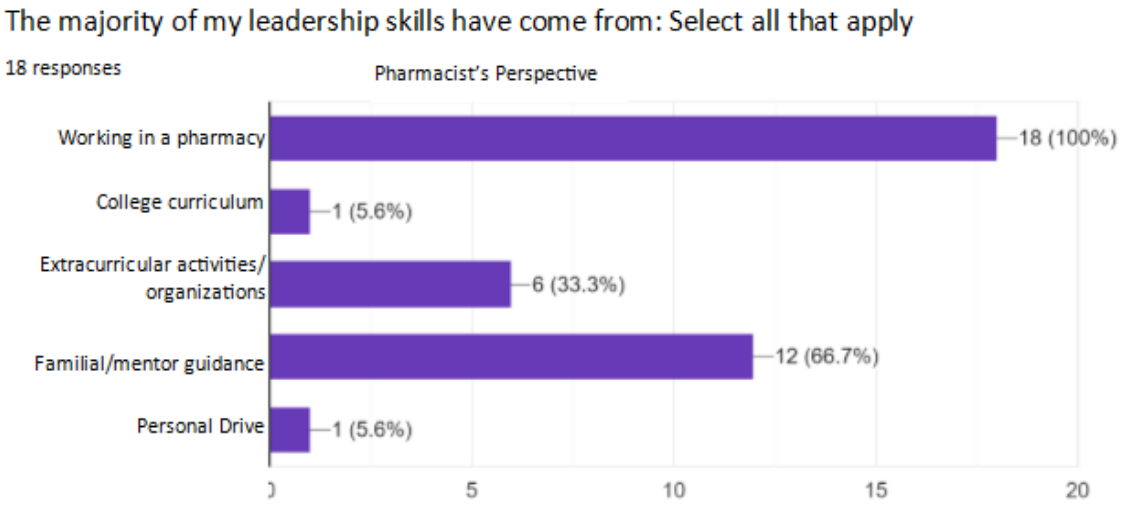
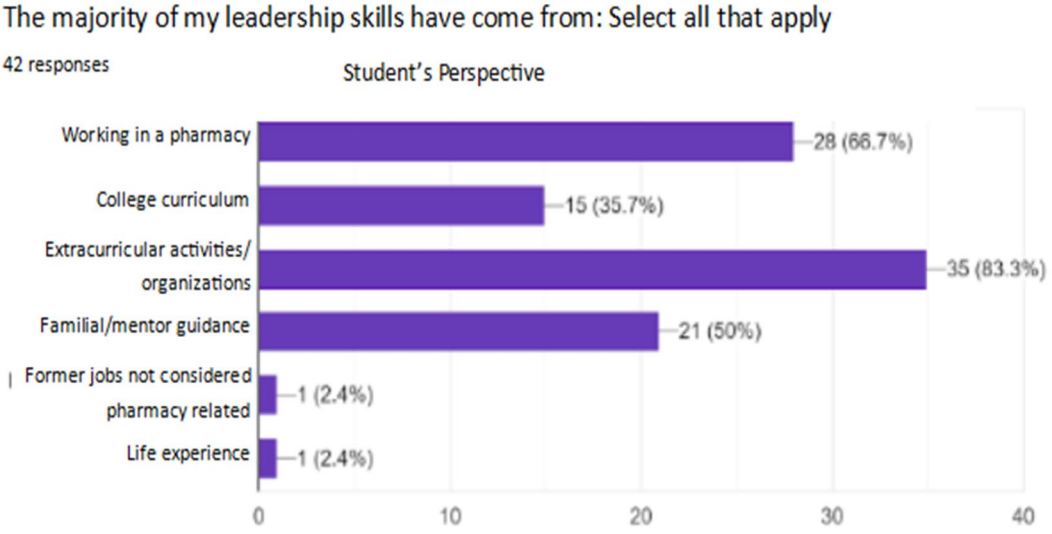


Figure 4. Leadership Skills Development, Student's Perspective



Conclusion

One major difference between pharmacists and pharmacy students is how likely they believe that newly graduated pharmacists are to obtain a leadership position. Pharmacists that have experience believe that a newly graduated pharmacist is likely to obtain a leadership position. This could be due to multiple different reasons. The first is from actually seeing newly graduated pharmacists obtaining leadership positions. This would be a very good indicator that would show differences between how pharmacists and students view the pharmacy field. Hiring and promotion to leadership positions is something that a pharmacy student would not experience unless they were actually working and directly involved in those scenarios. The second possible reason why pharmacists have this belief is because of how students are trained in college. Pharmacists with experience have seen potential changes within the pharmacy field, and one of those changes could be how students grow as leaders in college. College is always changing, and the way that students develop their leadership skills has changed and grown over time.

There is a disconnect between practicing pharmacists and pharmacy students about where leadership traits are developed. Both groups agree that they are developed by experience, but that experience differs slightly between the two groups. While pharmacists mainly got leadership experience from working in a pharmacy, students developed their leadership mainly from experiences in extracurricular activities, but partially from working in a pharmacy and college curriculum. This difference in leadership development could be due to multiple factors, including changes in college curriculum and emphasis on extracurricular involvement, or from students having limited experience working in a pharmacy. With more time spent in a pharmacy and holding leadership positions within their place of employment, pharmacy students would gain leadership skills that current practicing pharmacists already have.

The change in leadership development could lead to positive progression in the field of pharmacy. These changes could be positive because students would be able to take the leadership skills they learned in college curricula and extracurricular activities and supplement them with skills and traits they learn from working in a pharmacy as an intern and eventually a pharmacist. The more experience someone has in a leadership position, the better a leader they become. When a student graduates from college and holds their first leadership position, they are not going to be a fully developed leader yet. However, if they have previous experience in the college setting, they will at least have a base that they can continue to build up as they work as a pharmacist.

Strengths of the research included the comparison of thoughts between students and current practicing pharmacists,

the broad range of retail companies from which data was gathered, and a varying amount of experience levels from students to pharmacists. Weaknesses of the study included the small number of participants and participants being located in one geographical area. Future research within this area of pharmacy could pertain to how encouraged students are to obtain an internship or technician position while in college. Another area that can be researched in the future is looking deeper at what aspects of a student's life developed leadership skills best for them to become successful pharmacists. This study offers preliminary data and statistics on the area of leadership within pharmacy. While clinical knowledge is important, the impact of great leadership will continue to further the field of pharmacy and thus cannot be ignored.

Knowledge Check:
Which of the following are top characteristics for a pharmacist to have in order to be effective?

A. Communication
B. Professionalism
C. Selfishness
D. Efficiency

Answer: A,B,D

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Shingrix®: An Overview for Pharmacists

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Abstract

Shingrix® is a recombinant zoster vaccine (RZV) that contains a varicella zoster virus glycoprotein E antigen and the AS01B adjuvant system. This subunit vaccine is approved for the prevention of herpes zoster also known as shingles. A quarter of the population is at risk of developing herpes zoster during their lifetime and two thirds of people with the disease are aged 50 years or older.[1] With the rise in adults aged 50 years or older in the United States due to the aging "baby boomer" generation, it is important that health care providers are properly educated and armed with the information that is needed to understand, educate and administer the Shingrix® vaccination for their patients. It is important that healthcare professionals are comfortable navigating the challenges that result from the novelty of a new herpes zoster vaccine in order to ensure that their patients are effectively covered.

Primary varicella infection is typically seen in children as chickenpox, a disease that's characterized by a rash that progresses to lesions and is commonly accompanied by a fever.[2] Herpes zoster also known as shingles is primarily a disease of sensory nerve ganglia caused by the reactivation of the varicella zoster virus. The virus can remain in a latent state in the nerve ganglia for many years, and with waning immunity the reactivation of the virus results in herpes zoster.[2]

Herpes zoster presents as a painful vesicular rash which is usually distributed in a unilateral and dermatomal pattern along the dorsal root ganglia.[3] Pain is typically the first symptom followed by a rash within two to three days.[3] The site of the rash is usually hyperesthetic and accompanied by severe pain and lesions may continue to form for about three to five days.[3] Postherpetic neuralgia or persistent or recurrent pain, which can last indefinitely, may occur particularly in older patients as a result of a herpes zoster outbreak.[3]

Acute treatment for herpes zoster consists primarily of antiviral therapy and symptomatic treatment. Preventative treatment, however, is often effective and strongly recommended, particularly in older adults who may have been exposed to the primary varicella infection as a child.[3]

Since 2006, Zostavax®, a live attenuated vaccine, has been used as a preventative treatment for herpes zoster.[3] In 2017, a recombinant subunit vaccine, Shingrix®, was approved by the FDA and is now recommended by the Advisory Committee on Immunization Practices as the preferred vaccine for the prevention of shingles.[3]

Shingrix® is a non-live, recombinant subunit vaccine and a combination of an antigen (glycoprotein E), and an adjuvant system (AS01B).[4] That generates a long-term immune response.[5] The AS01B adjuvant induces a local and transient activation of the innate immune system by two immune enhancers: MPL, which signals through Toll-like Receptor 4; and QS-21, which acts through unknown receptors.[5] These two agonists activate antigen presenting cells that enable the recruitment of naive CD4+ T cells.[5]

Drug properties

The Varicella Zoster Vaccine, Shingrix®, is clinically indicated for the prevention of herpes zoster in patients 50 years of age or older.[6] The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of immunocompetent patients 50 years of age or older including those previously vaccinated with Zostavax® who report a previous episode of zoster and patients with chronic medical conditions.[6]

Shingrix® requires reconstitution before administration, and should be administered intramuscularly, preferably in the deltoid muscle of the upper arm.[6] An injection of 0.5 mLs is recommended to be administered as a 2 dose series, with the second dose administered 2 to 6 months after

the first dose.[6] There are no renal or hepatic adjustments required with administration of the vaccine.[6] The unopened vials of vaccine and adjuvant should be stored in the refrigerator, and after reconstitution can be stored under refrigeration for up to 6 hours.[6] If the vaccine has been frozen, or if reconstituted and not used within 6 hours, it should not be used and should be discarded.[6] The suspension of the reconstituted vaccine should be an opalescent, colorless to pale brownish liquid.[6]

The use of Shingrix® is contraindicated if a patient has had a severe hypersensitivity reaction to recombinant zoster vaccine or any component of the formulation.[6] The most frequently reported side effects include: pain, redness and swelling at the injection site, myalgia, loss of strength and energy, headache, shivering, nausea, vomiting, diarrhea, and abdominal pain.[6] Drug interactions include acetaminophen (category risk D: consider therapy modification), fingolimod (category risk D: consider therapy modification), immunosuppressants (category risk D: consider therapy modification), siponimod (category risk D: consider therapy modification), and venetoclax (category risk C: monitor therapy).[6] There is currently no generic available and pricing is about $173.04 per dose of vaccine.[6]

Review of Clinical Recommendations

The ACIP of the Centers for Disease Control (CDC) is the body responsible for making recommendations on vaccinations for the general public.[7] Currently ACIP recommends two licensed products for the prevention of herpes zoster. These products are Zostavax® and Shingrix®, with Shingrix® being the generally preferred agent of the two options.[7] It is recommended that patients 50 years of age or older that do not have a compromised immune system receive 2 doses of 0.5mL of Shingrix®, the first dose at the first visit and then another dose separated by 2 to 6 months.[7] If there is more than 6 months between doses the second dose should still be administered and the series does not need to be restarted.[7] However, if the second dose is given earlier than 4 weeks after the first dose, the second dose must be given again at the correct time interval.[7]

It is important to note that Shingrix® can be administered to a patient that has a minor acute illness, such as a cold.[7] Patients who have a severe anaphylaxis reaction to the vaccine or any of the components as well as patients that are currently infected with herpes zoster, should not receive the vaccine.[7] Shingrix® has not yet been studied in the pregnant or breastfeeding population and should be avoided at this time.[7]

If a patient is allergic to Shingrix®, prefers Zostavax®, or if the patient demands to be immunized and Shringrix® is unavailable, the ACIP recommends to vaccinate with Zostavax®.[7] If the patient does receive Zostavax® and later wants Shingrix®, there must be at least an 8 week interval before Shingrix® can be administered to that patient.[7]

In patients that are immunocompromised, it is important to note that ACIP has not yet made a recommendation for vaccination of this population, as these subjects were not included in clinical trials.[7] These patients also should not receive Zostavax® since, as a live vaccine, it is contraindicated in persons who are immunodeficient or immunocompromised due to disease or therapy. Further trials also need to be established to evaluate Shingrix® in this patient population.[7]

Comparison to Zostavax®

Zostavax® was marketed in 2006 and was the only vaccine available for herpes zoster until Shingrix® was released.[7] Currently, the CDC recommends Shingrix® as the preferred vaccine in the prevention of herpes zoster.[7] While there are no direct head-to-head trials comparing the efficacy between Shingrix® over Zostavax®, there are data in the clinical literature that present efficacy data for each of the two vaccines.

When comparing the efficacy of Zostavax® and Shingrix®, the CDC evaluated clinical trials for both vaccines in the United States. Zostavax® was shown to reduce the incidence of herpes zoster by approximately 51%. It was also shown, however, that the older the subject was, the less effective the vaccine was at preventing herpes zoster. It was estimated that efficacy was approximately 70% for ages 50-59 and declined to around 38% once a patient reached 70 years or older in age. Along with the decline in efficacy based on a patient's age, there was also a decline in the protection a patient had after vaccination.[7,8] After approximately 6 years, protection by the vaccine declined to 35% of the time.[7]

In comparison, in two large clinical trials, ZOE-50 and ZOE-70, it was shown that Shringrix® reduced the risk of herpes zoster in 97% of subjects 50-59 years old, and 91% in subjects aged 70 years or older; within those 70 years of age or older, protection was approximately 85% after 4 years from vaccination.[7,8]

The findings of these clinical trials have been influential in the recommendation of Shingrix® in clinical practice. Currently, more clinical trials are underway to evaluate the efficacy of this vaccine in populations not yet established.

Managing the Shortage

Many providers and pharmacies have had difficulty obtaining Shingrix® vaccine due to drug shortage. Because of its recent FDA approval and its CDC recommendation of use over Zostavax® (zoster live vaccine), the demand has outpaced the supply. In September of 2018, GlaxoSmithKline issued a statement indicating "the accelerated adoption of Shingrix® has led to an unprecedented level of demand," and that they were working on manufacturing more doses of the vaccine.[12] The shortage has led to issues including pharmacists and providers not starting the vaccine series in patients who are indicated because they are concerned a second dose won't be available or because

they are reserving their supply for those who need their second dose.[12]

The CDC acknowledged the shortage and has provided some guidance to providers to help them manage the issue.[12] One important point that they highlighted was educating patients on completing the two-dose series.[12] The CDC acknowledges that patients may remain at risk for herpes zoster if the interval between doses one and two remains longer than the 6 month period.[12] They recommend that if more than 6 months after the first dose has passed, the second dose should still be administered as soon as possible and that the series does not need to be restarted.[12] The second dose of Shingrix® should not be substituted with Zostavax®.[12] Other tips include using www.vaccinefinder.org to find providers who have the vaccine in stock or implementing an e-mail, phone, or text messaging system to alert a patient when a preferred pharmacy or physician office has the vaccine in stock.[12] To keep patients in the loop, the CDC recommends having a waiting list and advising patients to periodically check on vaccine availability.[12]

Cost-effectiveness

Shingrix® has been shown to be effective but one question that remains is, "How cost effective is it?". Randomized control trials show that Shingrix® reduces incidence of herpes zoster by 97% among those 50 years or older and is highly effective even after the age of 70.[9] In a study conducted by Le et al, a cost-effectiveness analysis was conducted comparing Shingrix® to Zostavax® to determine which is more cost-effective.[9]

A Markov model was simulated based on studies conducted from July 1st to July 31st, 2017 comparing no vaccination, vaccination with Zostavax® (1 dose) or vaccination with Shingrix® (2 doses, 2 months apart).[9] Analyses were conducted for persons 60, 70 and 80 year of age.[9] Follow up was 1 year and the primary efficacy endpoint was either experiencing shingles or attendant complications.[9] Incremental cost effectiveness ratios (ICERs) were conducted for costs divided by quality adjusted life years (QALYs), and willingness-to-pay (WTP) thresholds were chosen as $50,000 per QALY by the authors since there is no standard willingness-to-pay threshold in the United States.[9] Costs included direct medical costs and productivity losses.[9] Costs were adjusted for inflation using the Consumer Price Index for Medical Care and expressed in 2016 US dollars.[9] Costs for Zostavax® were based on the Centers for Disease Control and Prevention, and Shingrix® was assumed to be $280 for a 2 dose regimen because at the time of the study it was not yet licensed.[9] Other costs included administration costs based on Medicare's national reimbursement rate, travel and productivity losses for the second dose and productivity losses based on local reactions and hospitalizations.[9] Sensitivity analyses were conducted varying the cost of WTP values, costs for the Shingrix® vaccination, varying adherence and efficacy rates, and varying and excluding different costs.[9]

Based on conducted ICERs for vaccinations at the ages of 60, 70 and 80 years, Shingrix® was shown consistently to be more effective and less expensive than Zostavax® and thus dominated the live vaccine.[9] Sensitivity analyses showed that, at the current price of Zostavax®, Shingrix® would be less costly than Zostavax® up to a price of $350 per series and cost-effective up to a cost of $359 per series.[9] This is important because the current price of the Shingrix® series does fall below both of these prices.[9] Overall, regarding efficacy, duration, vaccine price, and probability of having herpes zoster with-in 12 months or longer after the vaccination, Shingrix® was never shown to be more expensive than Zostavax® and was more effective and less expensive.[9] The findings were insensitive to most model inputs, as long as the adherence to the second dose exceeded 50%.[9] The authors do mention that the updated ACIP recommendation stating a preference for Shingrix® over Zostavax® could affect the results of the study.[9]

Patient and Provider Education

As previously stated Shingrix® is indicated for immunocompetent adults aged 50 years and older. Shingles affects approximately 1 in 3 individuals during their lifetime and affects half of all individuals who live to the age of 85 years or older.[10] The CDC recommends that most adults 50 years and older receive the new shingles vaccine regardless of whether the patient has had chickenpox, shingles in the past, or has been vaccinated with Zostavax®.[10] In adults 50 to 69 years old who received two doses, Shingrix® was 97% effective in preventing shingles; among adults 70 years and older, Shingrix® was 91% effective.[10] In adults 50 to 69 years old who received two doses, Shingrix® was 91% effective in preventing postherpetic neuralgia, and was 89% effective in preventing PHN; among adults 70 years and older.[10]

Pharmacists play an integral role in ensuring that patients receive the vaccinations that they require. Therefore, it is incredibly important for pharmacists to increase their knowledge and awareness regarding vaccination with Shingrix®. Pharmacists should be aware that the vaccine is indicated for adults aged 50 years or older and should engage those individuals in a discussion about being eligible for vaccination with Shingrix®.[11] Pharmacists should understand the importance of adhering to the vaccination schedule for the vaccine. To help ensure series completion pharmacists should schedule their patient's for the second dose of Shingrix® anytime between 2 and 6 months after the first dose.[11] Pharmacists will need to manage the timing of the vaccinations in conjunction with the high demand for Shingrix® and the low supply. Patients should be referred to another provider in the community if they are due for their second dose and their original provider does not have a sufficient supply of Shingrix®.[7] Pharmacists should be sure that their patient's vaccination information is current with the state's immunization information system. This will help other providers access the patient's immunization

record, and it may help facilitate patient reminders to complete the Shingrix® series of doses. Pharmacists will also have to navigate questions concerning common adverse reactions to the vaccination such as pain, redness, and swelling at the injection site and understand the potential risks for various patient populations.

Conclusion

Shingrix® is a recombinant zoster vaccine (RZV) that was approved in 2017 for the prevention of herpes zoster, also known as shingles, in patients 50 years and older. Shingrix® appears to have greater efficacy and cost effectiveness against herpes zoster based on individual trials with either Shingrix® or the live zoster vaccine, Zostavax®. The CDC is a comprehensive resource that can provide pharmacists with education and help during challenging situations, such as a medication shortage. It is important that healthcare professionals, especially pharmacists, are well informed and up-to-date on their vaccination education in order to provide the best care for each individual patient.

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Antimicrobial Resistance: Updates to an Ongoing Global Crisis

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Abstract

Antimicrobial resistance is a threat that can no longer be ignored. Resistant bacteria pose a global threat that if not controlled, could be catastrophic. Antibiotics are used for many reasons other than treatment of infections in the 21st century, however their appropriateness in certain fields is being scrutinized by organizations like the CDC and FDA. In order to combat this, the CDC has invested in surveillance of resistant bacteria, antimicrobial stewardship programs, and many other areas of healthcare and public safety. Their 2013 report called great attention to the issue, and the 2019 update sheds light on just how much more work still needs to be done. Progress has been made to deter the resistant bacteria, but it will take a much larger scale, global effort in order to ensure the safety of the human population going forward.

Background

Antibiotic resistance is a rapidly developing issue in the field of healthcare, and in 2014, the White House announced the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB).[1] The CDC reports that more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result of these infections.[2] Bacteria develop resistance to antibiotics almost since the advent of them. However, only in the past few years have we started to recognize the true dangers of highly resistant organisms. Dangers such as multi-drug resistant (MDR) and even pan-resistant (organisms resisting all current therapeutic options) bacteria cause infections that are very difficult to treat, often leading to hospitalizations which necessitate the use of antibiotics that are considered our last line of defense. There are many possible factors leading to the development of resistance, including the widespread use of antibiotics in animal agriculture, overprescribing and misuse of antibiotics for viral infections, and increasing toxicities and black box warnings being issued by the FDA during post-market surveillance leaving prescribers with fewer and fewer options. Desptie all signs pointing to potentially catastrophic effects, only in the past few years has an effort been conducted to combat the issue.

Sources of Antimicrobial Resistance

The first step to slowing resistance is to identify and control the source. Developing and approving new antimicrobial agents is a process that takes time and it alone is not enough to slow resistance due to organisms' ability to adapt and resist new medications. Especially at the very slow rate that new antimicrobials have been developed and subsequently approved by the FDA, it is unlikely that drug companies would be able to keep up with the rates of resistance as older antibiotics become obsolete and the new ones replace them as the standard of care. According to a report by the World Health Organization (WHO), there has been a void in discovery/development of new antimicrobial agents since the late 1980s.[3] However, the number of antibiotics being submitted has started to increase very recently. As more antibiotics get approved, this source of antimicrobial resistance will shrink.

Another source of resistance that has been identified is overuse of antibiotics. In 1950, a study performed by American Cyanamid found that adding antibiotics to live-stock feed accelerated animal growth rates and dramatically changed the way farmers saw animal nutrition.[4] Shortly after this article was published, the use of antibiotics became more widespread for growth promotion and routine disease prevention. Despite warnings later published by the *New England Journal of Medicine*,[4] antibiotics continued to be routinely used in animal agriculture for growth promotion, feed efficiency, and disease prevention. This effect snowballed until the vast majority of antibiotics consumed in the United States were being used for these purposes, with human use of antibiotics only making up a very small portion of the total.[4] Even more concerning is the fact that of the over 9 million kg of active drug material purchased in 2013 for agricultural purposes, most of the sales were without any veterinary oversight.[4] Since then, the FDA responded in 2017 by

releasing a Guidance for Industry (GFI) document regarding the use of antibiotics in food and food-producing animals. In this document the FDA proposed two main rules to combat antimicrobial resistance: "(1) limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and (2) limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation."[5] This document attempted to solve theses two issues by preventing over the counter purchase of antibiotics, and removing the indication for "increased rate of weight gain" or "improved feed efficiency."[5] Looking at Table 1 in the Appendix, since the full implementation of GFI 213, the use of antibiotics for production purposes has dropped to 0 as it is no longer allowed by the FDA. However, it should be noted that a majority of the antibiotic use shifted to therapeutic use only. Since the FDA still considers the use of antibiotics for prevention of infection as "therapeutic use only," there is still much work to be done in defining the appropriate instances to use antibiotics in these animals so that the total amount of antibiotics being used annually drops significantly. Fortunately, the FDA and CDC are working closely together on this issue and more regulatory updates are coming in the future to ensure the safety of the human population.

Overuse of antibiotics isn't limited only to agriculture. Another source of resistance that has been suggested is unnecessary prescribing of antibiotics to patients without infections. The CDC is working to control this by funding antimicrobial stewardship programs in institutions across the United States.[6]

Effects on the Healthcare System

There are many uses for antibiotics aside from the treatment of bacterial infections. This is yet another factor contributing to antimicrobial resistance that must be considered when discussing the impact and the burden placed on the healthcare system and the population at large. There are some concerning situations that are likely to play out in a world where we no longer have effective antibioitcs. For example, antibiotics are routinely used in surgical procedures, cesarean sections in pregnant woman, and to paitents receiving chemotherapy. In any and all of these scenarios, patient outcomes would be much worse without antibiotics to protect against opportunistic infections. The British Medical Journal estimates that without antibiotic prophylaxis as a standard of care for hip replacement, the rates of infection will jump from 0.5-2% to 40-50%.[7] They also estimate that about 30% of those patients could die without proper antibiotics to fight the infection.[7] Of course, if this were the case, the rates of hip replacements would likely decrease, but that would also come along with reduced quality adjusted life years (QALYs) for patients and thus increased morbidity of hip pain.

Another negative impact of antimicrobial resistance is the economic burden it places on the healthcare system. Although it has been very difficult for researchers to quantify the economic burden of antimicrobial resistance, one study in 2002 estimated the total costs at roughly 55 billion USD.[8] However, it is estimated that the number would in fact be much higher.[7] A more recent review from 2013 would agree

with this thought, stating that the societal burden is closer to 150 billion USD.[9] The longer it takes for meaningful action to be taken, the more organisms will become resistant, and the more lives will be lost. There has yet to be an economic study with a better method for measuring the economic impact of antimicrobial resistance and it may take more time before we truly know how it compares to other diseases facing us today. However, it is not all bad news, as the CDC has recently updated their plan for combating antimicrobial resistance in 2019.

Action Plan

The CDC has been at the forefront of solving the antimicrobial resistance issue that we are currently facing. In the 2019 CDC update to *Antibiotic Resistance Threats in the United States*, CDC director Robert Redfield, MD, warned of some of the most important things to consider about the fight we are facing today. First, he suggested that we must realize that the post-antibiotic era is already here, and that we need to stop referring to it as if it is in the future.[6] In doing this, the threat seems further from us than it is in reality, possibly hindering progress toward solving the issue. He also advises that we must not rely solely on new antibiotics coming to market, for the reasons previously discussed in this article.[6] He ends his letter by outlining what will work to combat antimicrobial resistance, including prevention (whether it be hand washing or vaccinations), practicing antimicrobial stewardship, and detecting organisms that pose a threat before it is too late.[6]

The words of Dr. Redfield relate closely to the plan being implemented by the CDC. Their plan is not simple; it is as multifaceted as the issue itself, and it involves many organizations and individuals doing their part to combat the issue. They have invested over 300 milion USD in 59 state and local health departments to detect and prevent resistant threats.[6] They are taking advantage of new technologies such as whole genome sequencing in order to shed light on what may be the best way to attack the resistant organisms.[6] Another way they are combating resistance is investing in antimicrobial stewardship programs, which has helped decrease outpatient antibiotic prescribing by 5% in adults and by 16% in children.[6] The goal in this scenario is to prevent unnecessary prescribing of antibiotics to people complaining of cold and/or flu symptoms, as mentioned previously.

In the 2013 report on antimicrobial resistance, the CDC identified some of the major gaps in knowledge that needed to be more well understood and better funded. Since then, some of these knowledge gaps have closed, but there are still more that must be investigated further. The core actions that the CDC has proposed in 2019 seek to close the gaps in knowledge in the areas of infection prevention and control (immunization, sanitation, hand-washing, etc.), tracking and data, antibiotic use and access, vaccines, therapeutics, and diagnostics.[6] Many of these areas have been much improved since the 2013 report thanks to funding by the CDC through congressional approval.

However, antimicrobial resistance remains a global issue, and much more work must be done to contain and control the spread of infections as a whole in countries other than the United States.

Conclusions

In summary, there have been many advancements made thanks to the CDC and the FDA in combating antimicrobial resistance, but more work still needs to be done. In their 2019 report, the CDC calls upon everyone to do their part in combating antimicrobial resistance, stating that it will require a globally combined effort to get the situation under control. This means whether you are a regular citizen or someone in a healthcare profession, your efforts are needed in order to save the planet from the threat of deadly, resistant bacteria. From hand-washing to practicing antimicrobial stewardship, everyone can make a difference and doing so is crucial, now more than ever.

Appendix

Table 1	Indications		
	Production or Production/ Therapeutic Indications	**Therapeutic Indications Only**	**Total**
2009 Annual Totals (kg)[3]	5,563,029	2,123,536	**7,686,564**
2010 Annual Totals (kg)[3]	5,828,079	2,401,230	**8,229,309**
2011 Annual Totals (kg)[3]	5,770,871	2,484,827	**8,225,697**
2012 Annual Totals (kg)[3]	6,073,485	2,823,935	**8,897,420**
2013 Annual Totals (kg)[3]	6,664,835	2,528,458	**9,193,293**
2014 Annual Totals (kg)[3]	6,790,996,	2,688,343	**9,479,339**
2015 Annual Totals (kg)[3]	6,917,639	2,688,343	**9,702,943**
2016 Annual Totals (kg)[3]	5,770,655	2,585,685	**8,356,340**
2017 Annual Totals (kg)[3]	0*	5,559,212*	**5,559,212**
2018 Annual Totals (kg)[3]	0*	6,036,140	**6,036,140**
% Change 2009 – 2018	-100%	184%	**-21%**
% Change 2017 – 2018	**	9%	**9%**

Table 2					
Species	**2016 Estimated Annual Totals (kg)[3]**	**2017 Estimated Annual Totals (kg)[3]**	**2018 Estimated Annual Totals (kg)[3]**	**% Change 2016-2018**	**% Change 2017-2018**
Cattle	3,605,543	2,333,839	2,521,157	-30%	8%
Swine	3,133,262	2,022,932	2,374,348	-24%	17%
Chicken	508,800	268,047	221,774	-56%	-17%
Turkey	756,620	670,108	671,108	-11%	<1%
Other	352,114	263,564	247,753	-30%	-6%
Total	**8,356,340**	**5,559,212**	**6,036,140**	**-28%**	**9%**

Medically important antimicrobial drugs approved for use in food-producing animals
Actively marketed in 2016-2018
Domestic sales and distribution data
Reported by species-specific estimated sales

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Novel Drug Review of Select Neurologic Drugs Approved in 2019

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Abstract

Each year, the Food and Drug Administration (FDA) releases a comprehensive list of all novel drugs approved throughout the year. The FDA's Center for Drug Evaluation and Research strives to approve new drugs to fill the gaps in healthcare of unmet needs of patients. This article focuses on select novel drugs approved in 2019, specifically for neurologic conditions. Drugs included are Cyplyta, a second-generation antipsychotic used in the maintenance of schizophrenia; Ubrelvy, a CGRP antagonist used for acute migraine attacks; Zulresso, the first drug treatment indicated for postpartum depression; and Wakix, the first noncontrolled treatment for excessive daytime sleepiness in narcoleptic patients.

Each year the Food and Drug Administration's Center for Drug Evaluation and Research develops a report including novel drugs approved throughout the year.[1] These drugs are new and innovative drugs that have never been seen on the market before.[1] As healthcare is evolving, new drug approvals allow patients quality treatments and relief to symptoms of disease states that were previously unmet.[1] In 2019, 48 novel drugs were approved as either new molecular entities or biologics license application.[1]

Nearly 1 billion people in the world suffer from a neurologic condition.[2] These conditions range from migraines, Alzheimer's, Parkinson's and strokes to mental health disorders.[2] This article examines select drugs targeted toward specific neurologic conditions approved by the FDA in 2019.

Caplyta (lumateperone)

Schizophrenia is a severe, chronic disease effecting approximately 2.6 million adults in the United States.[3] Schizophrenia may be effectively treated, however noncompliance among patients is common due to factors of unintentional nonadherence as a result of distressing medication side effects.[4] Schizophrenia treatment is extremely individualized and must consider how side effects, medication regimens, and drug-drug interactions will affect each patient to optimize their treatment.[4]

In response to the need for a diverse variety of antipsychotic medications, the FDA recently approved Caplyta.[5] Caplyta is a first-in-class drug which selectively modulates serotonin, dopamine, and glutamate receptors.[5-7] Several second-generation antipsychotics are known for their partial agonism of D2 receptors and inhibition of 5-HT2 receptors which help control positive symptoms in the mesolimbic and mesocorticol parts of the brain.[6,7] The advantage of Caplyta is the potential increase in phosphorylation at NMDA receptors.[7] This combination of pharmacologic actions may enhance sleep while decreasing aggression and agitation at lower doses. At higher doses, this combination may produce an antipsychotic and antidepressant effect.[5-7] Due to the drug's modulation of NMDA receptors, with further studies, researchers hope to prove Caplyta's ability to increase cognition as well.[7]

As with many antipsychotics, Caplyta carries a boxed warning for increased mortality in elderly patients with dementia-related psychosis.[5-7] Caplyta should not be used in patients with hematological disease or severe liver disease.[5,6] Patients should be monitored for tardive dyskinesias, hypotension, cognitive effects, and motor stability.[5,6] Patients with dysphagia, who are at risk for aspiration pneumonia or seizures should be closely monitored while taking Caplyta.[6]

Ubrelvy (ubrogepant)

Migraine is a debilitating condition which affects about 37 million people in the United States.[8] Recently, the FDA has approved, Ubrelvy, the first oral calcitonin gene-related peptide (CGRP) antagonist to diminish acute migraine attacks.[8-10] CGRP is distributed throughout the central nervous system, specifically in places involved in migraine pathophysiology.[10] During a migraine attack the blood vessels in the brain vasodilate due to an increase in CGRP.

Ubrelvy's main mechanism is to decrease CGRP to cause vasoconstriction.[10]

The effectiveness of Ubrelvy for the acute treatment of migraines was shown in two randomized, double-blind, placebo-controlled trials of 1,439 patients.[9] In this study patients who took Ubrelvy had a significant reduction in pain and migraine symptoms such as nausea and light or sound sensitivity when compared to the placebo.[9,10] Ubrelvy is contraindicated in concomitant use with strong CYP3A4 inhibitors.[8-10] A patient should not use Ubrelvy if he/she has severe renal impairment (CrCl <15 mL/min) or severe hepatic impairment.[10] Side effects of this medication include nausea, dry mouth, and sedation.[9,10]

Zulresso (brexanolone)

In the United State alone approximately 1 in 7 women will experience postpartum depression (PPD) within the first year after giving birth.[11,12] PPD is a serious mood disorder causing delusions, hallucinations, and depression that does not pass with time.[11] In the US about 4 million births occur each year, leaving approximately 600,000 PPD patients in danger of harming themselves.[12] This year the FDA approved the first drug specifically indicated for PPD, Zulresso.[13] The mechanism of Zulresso is not fully known, but is thought to be related to a positive allosteric modulation of GABA-A receptors.[13,14] During the third trimester, an endogenous steroid hormone called allopregnanolone peaks then rapidly declines after birth leading to major depressive symptoms and potentially PPD.[14] Zulresso works as an analog of allopregnanolone which modulates GABA-A receptors.[14]

Zulresso's efficacy is shown through a meta-analysis comparing 3 RCTs (n=267). 77.9% of patients responded and 50.7% remitted on Zulresso infusion compared to the 55.3% and 24.0% on placebo.[15] Zulresso is given over a 60-hour infusion in an inpatient setting.[13-15] The patient must be monitored for loss of consciousness, decreased breathing, and worsening of depressive symptoms.[14,15] Zulresso should not be used in patients with renal impairment.[14] Patients must be enrolled in the Zulresso REMS program in order to receive treatment.[13-15]

Wakix (pitolisant)

Narcolepsy is a neurologic disease which severely decreases a patient's quality of life with excessive daytime sleepiness (EDS) and sudden loss of muscle tone.[16] Several drug options may be used by patients to treat EDS, but these drugs have a high potential for abuse, tolerability, and adherence issues.[16] Wakix is a newly approved FDA medication which is a competitive antagonist and partial agonist at histamine H_3 receptors.[16,17] Although effective at the H_3 receptor, the medication has little effect on other receptors.[16] In preclinical trials Wakix showed increased wakefulness, decreased abuse potential, and no effects on pain threshold.[16] Wakix showed efficacy through a randomized control trial of 94 narcoleptic participants.[16] This study found Wakix is noninferior to the first line treatment for excessive daytime sleepiness, modafinil.[16] During this study cataplectic symptoms were significantly decreased compared to the placebo.[16] Modafinil failed to decrease cataplectic symptoms when compared to the placebo.[16] These results

suggest Wakix may be superior to modafinil in reducing cataplectic symptoms.[16] Wakix shows promising results, but needs future research to confirm benefits of long term use.

Wakix is the first drug for narcolepsy that is not a controlled substance.[16,18] Adverse effects include nausea, abdominal discomfort, decreased appetite, xerostomia, and weight gain.[16,18] Insomnia and decreased sleep quality may also be noted in these patients.[18] Wakix is contraindicated in patients with severe hepatic impairment or renal impairment (<15 mL/min).[18] Currently Wakix's is only available in a 35.6 mg oral form which is only indicated for excessive daytime sleepiness.[18]

Conclusion

Each year the FDA approves more drugs to benefit patients with unmet healthcare needs. This year a total of 48 novel drugs were released.[1] These drugs cover a range of disease states such as infection, psychiatric conditions, cardiac disease, endocrine disease, autoimmune disorders and more. Above are a few drugs covering neurologic disorders, but the FDA's comprehensive list is much more extensive than what is covered above. For a full list of the FDA's novel medications, please visit: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019

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Descovy: New Indication for HIV Pre-exposure Prophylaxis

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Abstract

Human Immunodeficiency Virus (HIV) is a viral infection spread by contact with bodily fluids. If untreated, it results in severe immunodeficiency and ultimately death. In the 1990's, treatments to enhance the duration and quality of life were developed, and more recently, treatments have been designed to help prevent HIV infection. Currently, there is no cure for HIV infection; therefore, prevention is key to maintaining a healthy lifestyle in high risk patients. This article features a new indication for Descovy (emtricitabine and tenofovir alafenamide), which was approved by the FDA for HIV pre-exposure prophylaxis (PrEP).

Human Immunodeficiency Virus (HIV) is a viral infection spread through contact with bodily fluids.[1] There is no cure for HIV, although there are many treatment and prevention options. HIV, if not treated, can lead to Acquired Immunodeficiency Syndrome (AIDS). AIDS develops as a result of the HIV infection which reduces the number of CD4 T cells in the body, which causes an immunodeficiency. This lowers the individual's ability to fight off infections. Opportunistic infections and/or cancer can result from the bodies reduced ability to fight off infection.[1]

HIV exposure causes include unprotected sexual intercourse or sharing needles with an infected partner, mother to child during vaginal birth, and least commonly through blood transfusion.[1] Similarly, people at higher risk for contracting HIV include individuals who have unprotected anal sex, patients who participate in intravenous drug use sharing needles, uncircumcised heterosexual men, and people who have a sexually transmitted infection (STI) with open sores, allowing easier access for HIV to enter the body.[2]

Signs and symptoms vary within the different stages of HIV infection. Common signs when someone is initially infected (acute phase) include fever, headache, muscle/joint pain, rash, swollen lymph nodes, sore throat or painful mouth sores. If these symptoms are reported, the patient should be tested for HIV infection.[2]

Although there is currently no cure, there are treatments that when taken correctly, can decrease a person's HIV viral load to an undetectable level in their blood.[3] These HIV treatments are abbreviated "ART" which stands for antiretroviral therapy. According to the 2019 update from AIDS info and the National Institute of Health, it is recommended that ART therapy should be started immediately after diagnosis, on the same day if possible.[3] There are many first line treatment regimens which consist mostly of integrase inhibitors and reverse transcriptase inhibitors. These drugs work to inhibit the integration of the viral genome into the human genome and reverse transcription of the RNA to DNA, which is the mechanism that HIV uses to infect humans and cause immunodeficiency.[3] Treating HIV positive patients and getting their viral load to an undetectable level is a very effective way of preventing the spread of the infection.

There are multiple other methods for preventing the spread of HIV including abstinence, correct condom usage, and prophylactic drug therapy. Pre-exposure prophylaxis (PrEP) with Truvada (emtricitabine and tenofovir disoproxil fumarate) and the more recently approved, Descovy (emtricitabine and tenofovir alafenamide), are indicated for people who are HIV negative but at high risk of contracting the virus.[1] These individuals should take PrEP daily to reduce the risk of infection. PrEP should be combined with the

previously mentioned prevention methods for maximal reduction of risk.[1]

According to the 2017 CDC Pre-exposure Prophylaxis for the prevention of HIV guidelines, Truvada is the recommended first line therapy.[4] Truvada consists of two antiretroviral medications combined into one pill. These two medications and their strengths are emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg. The dosing is once daily for Truvada, and common side effects include nausea, flatulence, rash, and headache.[4] Adverse effects of Truvada include decreased bone mineral density and renal toxicity.[5] While on Truvada, it is recommended to assess the patient at least every three months for HIV infection.[4] This is due to the fact that if an individual does get infected, the drug should be discontinued to reduce the risk of resistance and anti-retroviral treatment therapy should be initiated.[4] Renal function should be assessed at three months, then every six months after due to the risk of nephrotoxicity. STI testing should also be completed at least every six months for sexually active individuals who are asymptomatic due to these patients being at high risk of contracting a STI.[4]

On October 3rd, 2019, the Food and Drug Administration (FDA) approved Descovy for PrEP.[6] Descovy has been on the market (originally approved in 2016) for HIV treatment. However, it was recently approved for a new indication, which makes it only the second drug to be approved for PrEP.[6] The study that led to the approval of Descovy for PrEP is the DISCOVER trial. Gilead Sciences is sponsoring the clinical trial to evaluate both safety and efficacy of Descovy as a daily oral HIV PrEP medication in comparison to Truvada.[7] The trial was a randomized (1:1), double blind, and active-controlled study that was carried out in North America and Europe. The study included 5000 participants, which looked at men and transgender women who have sex with men. Each participant ingested two pills: either Truvada or Descovy and one placebo look-alike pill for the medication they were not receiving.[7] Although the study is not scheduled to be complete until September 2021, the preliminary data demonstrated Descovy to be noninferior to Truvada in regard to efficacy, which led to its approval by the FDA for PrEP.[8] Given that this is preliminary data, limitations have not been well defined. A potential limitation is that this study only looked at men and transgender women, leading to the drug only being approved for this population. However, since this is only preliminary data and the study is not complete, we cannot be sure that they are not investigating this drug in other populations.

Descovy contains a different salt form of tenofovir (TFV), tenofovir alafenamide (TAF) as compared to Truvada, which contains tenofovir disoproxil fumarate (TDF).[9] TAF is a second-generation analog of TFV that is potentially less nephrotoxic based on its metabolism. The first-generation TFV molecule, TDF, undergoes rapid

metabolism in the plasma after oral administration. Subsequently, TFV is brought intracellularly and phosphorylated into its active molecule.[9] Due to the high rate of metabolism, higher dosing of TDF is required for the molecule to be internalized into the cells and be effective. TAF does not undergo rapid metabolism in the plasma allowing more drug to be brought intracellularly and activated into the active metabolite. Comparing the plasma concentrations of patients taking TDF or TAF, TAF was 91% lower and delivered 5.3 times as much TFV intracellularly.[7] Limiting plasma degradation of TFV allows there to be a 30-fold reduction in dosing which is hypothesized to be why there are fewer renal side effects and end organ damage reported.[9]

In a randomized phase 2 study published by Sax P et al. on September 1st, 2014, TAF showed similar viral replication suppression in infected individuals while having an improved renal safety profile compared to TDF.[9] In this study, 170 patients in total received treatment, 58 received TDF while 112 were treated with TAF.[9] Sax P. et al also reported less changes in the median serum creatinine in patients on TAF versus TDF however, these changes were not statistically significant. Significant changes were seen in renal tubular proteinuria/creatinine ratio with patients on TDF compared to TAF. Additionally, changes in bone mineral density were seen significantly less in patients on TAF compared to TDF.[9]

In conclusion, Descovy has been approved by the FDA for PrEP only in men and transgender women. However, these changes are not reflected in the most recent PrEP guidelines by the CDC in 2017. Currently, the recommended dosing of Descovy for PrEP is emtricitabine 200mg and tenofovir alafenamide 25mg once daily compared to the recommended dose of Truvada, emtricitabine 200mg and tenofovir disoproxil fumarate 300 mg once daily. [5] Based on the research that is available, TAF, the salt form of tenofovir in Descovy, may be safer for patients compared to TDF in Truvada, the current recommended therapy. Descovy may be a useful agent in the future that could impact future guideline updates.

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Pharmacogenomics in the Treatment of Multiple Sclerosis: A Guide to Siponimod

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Abstract

Pharmacogenomics is the study of personalized medicine based on a person's DNA. With a greater understanding of DNA in our modern society, pharmacogenomics is quickly changing the way we treat diseases. A new pharmacogenomic medication being used in the treatment of Multiple Sclerosis (MS) is siponimod (Mayzent). Mayzent has been approved as the first oral medication to treat secondary progressive MS with active disease. This is an important medication that may help to close the gap in therapy for patients who suffer from secondary progressive MS.

Multiple Sclerosis (MS) is a chronic multifactorial inflammatory disease that causes the immune system to destroy the protective covering of the nerves called the myelin sheaths.[1] The National MS Society estimates that roughly one million people suffer from MS in the United States and that roughly 2.3 million people suffer globally.[2] MS is an extremely aggressive disease that leaves many patients with an impaired quality of life. MS disrupts the normal functioning of the brain, optic nerves, and spinal cord through inflammation and tissue loss[3] that can result in lesions throughout the brain. The inflammation and demyelination causes lesions in the brain.[1] Depending on where the lesions are located will affect the types of symptoms individulas will display. These symptoms can be anything from slurred speech to losing the ability to walk.[4] Some patients only have minor symptoms, while other patient's symptoms could be debilitating. No matter the symptoms, the most important part of any treatment is preventing relapses, which causes new lesions to form, and can cause the progression of the disease to occur.

Patient's first encounter with MS is usually classified as Clinically Isolated Syndrome (CIS). This lasts for at least 24 hours with signs of the formations of one or more lesions. There are four types of MS. Relapsing-remitting MS (RRMS) which is the most common form of MS where remission is possible. Secondary progressive MS (SPMS) is defined as having little to no signs of remission. The symptoms steadily progress with time. Most people suffering from RRMS will one day progress to SPMS. Primary progressive MS (PPMS), has less inflammation than what is seen in RRMS. PPMS progresses from the beginning without relapse or remission. Progresive relapsing MS (PRMS) is a rare form of MS that progresses from the beginning and has acute relapse without remission.[5]

Over the last 50 years, the knowledge and understanding of genetic influences on an individual have advanced astronomically, leading to the development of medication With actionable pharmacogenomic information. Pharmacogenomics is the study of the effects an individual's DNA has on a medication. In theory, these medications would reduce many of the issues that current medications face, for instance improving effectiveness, preventing dangerous reactions, saving time, and money- because these medications would be designed to have the "perfect" dose for every patient. Unfortunately, this field is still very new and has its limitations. Even with these limitations, pharmacogenomics is a crucial part of modern medicine.

As of March 27, 2019, the Food and Drug Administration (FDA) approved the pharmacogenomic medication Mayzent for

the treatment of RRMS and SPMS. The FDA approval of this medication was extremely significant because few treatments for SPMS currently exist. Up to 80% of patients with RRMS will develop SPMS[3]. SPMS will continue to cause damage to the brain and spinal cord and will gradually progress over time without remission. Some patients may even suffer from the active form of SPMS meaning they have evidence of new relapses. Mayzent was needed to help fill this gap in therapy. Mayzent is a next-generation, selective S1P receptor modulator indicated for the treatment of relapsing forms of MS, to include CIS, RRMS, and active SPMS, in adults. Mayzent selectively binds to S1P1 and S1P5 receptors in the CNS. The S1P1 receptor, prevents the lymphocytes from egressing the lymph nodes and entering the CNS of patients with MS. This process leads to the anti-inflammatory effects of Mayzent[3]. Mayzent also enters the CNS and directly binds to the S1P5 and S1P1 sub-receptors on specific cells in the CNS known as oligodendrocytes and astrocytes to promote remyelination and prevent inflammation[3].

Before beginning treatment, genetic testing is required in order to determine the correct dosage for the patient. Patients will be tested for CYP2C9 variants and varicella-zoster virus (VZV) antibodies. If the patient is antibody-negative they should receive the vaccination before treatment with Mayzent. If a patient is currently taking or has taken an antineoplastic, immunosuppressive, or immune-modulating therapy, it is possible that they will have an increased immunosuppressive effect while taking Mayzent. It is also recommended that patients have an ophthalmic examination with a focus on the fundus and macula. Other prior testing that is recommended is an EKG, CBC, and transaminase and bilirubin levels within the last six months. Mayzent is contraindicated in pregnancy.[6]

Mayzent is an oral medication that can be taken with or without food. Patients with the CYP2C9 Genotype *1/*1, *1/*2, or *2/*2 will begin the initial dosage of 0.25mg once for the first two days. 0.5mg on the third day, 0.75mg on the fourth day and 1.25mg on the fifth day. After the fifth day, patients are to take 2mg daily for the duration of the treatment[7]. Patients with the CYP2C9 Genotype *1/*3 or *2/*3 will begin the treatment with an initial dose of 0.25mg for the first two days. On the third day, the dosage will be increased to 0.5mg and then be increased again on the fourth day to 0.75mg[7]. From the fifth day and on, the dosage will be 1mg[7]. If the treatment has been missed or interrupted after the initial titration for four consecutive days the treatment should be started over with the dosage beginning from day one[7]. The dosage does not need to be readjusted for patients with renal impairment or hepatic impairment.[7]

Upon the first dose patients should be monitored for the first six hours in case symptoms of bradycardia occur. The blood pressure and heart rate should be monitored every hour to monitor for symptoms. A second EKG should be administered to ensure that an AV blockage has not formed.[2]

The most common side effects of Mayzent are high blood pressure and headaches. Other possible side effects include the following: macular edema, vision changes, slowed heart rate, lung problems, liver damage, and birth defects.[6]

The FDA's approval of Mayzent was based on the Phase III EXPAND trial in 2016[8], which was the largest controlled clinical study of SPMS patients, showing that Mayzent significantly reduced the risk of the disease progression[8]. The EXPAND study is a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of Mayzent versus placebo in people with SPMS with varying levels of disability, Expanded Disability Status Scale (EDSS) scores of 3-6·5. The study consisted of 1651 patients from 31 countries. Mayzent was able to show improved confirmed disability progression by 21% (p=0.013).[3]

There is currently no generic version of Mayzent. The initial titration is available in a starter pack (Mayzent Starter Pack Oral) consisting of 0.25mg tablets. After the starter pack, 0.25 mg tablets cost $72.74 each. Each 2mg tablet costs $290.96.[7]

Upon review, Mayzent is an important new medcation in the treatment of SPMS. As mentioned previously, the gap in therapy poses a threat to the quality of life of patients suffering from MS. Mayzent gives patients more options and chances to find an effective treatment. As shown in the EXPAND study, Mayzent has shown great potential in helping to manage SPMS.

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