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Annual Review of Changes in Healthcare

Overview of Selected Novel Drugs Approved in 2018

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Abstract

2018 was a record setting year for new drug approvals by the FDA. This article highlights some of the drugs that have new mechanisms of action or have indications that have not previously been available. For example, Trogarzo is an IgG4 monoclonal antibody for the treatment of multidrug-resistant HIV. Xofluza, is a polymerase acidic endonuclease inhibitor that can be used to treat influenza by blocking a different step in the influenza lifecycle than previous flu medications, such as oseltamivir. Although smallpox has been declared eradicated for almost 40 years, TPOXX was approved for the treatment of smallpox in the event it is ever used as a bioterrorist agent. Epidiolex just became the first FDA-approved medication to contain an active ingredient derived from marijuana, and is the first medication approved for the treatment of Dravet syndrome. Three new medications for preventative migraine treatment were also approved. These agents (Aimovig, Ajovy, and Emgality) are calcitonin gene-related peptide receptor antagonists, which has been shown to be involved in migraine attacks.

The FDA set a record in novel drug approvals this past year. A total of 59 new molecular entities (NMEs) were approved in 2018, which surpassed the previous record of 53 NMEs from 22 years prior in 1996.[1] This record follows 46 NMEs approved in 2017.[1] In addition, there has been a recent spike in the number of drugs approved since 2016 when only 22 NMEs were approved.[1] The 59 NMEs approved cover a myriad of more common indications such as cancer, human immunodeficiency virus (HIV), migraines, influenza, and COPD, as well as rare conditions such as paroxysmal nocturnal hemoglobinuria and Lambert-Eaton Myasthenic syndrome.[1] Out of the 59 novel drugs approved, cancer drugs came out on top with the most approvals and included NMEs for a variety of both blood and solid tumors.[1] Unlike past years, there were no NMEs approved for hepatitis C.[1] Because there were drugs approved for numerous conditions, the remainder of the paper highlights drugs approved for several different indications.

Trogarzo™ (ibalizumab-uiyk)

Although most patients with HIV can be treated using a combination of two or more antiretroviral drugs, there are some patients who have developed multidrug-resistant HIV.[2] This greatly limits treatment options for these individuals and also puts them at a higher risk for complications, such as infections and cancer, and a higher risk for death.[2] Therefore, current research has its focus on drugs with new mechanisms of action (MOA) for multidrug-resistant HIV. One newly approved drug, Trogarzo, is indicated for multidrug-resistant HIV-1, and it is the first HIV therapy with a new MOA approved in more than ten years.[3,4] Trogarzo is a humanized IgG4 monoclonal antibody that targets the second extracellular domain of the CD4+ T-cell receptor inhibiting the viral entry process by preventing the binding of HIV to the cell.[3,5] The binding site of ibalizumab is distant from the major histocompatibility complex II binding sites.[3,5] This allows MHC class II molecules to still interact with CD4, and thus does not inhibit CD4-mediated immune functions so it does not cause immunosuppression.[5] Trogarzo is approved for use in combination with other antiretroviral medications.[3] In clinical trials, 33 of 40 patients (83%) treated with Trogarzo experienced a significant decrease in human immunodeficiency virus (HIV)-RNA levels after one week of adding Trogarzo to their failing antiretroviral therapies.[4] After 24 weeks of initating Trogarzo, 43% of the patients achieved HIV RNA suppression.[4] It is administered as an IV infusion by a health care professional every two weeks.[3,6] The first dose is 2,000 mg, and every dose thereafter is 800 mg.[3,6] The infusion takes 15-30 minutes to perform.[3,6] The most common side effects include dizziness, nausea, and rash.[3,6]

Xofluza™ (baloxavir marboxil)

According to the Centers for Disease Control and Prevention (CDC), on average each year, 5-20% of the U.S. population contracts the flu.[7] In addition, tens of thousands are hospitalized and thousands die from flu-related illnesses each year.[7] Therefore, having effective treatment alternatives readily available is crucial. If treatment with antiviral drugs is started within 48 hours of symptoms appearing, it can lessen the time the patients feel sick.[8] However, because flu viruses can become resistant to drugs, researching drugs with different MOAs is critical. Xofluza is the only treatment for the flu with a new MOA

that has been approved in almost twenty years.[8]

Xofluza is indicated for patients 12 years of age and older who have acute uncomplicated influenza and who have been symptomatic for no more than 48 hours.[9,10] Xofluxa works differently than oseltamivir (Tamiflu), which is used to prevent and treat influenza by inhibiting a viral enzyme neuraminidase.[6] Unlike oseltamivir, Xofluza is a polymerase acidic endonuclease inhibitor which inhibits viral replication early in the influenza lifecycle.[9] The CAPSTONE-1 clinical trials compared Xofluza to placebo and oseltamivir.[10,11] Xofluxa significantly reduced the duration of flu symptoms compared to placebo.[10,11] The median time to alleviation of symptoms was 53.7 hours with Xofluza compared to 80.2 values with placebo ($p<0.001$).

Xofluza is administered orally as a single dose.[6,9] It is recommended that patients 40-80kg take a single dose of 40 mg and patients over 80 kg should take a single dose of 80 mg.[6,9] It is important to avoid taking Xofluxa with polyvalent cation-containing laxatives or oral supplements, dairy products or other beverages containing calcium.[6,9] Adverse reactions that were common in the CAPSTONE-1 Trial include diarrhea (3%), bronchitis (2%), headache (1%), nausea (1%), and nasopharyngititis (1%).[6,9]

TPOXX™ (tecovirimat)

Before 2018, there were no drugs indicated for the treatment of smallpox; only vaccines for prevention of smallpox were available.[12] Almost 40 years ago in 1980, the World Health Assembly declared smallpox eradicated.[12] However, in the United States, smallpox research still continues as a protective measure in the event that it is used as an agent for bioterrorism.[12]

TPOXX is the only drug approved for the treatment of smallpox disease in adults and children weighing at least 13 kg.[6,13,14] It is the only product to receive a Material Threat Medical Countermeasure priority review voucher from the FDA.[14] This allows priority review from the FDA for medical products, including drugs, for conditions associated with biological, chemical, nuclear, or radiological threats.[14] TPOXX works by inhibiting the orthopox virus VP37 envelope wrapping protein which is needed for the production of extracellar virus (variola virus).[6,14] By inhibiting this process, the virus cannot leave an infected cell. Therefore, the spread of the virus in the body is prevented. To establish efficacy, clinical trials were conducted in animals that were infected with viruses that are closely related to the virus that causes smallpox.[15] Outcomes measured survival at the conclusion of the study, and more animals treated with TPOXX lived compared to animals who received placebo.[15] To establish safety, TPOXX was administered to over 350 healthy human patients.[15] The most common adverse reactions (>2%) were headache, nausea and vomiting, and abdominal pain.[15] TPOXX is given orally twice a day for 14 days within 30 minutes after a full meal containing fat.[6,13]

Epidiolex™ (cannabidiol)

It is important to recognize that certain active ingredients found in marijuana can have medical benefits, such as cannabidiol (CBD).[16] In 2018, Epidiolex became the first medication that contains a substance derived from marijuana to be approved by the FDA.[16] CBD is not known to cause the psychoactive or euphoric effects

found in marijuana, which are instead related to the chemical tetrahydrocannabinol (THC).[16] THC is not present in Epodiolex and therefore does not create the same "high" feeling as marijuana.[16]

Epidiolex is FDA approved for the treatment of two severe, but rare, forms of epilepsy in patients age 2 and older.[16] Lennox-Gastaut syndrome is a multi-seizure disorder that begins in early childhood and can cause frequent tonic seizures in 3 to 5 year olds.[16] This disorder can lead to developmental problems such as delayed motor skills (walking or crawling), and learning or intellectual disability.[16] Epidiolex also became the first FDA-approved drug for the treatment of Dravet syndrome.[16] Dravet syndrome usually appears during the first year of life as febrile seizures, but can later evolve to all types of seizures.[16] This can potentially cause a child to go into status epilepticus, which requires emergency care and is life-threatening.[16] Both of these syndromes are difficult to control and have a significant impact on a patient's quality of life.[16] Epidiolex was studied in different randomized, double-blind, placebo-controlled clinical trials involving patients with either syndrome.[17] These patients were currently not controlled on their seizure medications. Epidiolex was shown to be effective at reducing the number of convulsive seizures compared to placebo.[17] Epidiolex decreased seizure frequency by 37-44%, whereas placebo only showed a 13-22% decrease.[17]

Epidiolex is only available in a liquid solution form, and is taken twice daily based on weight.[6,17,18] The dosing is the same for children and adults with an initial dose of 2.5 mg/kg twice daily for the first week. It should then be titrated to 5 mg/kg twice daily for the minimum maintenance dose.[6,18] Epidiolex can be titrated weekly up to a 10 mg/kg twice daily max dose, but should not be discontinued immediately without proper titration down.[6,18] It should be taken via a syringe and it does not need to be taken with or without food, but the patient should be consistent.[6] Liver function should be assessed prior to treatment and monitored periodically as increased serum alanine aminotransferase >3x ULN has been shown in patients (13-17%).[6,18] Daily doses need to be decreased in patients with moderate to severe hepatic impairment.[6,18] Some common side effects a patient may experience include fatigue, weight loss, anemia, lack of appetite, diarrhea, or difficulty sleeping.[6,18] The patient should notify their doctor immediately upon any signs of liver problems, signs of depression and mood changes, or signs of infection.[6,18] Epidiolex is a moderate CYP2C19 inhibitor, so the majority of drug interactions invoke increasing the serum concentration of CYP2C19 substrates.[6]

Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists

Migraines affect more than 10% of people worldwide, and can be very painful or debilitating.[19] In 2018, the FDA approved 3 new medications for a new class of preventative migraine treatment.[19] This class blocks the activity of CGRP, which is known to be involved in migraine attacks.[19] These new medications are all monoclonal antibodies and include Aimovig™ (erenumab-aooe), Emgality™ (galcanezumab-gnlm), and Ajovy™ (fremanezumab-vfrm).[19]

All 3 of these medications are subcutaneous injections that are to be given monthly (Ajovy has an every 3 month option).[6,20-22] These medications are only indicated for adults (18 years and older), and do not require any dosage adjustments for renal or hepatic impairment, or geriatric patients.[6,20-22] All of these medications come in a prefilled syringe in the typical monthly dose.[6,20-22] Each medication should be stored in the refrigerator, but taken out 30 minutes before administration to allow it to reach room temperature. [6,20-22] The syringe should not be shaken. To use, the syringe can be injected into the abdomen, thigh, or upper arm.[6,20-22] For doses that need more than 1 injection, (Emagily has a loading dose of 2 injections, and Ajovy 3-month dosing takes 3 injections) the injections should be given on the same location on the body, but not in the exact same spot.[6,20-22] Ajovy must be used within 24 hours from becoming room temperature, but Emagily and Aimovig are good for 7 days outside of the refrigeration.[6,20-22]

Emagily and Ajovy should be used cautiously in patients with cardiovascular disease, as those patients were excluded from all clinical trials.[6,21,22] The most notable side effect is injection site reactions (pain, swelling, or redness).[6,20-22] Aimovig also had side effects of constipation and muscle cramps or spasms.[6,20] Finally, Emgality and Aimovig should be avoided in patients on belimumab, as they can increase the adverse or toxic effects of belimumab.[6,20,22]

Knowledge Check: Multiple Choice
Xufluza is indicated for patients 12 years of age and older who have acute uncomplicated influenza and who have been symptomatic for no more that how many hours?

A. 12
B. 24
C. 36
D. 48

Answer: D

Conclusion

2018 provided U.S. citizens treatment options for not only a variety of disease states, but also the first treatment options for several rare disease states as well. Above are just a few novel medications from 2018. The full list of FDA approved medications in 2018 can be viewed here: https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm

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Ceiling dose of Ketorolac in Treatment of Moderate to Severe Acute Pain in an Emergency Department Setting

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Abstract

Ketorolac is a nonsteroidal anti-inflammatory medication that is commonly used in emergency department settings for patients with moderate to severe acute pain. Because ketorolac use is not recommended to exceed 5 days due to adverse effects, it's use is most commonly seen for acute pain than chronic pain. Some cautions with this medication include increased risk for cardiovascular events, gastrointestinal complications, renal complications, and increased risk for bleeding. These adverse effects typically cause providers to refrain from use in an outpatient setting. Various studies look at ketorolac's ceiling dose in order to limit unnecessary amounts of drug administered to a patient. With this, various studies were taken into consideration to see what the ceiling dose for ketorolac is, and if providers follow the results of these studies. Results are conclusive that a ceiling dose of ketorolac is 10mg, as3 opposed to the typical dose of 30 to 60 mg; yet prescribers continue to administer greater than the ceiling dose for ketorolac.

Ketorolac (Toradol®) is a nonsteroidal anti-inflammatory drug that reversibly inhibits COX-1 and COX-2.[1] With this inhibition, there is prevention of the precursors of prostaglandins, with demonstrated efficacy to treat moderate to severe pain.[2] In 1990, ketorolac was first used to treat acute pain, more specifically postoperative pain. Today, ketorolac use is common in an emergency department setting for acute moderately severe pain management. Ketorolac is void of euphoria, dependence, and respiratory depression, as opposed to alternative agents used in acute pain including opioids. There are a wide variety of routes of administration which include intramuscular, intranasal, ophthalmic, intravenous, and oral providing greater convenience for providers.[3] Doses for pain management intramuscularly is 60 mg as a single dose or 30 mg every 6 hours; alternatively can be given as 10 to 30 mg as a single dose according to Canada product labeling.[2] Intravenously, doses include 30 mg as a single dose or 30 mg every 6 hours.[2] Each have a max of 120 mg per day, with a max use of 5 days.[2]

Although there are many benefits associated with the use of ketorolac, this drug is not void of side effects. Some common adverse effects include headache, gastrointestinal pain, dyspepsia, and nausea.[1] More specifically, 1.2% of patients greater than 65 years old experienced a peptic ulcer with ketorolac doses less than or equal to 60 mg for a total daily dose and with doses of 90-120 mg daily, the rate was 2.2%.[1] To this day, there are multiple black box warnings, cautions, interactions, and contraindications that requires weighing the risk verses benefits for each patient case. Ketorolac has many disease and drug-drug related concerns and other considerations prior to the administration to a specific patient. This includes the various black box warnings of bleeding and hemorrhagic effects, increased cardiovascular events, gastrointestinal events, and hypersensitivity reactions. Other considerations include central nervous system effects, hepatic effects, hyperkalemia, renal effects, and skin reactions. The considerations for special populations include patients greater than 65 years old, patients during labor and delivery, pediatric patients, and patients weighing less than 50 kg. Pharmacokinetics also plays a role in specific patients; as half-life is greater in elderly patients, and clearance is decreased in renal impairment. With these various concerns, it is important to administer the lowest effective dose to limit these adverse effects. Like with most drugs, the greater the dose and extended duration of therapy; the increased risk for complications. In order to limit the number of adverse reactions, while still allowing for a max benefit of pain relief, various studies looked at ketorolac effectiveness at various doses; since being released in the early 1990's.[4,5,6] There have been multiple studies demonstrating a ceiling dose associated with ketorolac; yet one piece of literature demonstrates practitioners in an emergency

department setting are prescribing greater than the ceiling dose, with about 97% of prescribers prescribing doses greater than the doses seen in literature.[7] There is a lull in literature looking at the implementation of the ceiling dose of ketorolac, with many studies demonstrating ceiling doses in various hospital settings. The purpose of this review is to increase awareness of this practice that can potentially increase patient outcomes.

CEILING DOSE OF KETOROLAC

A ceiling dose is the most effective dose to treat a certain disease state, with limiting the number of adverse effects. With ketorolac, a ceiling dose has been established in various studies.[4,5,6] For example, in Motov 2017, a randomized control trial was conducted in an emergency department setting investigating three doses of ketorolac; 10, 15, and 30mg. Patients part of this trial required to have moderate to severe pain, a pain score of 5 or greater on a numeric pain scale ranging from 0-10.[6] Patients were excluded if there was chronic pain lasting greater than 30 days, any contraindications, or use of other additional analgesia. This blinded trial had one arm for each dose of ketorolac, with follow-up at baseline, 15, 30, 60, 90, and 120 minutes.[6] The primary outcome looked at the delta between pain rating score at baseline and at 30 minutes; with a significant value being considered 1.3.[6] There was no significant difference in efficacy between the three arms. For instance, the baseline for 10, 15, and 30 mg are as follows: 7.7, 7.5, and 7.8 with reduction to 5.1, 5.0, and 4.8 at 30 minutes respectively. Rescue analgesia used was morphine, which had similar use between the three groups. Some limitations include selection bias, as this was a single-center study with convince sampling according to variable of the research and pharmacy. Another limitation includes duration of follow up, which limits the ability to differentiate long term adverse effects between the three groups including renal and gastrointestinal. These both should be considered when determining the validity and impact of this trial. Overall, based on the results, Motov considered the ceiling dose for ketorolac to be 10 mg. Based on a recent letter to the editor in the Annals of Emergency Medicine, Heller demonstrated concern with Motov 2017 and the conclusion of similar analgesic efficacy between the three doses of 10, 15, and 30 mg.[8] Heller states a lack of consideration for the area under the curve for ketorolac at lower doses, meaning that the duration of

Knowledge Check: True or False?
One conclusion from Motov 2017 was that there was increased efficacy seen with higher doses of ketorolac.

Answer: False

effect for ketorolac was not addressed for the various doses. There is discussion concerning the variable half-life of ketorolac, and since the follow up time was only until 120 minutes in Motov 2017. Heller states that there is limitation as to how clinically significant the results were.

Broadening the spectrum to look at other studies that are not specific to the emergency department are also considered in order to see the trends of recommended ketorolac doses. Around the time ketorolac being used on the market; Staquet 1989 published a double-blind study looking at intramuscular administration of ketorolac in cancer pain.[9] 126 patients were administered either 10, 30, or 90 mg and assessed level of pain via the standard verbal scale.[9] The authors concluded that there was a statistical superiority to placebo for each dose of ketorolac, including the 10mg dose.[9] This was determined by the pain intensity differences, with similarity between 90, 30, and 10mg at six hours 6.68, 6.85, and 7.40 respectively.[9] It was also noted that 10 patients experienced an adverse effect post administration of ketorolac, with there being a relationship with the lower number of adverse effects with the lower dose. The mean time to remediation, because of inadequate pain relief for the three doses was 7.04 hours combined, with little difference between the three doses.[9] Another study by Minotti 1998, compared two doses of ketorolac, 10 and 30 mg, and diclofenac 75 mg.[5] Pain was assessed at various points in therapy from 30 minutes to 6 hours, focusing on if there was a need for rescue analgesia. Overall, there were no statistical differences between the efficacy of the pain relief for the three arms.[5] This study also concludes with the two other studies previously mentioned, that 10 mg of ketorolac is non-inferior to higher doses.[5]

IMPLEMENTATION OF CEILING DOSE

In order to see if the ceiling dose is implemented in an emergency room practice, Soleyman-Zomalan 2017 conducted a retrospective observational study.[7] Data was collected over a ten-year period noting the dose of ketorolac administered; in addition to indication and various patient demographics. The three main indications for the use of ketorolac included pain associated with urinary tract, lower back, and abdomen. The main route of administration for treating these conditions with ketorolac was intravenous (77.9%) followed by intramuscular, and then oral. Of the 49,605 doses of ketorolac included in this study; 48,117 patients received supratherapeutic doses greater than or equal to 15 mg.[7] Specific trends for each route of administration are as follows: 95.5% of all administrations for intramuscular were given at doses of 30 and 60 mg, and the intravenous trend was 84.9% for doses given at doses of 30 and 60 mg. The results showed that that in the emergency department, 97% of prescribers used above the ceiling dose for acute pain.[7] This leads to an increased likelihood for adverse effects

giving the patients without a benefit for their pain.

CONCLUSION

With this review of literature; there is seen to be a lack of implementation for the ceiling dose of ketorolac, although there are various studies to demonstrate a ceiling dose. The main question, based on this information, why are providers still using greater than the ceiling dose? Some possible reasons include lack of knowledge and awareness. Practitioners may have not reviewed the recent literature for the ceiling dose for ketorolac. A force of habit could be another reason for the continued use of the higher doses. Also, practitioners may use drug databases including Lexicomp or Micromedex in order to determine dosing, which would also explain the elevated doses; as these databases recommend elevated doses. Lastly, there could be concern based on the current literature; as to how clinically significant they are in practice. With this, there should be education for the various providers in the emergency department including practitioners and pharmacists in aims of increasing awareness and knowledge of 10 mg ceiling dose of ketorolac. By increasing the knowledge and awareness, pharmacists will be more comfortable being able to make a recommendation to use the ceiling dose of ketorolac in the emergency department setting. In addition to education, there should be further research in the ceiling dose of ketorolac, pharmacokinetics, and clinical significance of implementing lower doses of ketorolac.

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Breakthrough Therapy Designation Awarded to Crizanlizumab, a New Treatment Option for Sickle Cell Disease

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Abstract

Sickle cell disease is an inherited disease that affects hemoglobin of red blood cells. It can cause patients extreme pain due to the blockage of small blood vessels. These episodes of extreme pain are called vaso-occlusive crises, or pain crises, and they can lead to increased morbidity and mortality for patients with sickle cell disease. Crizanlizumab is a new therapy that recently received Breakthrough Therapy designation from the FDA. This medication helps reduce the amount of pain crises by blocking P-selectin on sickle cells from binding to one another, preventing the stasis of blood flow. This new therapy is unlike any treatment currently available and is very hopeful for patients with sickle cell disease.

Sickle cell disease, also known as SCD, is a group of disorders that affects red blood cells. The disease specifically affects hemoglobin, which is responsible for helping red blood cells with the delivery of oxygen throughout the body. This abnormal hemoglobin protein in SCD patients is referred to as hemoglobin S. While normal red blood cells are round in shape, hemoglobin S causes red blood cells to be shaped like a sickle or crescent.[1] Normal red blood cells are also flexible and move more easily through the bloodstream. However, sickle-shaped blood cells are harder and able to stick together more frequently and more easily. When the sickle cells adhere together, they can cause a block in blood flow that can lead to pain, infection, acute chest syndrome, a decline in the function of multiple organs, or stroke. Sickle cells also have a shorter lifespan than normal red blood cells resulting in a constant deficiency of red blood cells in patients with SCD.[2]

Sickle cell disease is caused by an inherited genetic mutation. It is inherited in an autosomal recessive pattern, which means that the HBB hemoglobin genes from both parents are mutated.[3] It is the most common blood disorder in the United States and most commonly affects people of African descent. Millions of people are affected worldwide, and up to 80,000 Americans are affected.[1]

There are several types of sickle cell disease. HbSS is a form of SCD called sickle cell anemia in which the patient inherits two "S" sickle cell genes, and it is usually the most severe form of SCD. HbSC is a form in which one of the abnormal genes inherited is for the S gene, and the other gene is for an abnormal hemoglobin called "C". Rarer types of SCD include HbSO, HbSE, and HbSD. All of these types have one abnormal hemoglobin gene along with one "S" sickle cell gene.[2]

Newborns are screened for SCD either before or after birth, but signs and symptoms may not appear until the child is about 6 months old.[3] Signs of SCD are usually due to complications of the disease and may include: yellowing of the skin due to widespread hemolysis of the red blood cells; fatigue, dizziness, and shortness of breath due to anemia; and painful swelling of the hands and feet called dactylitis. More serious complications of SCD include severe anemia, chronic pain, acute chest syndrome, chronic infections, stroke, and pulmonary hypertension.[3]

Currently, the only potential cure for SCD is a bone marrow or stem cell transplant.[3] However, these procedures pose great risks, and donors must be very closely matched with the recipient for the transplant to be effective.[2] Therefore, very few SCD patients are actually able to undergo this risky procedure. While a transplant may be the only cure for this disease, there are various treatment options utilized to prevent serious complications. Antibiotics, such as penicillin, are used in patients with SCD to prevent recurrent infections along with vaccinations. Blood transfusions are also a common treatment in patients with SCD to prevent stroke.[3]

A vaso-occlusive crisis (VOC), also called a pain crisis, is another major complication of sickle cell disease. Pain crises result from the blockage of blood flow due to the clustering of cells in the vasculature and inflammation. They cause patients excruciating pain and are the leading cause for SCD patients to be

admitted to the emergency department. Pain crises are directly correlated with increased morbidity and mortality in patients with SCD.[4] They can cause stroke, organ damage, and even death.[5] Most SCD patients have multiple pain crises each year, and the episodes can vary in both intensity and frequency.[5] Between pain crises, it's common for younger children to be pain free and have virtually no discomfort. On the other hand, older children and adults tend to experience a more continuous or chronic discomfort between crises.[3] Unfortunately, there are very few therapy options for preventing patients from experiencing pain crises.[4] Hydroxyurea is the most common medication used to reduce the number of pain crises in SCD patients. L-glutamine is another very common medication that was FDA approved in 2017 to reduce complications in patients with SCD.[5] Crizanlizumab is the latest drug in development for the treatment of SCD and the prevention of its complications.[5]

Crizanlizumab belongs in the drug class of humanized monoclonal antibodies. Monoclonal antibody therapy stimulates the patient's immune system to attack the cells that the medication targets. While there are many medications within this drug class used to treat various disease states, crizanlizumab is the only humanized monoclonal antibody used specifically to treat sickle cell disease and to reduce its corresponding pain.[6]

P-selectin is a cell adhesion molecule expressed on activated platelets and vascular endothelial cells. The role of P-selectin is to recruit leukocytes to the site of injury during inflammation. P-selectin normally works to control the flow and adherence of leukocytes to blood vessel walls. However, in patients with SCD, the abnormal sickle shape of hemoglobin causes red blood cells to adhere to blood vessel walls or other platelets when they shouldn't, which results in the stasis of blood flow in small vessels. This stasis is what causes pain crises.[6] Crizanlizumab works by preventing this stasis in SCD by blocking the specific P-selectin protein on the platelets to stop them from adhering to each other or blood vessel walls.[7]

In the SUSTAIN phase 2 clinical trial, crizanlizumab was evaluated for safety and efficacy. The study was double-blind, randomized, and placebo-controlled.[8] Participants in the study had at least two previous episodes of pain crises in the last year. There were a total of 198 patients included in the study, and they were given either a low dose of crizanlizumab (2.5 milligram per kilogram of body weight), a high dose (5 mg/kg) or a placebo. The injection was given about once every four weeks (14 out of 52 total weeks).[7] The results of the study showed that a high dose of crizanlizumab reduced the frequency of pain crises by 45.3% (P=0.01), and a low dose of crizanlizumab reduced pain crises by 32.6% (P=0.18). The results also showed that with high dose crizanlizumab, the median time to first pain crises was significantly longer than with placebo (4.07 vs. 1.38 months, P=0.001). The median time to second pain crises was significantly longer with treatment with crizanlizumab as well (10.32 vs. 5.09 months, P=0.02).[8] Some patients were also taking hydroxyurea to treat their SCD, and the reduction of pain crises occurred with crizanlizumab regardless of if they were also taking hydroxyurea.[7] The most common side

effects experienced during the trial were diarrhea, nausea and vomiting, itching, and pain in the back, chest, joints, and limbs.[6]

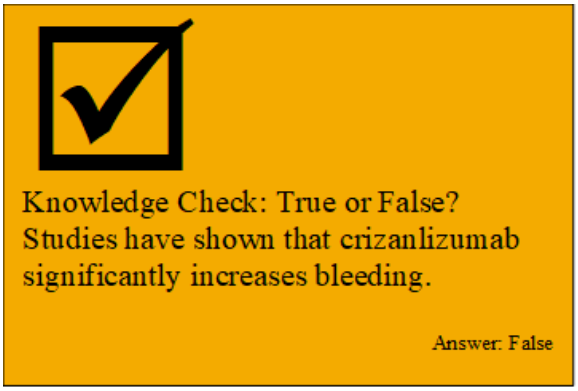
While the study demonstrated that crizanlizumab increased the time to a pain crisis overall, it also highlighted some limitations of the drug. The most common side effects observed from the trial were experienced in at least 10% of participants. There were also incidences of infections such as upper respiratory tract infections and urinary tract infections. More serious side effects included pyrexia and influenza, of which were recorded more frequently in the groups taking crizanlizumab.[5] Additionally, a life-threatening incidence of anemia and intracranial hemorrhage was also reported with one patient in the low-dose crizanlizumab group. This patient was also receiving concomitant ketorolac.[5]

Death was also noted to have occurred during the trial. Included in the five total patients who died, there were two in the high-dose crizanlizumab group that died due to endocarditis and sepsis, and there was one death in the low-dose group due to multiple reasons such as ACS and respiratory failure.[5] By inhibiting P-selectin and therefore platelet aggregation, crizanlizumab would be expected to increase bleeding risk upon reducing the formation of thrombi. This could potentially explain why one patient in the trial experienced life-threatening anemia and intracranial hemorrhage with low-dose crizanlizumab. However, there has been no conclusive evidence that crizanlizumab itself has increased bleeding-related adverse effects. This relationship between a P-selectin inhibitor and bleeding risk has only been studied in mice and baboons in regards to deep vein thrombosis.[9] The results have shown that a P-selectin inhibitor does not affect the rate of bleeding or increase bleeding risk.[9] This also could potentially explain why only one patient from the trial experienced increased bleeding. Furthermore, this patient was also taking ketorolac while receiving crizanlizumab which is known to significantly increase bleeding. Because crizanlizumab is the only medication in its class that selectively inhibits P-selectin, more trials and research must be completed in order to make a more definitive, human evidence-based conclusion on whether crizanlizumab increases bleeding risk.

The investigators of the trial have proposed that crizanlizumab could also be used to treat pain crises in patients with sickle cell anemia.[6] Currently, there are plans for another phase 2 trial to investigate the efficacy and the effects of the high dose of crizanlizumab in adult patients with sickle cell anemia.[6]

Patients with SCD experience healthcare costs of more than $30,000 annually due to pain crises and the corresponding hospitalizations.10 Hydroxyurea and L-glutamine are both taken orally and cost less than $2 and $1 per capsule, respectively.[11] Crizanlizumab is a monthly infusion, but since it is not yet FDA approved and therefore is not yet on the market, its cost is unknown. While the price of crizanlizumab is expected to be expensive after it gains approval, its benefits and status of an “FDA Breakthrough Therapy” are worth taking note of and considering for the treatment of SCD patients experiencing pain crises.

Crizanlizumab has been granted "Breakthrough Therapy designation" which means that the development and review of crizanlizumab has been accelerated due to it having already exhibited great potential benefit in the treatment of very serious instances of pain crises. The Phase 2 SUSTAIN clinical trial has shown a clear advantage over available therapy, which is why it was granted Breakthrough Therapy.[12] It shows such potential benefit that the FDA is trying to accelerate the approval process so that it can benefit patients sooner. Preventing pain crises is important because they disrupt patients' lives and cause pain, hospitalizations, and even death. Although crizanlizumab will be expensive once it is on the market and SCD patients already incur a heavy economic burden with the disease, it may be extremely beneficial for patients who experience a great number of pain crises annually. Decreasing the number of hospitalizations and emergency room visits due to VOCs could potentially save patients a lot of money.



In conclusion, crizanlizumab is a new Breakthrough Therapy for the treatment of patients with sickle cell disease suffering from vaso-occlusive crises. It is expected to provide great advancement in the prevention of these patients' pain crises and to improve their quality of life. However, it is not without limitations. The drug's potential major adverse events that include influenza, pyrexia, and various infections could restrict its use, especially in certain populations such as the elderly. There needs to be additional research and trials in order to firmly establish its effect on bleeding. Confirming whether it increases bleeding risk will allow more precise decision making regarding the prescribing of this drug for special populations.

Further clinical trials are needed for the approval of crizanlizumab to enter the drug market. A Phase 2 trial for this drug is currently undergoing development and may last a couple of years. Upon successful completion of Phase 2, the drug will move into the clinical trial of Phase 3 in which it may spend up to four years. Additionally, with crizanlizumab being deemed a Breakthrough Therapy drug and being granted accelerated review and approval, there is increased uncertainty of how long it will take it to gain FDA approval and reach the market.

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The Watchman Device: An Alternative Treatment in Atrial Fibrillation

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Abstract

Stroke prevention is an important aspect in the management of Atrial Fibrillation (AFib). The 2019 Guideline for Management of Patients with Atrial Fibrillation recommends DOACs as first line, but warfarin is also still widely used. These medications are effective but their systemic effect on the body require careful monitoring to avoid serious adverse events, contraindications, and other drug-drug interactions. As a result, many patients do not adhere or cannot tolerate the medications, therefore physicians continue to search for alternatives. The latest focus has been on the Watchman Device, a device that essentially seals off the left atrial appendage closure (LAAC). The LAAC is an area in the heart where blood clots often form in patients with AFib. The Watchman device prevents the clots in this area from escaping, lowering the risk of stroke. Though the Watchman device has been shown to be an effective non-pharmacological substitute, careful patient consideration remains an emphasis when choosing treatment. Staying informed and knowing what treatment options are available, along with understanding the patient and his/her preferences, can aid in deciding on the most effective option to prevent stroke.

Atrial fibrillation (AFib) affects approximately 2.7–6.1 million people in the United States.[1] While some patients are asymptomatic, others may experience symptoms such as tachycardia, heart palpitations, dizziness, fatigue or shortness of breath.1 One of the greatest concern with AFib is that AFib increases a person's risk for stroke by four to five times when compared to people who do not have AFib.[1]

Treatment

The American Heart Association (AHA) treatment goals for atrial fibrillation (Afib) are reducing the heart rate < 80 bpm (rate control), restoring the heart to a normal rhythm (rhythm control), preventing thromboembolism, reducing the risk of developing stroke or heart failure, and preventing additional heart rhythm problems.[2] Rate control is preferred over rhythm control.[2] The need for anticoagulation therapy is determined by the CHA_2DS_2-VASc score. The score is calculated by scoring the following risk factors: congestive heart failure (CHF), hypertension, age $\geq$ 65, diabetes, stroke, vascular disease (heart attack, peripheral artery disease, or aortic plaque), and female sex.[2] Adults between 65 and 74 receive one point for their score, while age over 74 receive two points. A CHA_2DS_2-VASc $\geq$ 2 for men and $\geq$ 3 for women indicates the need for anticoagulation. According to the AHA Afib treatment guidelines, there are several options used to treat Afib: medications, nonsurgical procedures, and surgical procedures.[2]

Medications, for most patients, are the most preferred method of treatment.[3] Medication options may include anticoagulants, rate control medications, and rhythm control medications.[3] Anticoagulants, such as warfarin, Direct Oral Anticoagulants (DOACs), and aspirin are prescribed to prevent and treat blood clots.[2] Beta blockers, non-dihydropyridine calcium channel blockers (non-DHP CCB), digoxin, and amiodarone can be all used for rate control.[2] The AHA guidelines recommend a beta-blocker or non-DHP CCB as first-line therapy for paroxysmal, persistent, or permanent Afib.[2] Sodium channel blockers (lidocaine, procainamide, flecainide) and potassium channel blockers (amiodarone, dronedarone, dofetilide) can be used for rhythm control.[2] Amiodarone is usually reserved when other methods are unsuccessful or contraindicated.[3] The heart rhythm can be more difficult to control, especially if patients are untreated for an extended period of time.[3]

Nonsurgical procedures used to treat Afib are electrical cardioversion or ablation.[2] Electrical cardioversion uses an electrical shock to reset the heart to a normal rhythm. The procedure is similar to defibrillation, but uses much lower energy. The risk with cardioversion is that it may free loose clots from the heart and into the blood vessels. Therefore, transesophageal echocardiography (TEE) is also recommended to check for blood clots in the atria before the procedure.[3,5] Ablation is a nonsurgical, catheter-based procedure used when medications or cardioversion is not preferred or effective.[3] Ablation can be done by radiofrequency, laser, or cryotherapy to scar problematic areas of the heart that cause irregular rhythm.[3] The common sites for ablation in Afib are the pulmonary vein and AV node.[3] Ablation is generally safe, but there is an increased risk of Afib returning within a few months and the patient would

have to repeat the procedure or take rhythm control medication.[6]

There are also surgical procedures for the treatment of Afib, which includes implanting a pacemaker and open-heart maze surgery, that are last line treatment.[3] A pacemaker is usually implanted under the skin and sends electrical signals to maintain a steady contracting rhythm. Open-heart maze surgery is a complex procedure in which a surgeon creates small incisions in the upper part of the heart.[3] The incisions are then stitched together causing scar tissue to form, which interferes with the transmission of electrical impulses that can cause Afib.[3] Normal heartbeat is usually restored in these procedures but they are invasive and possess risks such as infection or developing new arrhythmias.[7,8]

Pathophysiology

Recently in 2015, the FDA approved a new medical intervention called the WATCHMAN device.[9] The WATCHMAN device may serve as an alternative for patients who cannot tolerate the use of oral anticoagulants or who do not qualify/failed surgical procedures to restore normal sinus rhythm. To understand the importance of the WATCHMAN device, the pathophysiology of AFib should first be reviewed. The heart acts as a pump with its own very sophisticated electrical system. Disrupting the electrical system leads to heart rhythm issues, such as AFib. In normal electrical conductance, the sinoatrial (SA) node sends signals to the atrioventricular (AV) node and there is normal rhythm. However, when a patient has AFib, there are signals in the atria that are originating in areas of the heart other than the SA node. The signals spread through the atria in a rapid, disorganized way. The result is a very fast and irregular contraction of the atria in a quivering manner.

In Afib, the heart works less efficiently as a pump. Blood flow within the heart chambers have slowed so stagnant blood flow occurs and blood clots can form, causing stroke associated with AFib. For patients with Afib, over 90% of stroke causing clots that originated in the heart are formed in a structure called the left atrial appendage (LAA).[10] This small pouch resides on the left side of the heart. The clots that form in the LAA may break away into an arterial highway and travel directly into the brain. As the blood vessels branch off and become finer, the clot will block further blood flow to the brain. The nerve cells in these area of the brain are deprived of oxygen and die. This complication is known as an ischemic stroke. Since clots that are formed in the heart are rather large, ischemic stroke caused by AFib can be fatal or cause permanent disabilities.

The WATCHMAN Device

The WATCHMAN device is a 2015 FDA-approved left atrial appendage closure (LAAC) device for reducing the risk of stroke in non-valvular AFib patients.[11] Performed in a one-time procedure, the WATCHMAN is an implant that fits directly in the left atrial appendage to permanently seal it off to prevent blood clots from escaping.[11] Roughly the size of a quarter, the WATCHMAN is created from light and compact materials commonly used in other medical device implants such as nickel or titanium.[11] To implant this device, a small incision is made in the upper leg to allow a catheter to be inserted, such as in a standard stent procedure.[11] Then, the WATCHMAN device is guided into the LAA of the heart; this procedure takes about an hour with patients

under general anesthesia.[11] Patients who receive this procedure normally stay overnight in the hospital and go home the following day.[11]

Following the WATCHMAN implant procedure, patients are typically given warfarin up to 45 days after the procedure until the LAA is permanently sealed off.[11] Over 45 days, the tissue of the heart will grow over the implant, forming a barrier against future blood clots.[11] Once this tissue has efficiently grown to cover the implant, warfarin will be stopped and clopidogrel will be initiated, as well as aspirin to be taken orally for the next six months.[11] Once the six months has been completed, aspirin will likely be recommended on an ongoing basis to ensure maximal reduction in the risk of thrombi development.[11]

In a recent clinical trial by EWOLUTION, the WATCHMAN was implanted successfully in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of patients.[4] More than 60,000 the WATCHMAN procedures have been executed worldwide and did not have the same high bleeding risk as patients using long-term warfarin therapy.[11] Important safety information in the EWOLUTION study revealed risks that were associated with the general implant procedure, as well as use of the device. Such risks included, but were not limited to: accidental heart puncture, air embolism, arrhythmias, anemia, anesthesia risks, allergic reactions, excessive bleeding, blood clot or air bubbles in the lungs or other organs, renal failure, stroke, thrombosis, and in rare cases, death.[11] Therefore, patients must talk with their physician prior to initiating the WATCHMAN device to make sure the WATCHMAN is right for them.

There has also been data on the overall prevention of stroke and decreased mortality rates with the WATCHMAN device. The data from two randomized studies (PROTECT-AF and PREVAIL) and multiple registries formed the basis for the FDA's approval as the only endovascular device indicated for stroke prevention.[12] In the PROTECT-AF study, the WATCHMAN device was shown to be noninferior to warfarin for overall stroke prevention but superior in respect to a decrease in hemorrhagic stroke and long-term bleeding, and to be associated with a reduction in all-cause mortality.[12] The meta-analysis of PROTECT-AF and PREVAIL also showed similar all-cause stroke or systemic embolization rates between the WATCHMAN and warfarin, with lower hemorrhagic stroke and cardiovascular mortality with the WATCHMAN.[12]

Knowledge Check: True or False? The Watchman device is the only endovascular device that is FDA approved for stroke prevention.

Answer: True

Conclusion

As an alternative to chronic anticoagulant therapy, the WATCHMAN device is becoming more widely used in the treatment of Afib as more literature has becomes available. Patients who have been on long-term anticoagulants may be concerned with the risk of side effects and

increased drug interactions with other medication therapies. In addition, a higher amount of bleeding episodes may be a reasonable justification for seeking an alternative intervention. Regarding warfarin, bleeding risks greatly impacts the patient's life and there is the need to periodically check INR, go to follow-up visits, and have constant wary of diet and activities. On the contrary, the WATCHMAN is a one-time permanent implant and does not have the same high bleeding risk as patients using long-term oral anticoagulants. If patients are at a high-risk of bleeding or have increased bleeding complications due to lifestyle factors, they may benefit from the WATCHMAN device and be further assessed as candidates for the implant procedure. In conclusion, the new development of the WATCHMAN device may serve as an effective alternative in AFib treatment and provide an overall more healthful quality of life.

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Electronic Cigarettes: Ongoing Research

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Abstract

Electronic cigarettes have been steadily increasing in popularity over the last few years. The sudden inflation in the use of e-cigarettes has raised interest regarding the safety and composition of these devices. With a large portion of users being adolescents, the concern has prompted investigators to research what the devices contain and try to qualitatively define the chemicals present as well as assess the associated health complications that may arise. Despite the potential health implications associated, e-cigarettes have found a place as an alternative to traditional nicotine replacement therapy as an option for smoking cessation in users who are trying to quit. Recent evidence has indicated a potentially promising place for electronic cigarettes in this facet of the market, however more research is necessary to determine the safety and the future role for these devices.

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Introduction

Electronic cigarettes are battery operated devices that are utilized to deliver aerosolized liquid which often contain nicotine, flavorings and other chemicals. They resemble traditional tobacco cigarettes, pens, or memory sticks and can be recognized by the common names of e-cigs, JUULs, or vapes. Today there are more than 460 e-cigarette brands on market.[1] The e-cigs consist of four different components including; a cartridge or reservoir that holds the liquid solution, a heating element, a power source, and a mouthpiece. Most electronic cigarettes are activated by puffing which powers the heating device and vaporizes the liquid in the cartridge. The aerosol or vapor can then be inhaled by the user. [2]

The liquid solution is typically known by the names "e-liquid" or "e-juice" and contains nicotine, flavorings and other chemicals such as propylene glycol and glycerin.[2]

A Juul is a small form of an electronic cigarette and has shown an increase in popularity. A Juul starter kit costs $50 which contains the Juul device, a charger and four Juul liquid cartridges called pods. A pack of four flavored pods alone costs $16 and each pod has the nicotine content equivalent to that of 1 pack of cigarettes.[3] Juul pods have been shown to contain varying concentrations of nicotine ranging from 25-50 mg/mL.[4] Other vaping devices can range anywhere from $20-$100.[5] E-liquid varies from $7-30 depending on the bottle size and concentration of nicotine.[6] Bottle sizes range from 10-100 mls and typical juice concentrations are 3, 6, 12 mg/ mL.[5]

E-cigarette use on the rise

There has been a rapid evolution in the development of e-cigarettes in the past decade and a dramatic rise in their popularity. From 2008 to 2012, the use of e-cigarettes has doubled in North America.[2]

With e-cigarettes on the rise there is concern with the increase in use among adolescents. The U.S. Surgeon General and Commissioner of the Food and Drug Administration have both declared the rapid rise in rates of youth and e-cigarette use an "epidemic". Deferred enforcement by federal regulation of electronic nicotine delivery system (ENDS) has prompted the industry to boom.[7] Center for Disease Control (CDC) data has showed that while tobacco use has remained steady from 2011-2016, the use of e-cigarettes has increased rapidly.[7] Tobacco use is established among adolescents. Each day about 2,000 individuals, under 18 years of age, smoke their first cigarette and more than 300 individuals become daily cigarette smokers.[8] Flavorings make the tobacco products more appealing to youth as well. In 2014, 73% of high school students who used tobacco products in the past 30 days reported using a flavored tobacco product.[8] Recent increase in e-cigarette usage is driving tobacco usage among adolescents. In 2017, an estimated 2.1 million middle school and high schoolers used e-cigarettes which rose to 3.6 million in 2018.[8] The increased

prevalence in e-cigarette usage has prompted recent studies to be conducted regarding the safety and efficacy of these devices. Some studies have addressed the side effects and health implications that users of e-cigarettes may be at risk for.

The findings of this research could lead healthcare providers, as well as the public to better informed conclusions regarding the use of these devices.

Nicotine Component

Nicotine is the addictive component that is extracted from tobacco and found in regular cigarettes as well as the e-cigarettes.[9] In the article, "Electronic cigarettes and nicotine clinical pharmacology", a literature search was performed to help gain an understanding on the physical impact of nicotine contained in e-cigs regarding dependence and public health.[10] The authors concluded that nicotine yields from the e-cigarettes deliver less nicotine than traditional cigarettes and deliver only modest nicotine concentrations to the inexperienced e-cigarette user. Those that currently smoke are able to achieve concentrations similar to traditional concentrations illustrating the importance of nicotine exposure as a potential smoking cessation aid. The article also touches on potential physical impacts of nicotine in which they mention that nicotine affects the central and peripheral systems and has been shown to be associated with increasing heart rate, blood pressure.[10] While this article shows that there may be a role for e-cigarettes in smoking cessation, it also illustrates that there are health implications associated with the drug as well.[10]

In the article by Schroeder M *et al,* a literature search was done comparing the nicotine yield in varying amounts of inhalations compared to the nicotine yield from a traditional cigarette. The average nicotine yield, based on the International Organisation for Standardization (ISO) smoking conditions, from a single traditional cigarette ranges from 0.5 to 1.5 mg/cigarette.[10] In regards to e-cigarettes, nicotine yields measured from a 100 mL puff ranged from 0.35 mcg/100 mL puff to 31.5 mcg/100 mL puff while another study measured nicotine yields ranging from 0 to 43.2 mcg/100 mL puff.[10] These studies indicate that e-cigarettes deliver less nicotine than traditional cigarettes and also show that there are varying amounts of nicotine that can be obtained from these devices.[10]

Electronic cigarettes have been shown to have varying amounts of nicotine levels contained in them ranging anywhere from 0 to 36 mg/ml, depending on the manufacturer.[9] One study, conducted by Hahn et al. in 2014, sampled 54 different e-cigarette liquid samples. Among those samples, 63% contained nicotine above the detection limit and 5 samples that were allegedly "nicotine free" contained 0.11 mg/ml to 6.9 mg/ml of nicotine.[11]

While nicotine is the primary addictive component in tobacco, non-nicotine tobacco constituents have also been identified in these devices. In the article by Schroeder *et al*, a study was mentioned by

Etter *et al* in which the investigators measured the presence of nicotine-related alkaloids including nornicotine and anabasine in the e-liquid from 20 different e-cigarette models. The two alkaloids were found to range from 0.04% to 0.45% and 0.02% to 0.1%, respectively.[10] The extent to which these constituents may contribute to dependence is unknown.[10]

Not only can the the concentrations of nicotine vary among samples, but some samples have been shown to contain inaccuracies in their nicotine content claims.[9-11] In addition, it has been shown that e-cigarettes may also contain other tobacco constituents, with the role in dependence being unknown.[10] This reinforces the importance of informing individuals about the contents in these devices as there may be deviations from the labelling in some of these products.

Additional components

The main components of the liquid solution are propylene glycol, which creates the artificial smoke of the e-cigarette as well as glycerol, which contains the flavoring agents.[3] The ratio of these ingredients varies from 0:100 (propylene glycol to vegetable glycerin) to 100:0.[9] In the study mentioned previously, conducted by Hahn et al, the authors sampled 54 differetnt e-cigarette liquid samples. Glycerol, propylene glycol and lower levels of ethylene glycol were detected in all samples. Glycerol was not labelled on 5 of the products, propylene glycol on 2 of the products and the presence of ethylene glycol was not labeled on any of the samples.[11] Another study conducted by Tierney et al. looked at two brands of electronic cigarette fluids and the different ingredients contained within 30 different e-cigarette fluids. They took a qualitative approach to the analysis of the fluids and overall, they found that a significant amount of flavoring chemicals were aldehydes (six out of the twenty four different compounds found) which are compounds recognized to be primary irritants of the mucosa of the respiratory tract.[12] Alcohols, esters and ketones were among some of the other components in the liquids.[12] The study found that product labels rarely provided ingredient information beyond the level of nicotine, and the inclusion of propylene glycol and/or glycerol and it concluded that certain concentrations of some flavoring chemicals in e-cigarette fluids are high for inhalation exposure by vaping and can be considered concerning in terms of toxicology.[12] Investigators suggested that regulatory limits should be considered for levels of some of the chemicals as well as for total flavour chemical levels, and the investigators also believe that ingredient labeling should be required.[1] Other investigations conducted by Bahl et al. and Behar et al. looked into the cytotoxicity in comparison to levels of cinnamaldehyde, 4-methoxycinnamaldehyde and vanillin for 10 different cinnamon flavored fluids. For the three compounds, the highest concentrations were ~40, 3 and 8 mg/mL, respectively (~4%, 0.3% and 0.8% by weight or volume).[13,14] In a separate study

conducted by the same investigators cytotoxicity was evident in the form of human pulmonary fibroblasts, human embryonic stem cells and mouse neural stem cells in liquids that were considered to be cinnamon-flavoured.[13]

Role in Smoking Cessation

Electronic cigarettes have been increasing in use and recent evidence has suggested their use as a potential smoking cessation tool. As mentioned before, in the nicotine component section, there has been recent evidence which suggests that they may be effective as a smoking cessation aid. More research has recently been conducted indicating that they may be more effective than traditional nicotine replacement therapy at achieving long term abstinence. A randomized control trial performed in 2019 conducted by Hajek et al. randomized 886 participants into groups that utilized nicotine replacement therapy and e-cigarettes as smoking cessation.[15] Both treatment groups were supported for at least 4 weeks with behavioral support, and the measured primary outcome was sustained abstinence for 1 year. The results found 18% abstinence among the e-cigarette group as compared with 9.9% in the nicotine replacement group. The study concluded that electronic cigarettes were more effective for smoking cessation than other forms of nicotine replacement therapy when both products were accompanied by behavioral support.[15] This recent study shows that there may be a potential role in using these devices as a quitting aid but more research needs to be conducted before the devices can be classified as nicotine replacement therapy.

Conclusion

In conclusion, electronic cigarette use has been increasing steadily over the past decade and has recently rose in the past couple years. There is concern for the users of these devices regarding effects on long term health, especially due to the rapid prevalence in use among adolescents. Research has been conducted to dive into the constituents of the devices and potential health complications from some of these components have been identified. Despite potential implications, electronic cigarettes have recently found their place as a potential smoking cessation tool. With the varying amounts of chemicals and components that have been identified in the devices and the increase in use, it is important that research continues to be done to understand what these devices are made of and what long-term health consequences can be associated. The recent role as a smoking cessation aid is something that has promise but needs to be explored more.

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Annual Review of Changes in Healthcare

GOLD 2018 Report: A Review

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Abstract

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report provides research-based recommendations on the diagnosis, treatment, and evaluation of COPD. The GOLD 2018 Report was conducted to detail new research gathered between January 2016 and July 2017. This report was produced using a PubMed search for titles approved by the GOLD Science Committee. This article describes new data added to the GOLD Report and provides a review on the diagnosis, treatment and evaluation of COPD patients.

Background

The *Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report* offers research-based recommendations on the treatment and evaluation of chronic obstructive pulmonary disease (COPD). GOLD includes information gathered from January 2016 - July 2017 and contains a revised look at data collected in the 2017 report. This article details changes made to the 2018 Report and provides a review of diagnosis, assessment, treatment, and pharmacotherapy.

Summary of Changes

Allinson et al, investigated the role of adverse early life exposure on FEV_1 and FVC in adults. Early life exposures recorded in this study were infant lower respiratory infection, manual social class, home overcrowding, and pollution exposure. The results of this study suggest that smoking accelerated adult FEV_1 decline and could be associated with early-life exposures influence on FEV_1 and FVC in middle-aged adults.[1] This trial is unique in that it shows how smoking influences adverse early life exposures and how these early life exposures impact adult lung function. These findings allow healthcare practitioners to better identify individuals who might be more susceptible to developing COPD. This data from 2017 was added to corroborate several studies suggesting that processes occurring during development and childhood affect lung growth.[2]

Similarly, a study conducted in China was designed to evaluate the association between ambient particulate matter and adult lung function. This was a cross sectional analysis that examined participants via questionnaire and spirometry.[3] The results showed an association between the amount of ambient particulate matter over 1 year of sampling and the prevalence of COPD. This added to data from the 2017 report warning of the dangers that cigarette smoke, occupational exposures, and urban pollution pose. This study allows healthcare professionals and researchers to identify areas where COPD might be more prevalent and warn the public about the dangers of particulates in the air.

Data collected from two studies recommend confirming a patient's post-bronchodilator FEV1/FVC ratio by repeat spirometry on another occasion if the value is between 0.6 and 0.8.[4] Aaron et al, analyzed two prospective cohorts for frequency of diagnostic instability and diagnostic reversals, and determined that using only one spirometry measurement was not reliable in diagnosing COPD in patients with mild to moderate airflow limitations.[4] Another study by Schermer et al, looked at shifts in obstructed versus non-obstructed diagnostic criteria and found that patients often changed from non-obstructed COPD to obstructed COPD based on BMI, older age, and smoking status among other factors. These results suggest that the use of a single spirometry value in diagnosing a patient with COPD may be inappropriate, and that multiple spirometry tests could allow for more efficient treatment. If a patient's FEV1/FVC is less than 0.6, it is unlikely that this value will improve at that visit.[4] The GOLD Report recommends classifying airflow limitation in patients with COPD as FEV1/FVC <0.7. This update from Aaron et al, allows healthcare practitioners to more accurately assess patients with COPD.[4-6]

Several studies have been conducted on the qualities of the GOLD spirometric grading system, and a new study suggests that exacerbation rates vary greatly during follow up. A longitudinal prospective study by Han et al, focused on individuals between 40 and 80 years old with COPD and their yearly exacerbation frequency. 1105 participants met the criteria and 49% had at least one exacerbation during the three year follow-up. In patients with exacerbations during the three year follow up period, few had two or more exacerbations per year. Patients with consistent exacerbation patterns were associated with higher baseline symptom burden, CT airway abnormalities, and high interleukin-15 and 8 concentrations.[7] This data is relevant to healthcare practitioners because it would allow them to more readily identify COPD patients who would have consistent exacerbations. Recognizing consistent exacerbation patterns would aid practitioners' efforts in treating COPD.[7]

Another study added to the GOLD 2018 Report was conducted on the effects of e-cigarette use on participant's airways. [8] Sputum samples from tobacco smokers, e-cigarette users, and nonsmokers were analyzed and it was determined that e-cigarette users had increased markers for inflammation than nonsmokers. The results of this study suggest that e-cigarette use alters the body's innate immune system and causes changes similar to those seen in those who smoke tobacco.[8] This study is beneficial to healthcare practitioners working with patients who may be interested in switching from regular cigarettes to e-cigarettes and provides evidence that e-cigarettes may not be a healthier alternative to cigarettes.[8]

Data on the efficacy of triple therapy with LABA/LAMA/ICS is limited, so researchers designed the FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) to compare participants with COPD receiving once-daily triple therapy and twice-daily ICS/LABA therapy.[9] The FULFIL trial was a randomized, double-blind, double-dummy, study occurring over 24 weeks with co-primary endpoints of change from baseline in trough FEV_1 and change in St. George's Respiratory Questionnaire score. This is a standardized assessment completed by patients to measure the impact of airway disease on health and perceived quality of life.[10] The results of this study suggest that the use of single-inhaler triple therapy is beneficial when compared to ICS/LABA therapy in patients with severe COPD. This information is crucial for healthcare practitioners treating patients with advanced COPD.[9]

Another trial conducted on the efficacy of triple therapy in patients with COPD was the TRINITY trial.[11] This was a double-blind, parallel-group, randomized control trial comparing treatment with extrafine beclometasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium bromide (GB) (fixed triple) versus tiotropium and BDP/FF with tiotropium (open triple). Included participants were required to have an FEV_1 <50%, at least one moderate to severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test (CAT) score of at least ten. A CAT score is generated based on an eight-item questionnaire designed to evaluate the impact of a patient's COPD

symptoms. 1078 patients received fixed triple, 1075 received tiotropium, and 538 received open triple. The fixed triple arm reported moderate-to-severe exacerbation rates of 0.46 (95% CI 0.41-0.52). These results were 0.57 (95% CI 0.52-0.63) for the tiotropium arm and 0.45 (95% CI 0.39-0.52) for the open triple arm. Fixed triple proved to be superior to tiotropium (0.80 [95% CI 0.69-0.92], p=0.0025) when comparing rates of moderate-to-severe exacerbation rates. Adverse events were reported by 55% of patients in the fixed triple, 58% of patients receiving open triple, and 58% of patients receiving tiotropium. The results of this trial concluded that treatment with fixed triple therapy was beneficial over tiotropium in patients with symptomatic COPD, FEV_1<50%, and a history of exacerbations.[11]

A randomized controlled trial performed on azithromycin and its benefit in COPD was added to the GOLD 2018 Report.[12] This study evaluated azithromycin and its ability to decrease exacerbations in participants with COPD at an increased risk for exacerbations. Patients excluded from this trial were those without hearing loss, resting tachycardia, or prolonged QT interval. Of 1142 patients, 570 were randomly assigned to receive 250mg azithromycin daily, and 572 were randomly assigned to receive placebo.[14] Participants completed these treatments for 1 year in addition to their normal therapies. Median time to exacerbation was 266 days (95% CI 227-313) in the azithromycin arm and 174 days (95% CI 143-215) in the placebo arm (P<0.001).[12] Participants were evaluated using St. George's Respiratory Questionnaire, and patients treated with azithromycin saw more improvement in these scores than those treated with placebo (SD decrease of 2.8±12.1 compared to 0.6±11.4, P=0.006).[12] The results of this trial concluded that patients taking azithromycin 250 milligrams daily for a year along with traditional therapy had a decrease in the frequency of exacerbations and improved quality of life over those taking placebo. This evidence supports recommending macrolide antibiotics for patients with an increased risk of exacerbations to reduce exacerbations and improve quality of life.[12]

Another study which added data to the GOLD review was a randomized clinical trial designed to evaluate the effect of adding home noninvasive ventilation (NIV) to home oxygen therapy.[13] Researchers were interested in knowing whether or not this addition would prolong time to readmission or death in patients with COPD and persistent hypercapnia following an exacerbation. 59 patients were randomized to home oxygen alone, while 57 patients received home oxygen plus home NIV. Outcomes included the time to readmission or death within 12 months (adjusted for previous COPD admissions), previous use of long-term oxygen, age, and BMI. The results suggest that within this patient population the addition of NIV to home oxygen prolonged the time to either readmission or death within 12 months. This data is important to individuals using home oxygen therapy and shows how health outcomes might be improved in patients with COPD following an admission.[13]

A study conducted on the association between ambient particulate matter and COPD in China assessed questionnaires and spirometry values of ≥20 year old residents of four different cities. An increase in

particulate matter with a median aerodynamic diameter less than 2.5µm ($PM_{2.5}$) of 10 µg/m^3 was associated with a 26 ml decrease in FEV_1 (95% CI -43 to -9), a 28 ml decrease in FVC (-49 to -8), and 0.09% decrease in FEV_1/FVC (-0.170 to -0.010).[14] These results suggest that exposure to higher concentrations of particulate matter is associated with an increase in COPD prevalence and a decline in patient respiratory function. This data is useful to healthcare practitioners looking for patient populations with high prevalence of COPD looking to make an impact in patient outcomes.[14]

A meta analysis of randomized controlled trials comparing procalcitonin-based protocols for continuing or discontinuing antibiotics versus the standard of care for acute exacerbations in COPD was conducted by researchers to evaluate the efficacy of procalcitonin based protocols.[15] Eight trials containing 1062 patients with acute exacerbations revealed procalcitonin-based protocols decreased antibiotic prescription (0.56, 95% CI (0.43 - 0.73)) and total antibiotic exposure (-3.83, 95% CI (-4.32 - -3.35)) without affecting clinical outcomes. Clinical outcomes reviewed during this meta-analysis include treatment failure, length of hospitalization, exacerbation recurrence rate, and mortality.[15] The small study populations used in this review sacrifices validity and may reduce the quality of evidence.[15]

Diagnosis, Assessment and Treatment

COPD is characterized by respiratory symptoms and airflow limitation resulting from exposure to toxic particulates. Inhaled particles cause oxidative stress which triggers the inflammatory response, leading to an imbalance in proteinases and antiproteinases. These enzymes are important to the body's repair process used in the lungs. Physiological changes that occur as a result of this imbalance and subsequent inability to repair damage include mucus hypersecretion, airflow limitation, the destruction of lung parenchyma, and hyperinflation.[16] The net effect of these changes is a decrease in the ability of the lungs to remain open during expiration and an inability to supply the blood with oxygen.

Spirometry values are used to diagnose and categorize COPD. Values used in the measurement of airflow limitation include forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). A patient's FVC is the volume of air exhaled from the point of maximal inspiration. FEV_1 is the volume of air exhaled during the first second of performing an FVC.[2] The ratio of these values is recorded as FEV_1/FVC, and a post-bronchodilator score FEV_1/FVC of <0.70 indicates airflow limitation that is not completely reversible. This helps confirm a diagnosis of COPD in patients with other symptoms and exposure to toxic particulates.[16,17] Common symptoms of COPD include shortness of breath, chronic cough, and sputum production, and risk factors for COPD include tobacco use, occupational hazards, or exposure to other pollutants. Airflow severity is used to classify COPD and is based on a patient's post-bronchodilator FEV_1. Mild COPD is classified as GOLD 1 and indicates an FEV_1 of 80% of the predicted value. Moderate COPD is classified as GOLD 2 and indicates an FEV_1 between 50-80% of the predicted value. Severe COPD is classified as GOLD 3

and indicates an FEV_1 between 30-50% of the predicted value. Very severe COPD is classified as GOLD 4 and indicates an FEV_1 of <30% of the predicted value.[17]

COPD symptoms are commonly assessed by two different methods. The Modified British Medical Research Council (mMRC) Questionnaire is used to evaluate the degree of a patient's breathlessness. The mMRC scale begins at Grade 0 and ends at Grade 4. Grade 0 is characterized by a patient who is only breathless with strenuous exercise. Grade 4 is characterized by a patient who is too breathless to leave the house, dress, or undress themselves. A more comprehensive assessment can be performed using the COPD Assessment Test (CAT). The CAT evaluates a patient's symptomatic burden resulting from COPD and should be used every 2-3 months to assess trends in a patient's COPD. This test is available at www.catestonline.org. Scores <10 are uncommon in patients diagnosed with COPD and scores ≥10 are uncommon in healthy patients.[17]

In order to fulfill a complete understanding of a patient's COPD, it is necessary to combine these assessment tools and evaluate a patient's "ABCD" rating. These values are determined by a patient's spirometry grade, either mMRC or CAT, and history of exacerbations. Patient's are categorized into group A, B, C, or D, with A indicating a lesser symptom burden and risk of exacerbation *(See Table 1)*. This assessment tool is then used to determine the appropriate therapy for each patient. Patients classified as Group A should begin treatment with a bronchodilator and either continue or attempt a new bronchodilator depending upon the outcome of therapy. Bronchodilators that have proved to be effective treatment agents include short and long-acting $beta_2$-agonists (SABA, LABA) and short and long acting muscarinic antagonists (SAMA, LAMA). Patients classified as Group B should begin treatment with a LABA or LAMA.[17] If symptoms persist, Group B patients may begin a combination of LAMA and LABA therapy.[17] Group C patients should begin therapy with a LAMA and proceed to either a LAMA/LABA combination or LABA/ICS combination if they experience further exacerbations.[17] Group D patients should begin therapy with either a LAMA or a LABA and an inhaled corticosteroid (ICS).[17] If symptoms persist, these patients should be treated with LABA/LAMA combination therapy, and then LABA/LAMA/ICS therapy if symptoms persist further.[17] If this triple therapy does not provide appropriate relief to a Group D patient, prescribers can consider one of two options: Roflumilast may be used in these patients who have an FEV_1 <50% of the predicted value and chronic bronchitis. This recommendation is based on new data on the effects of roflumilast in patients with COPD.[18] Macrolides may be considered if the patient is a former smoker (See Table 2).

Pharmacotherapy

Common bronchodilators used in the management of COPD include $beta_2$-agonists. Their effect is carried out by action on $beta_2$-adrenergic receptors which increase cyclic AMP and inhibit bronchoconstriction.[19] Short acting $beta_2$-agonists (SABAs) provide relaxation of airway smooth muscle for approximately 4-6 hours while the effect of LABAs lasts for approximately 12 hours.[17] Commonly used

SABAs include levalbuterol and albuterol. Patients should be aware that SABAs may be associated with an accelerated heart rate after administration. It is also important to counsel patients on proper usage and storage of their SABAs.[20] Commonly used LABAs include formoterol and salmeterol, which are also associated with a rapid heart rate. Patients should be counseled on the appropriate use and storage of their LABA.[20]

LAMAs facilitate the inhibition of acetylcholine on M3 muscarinic receptors to block bronchoconstriction in airway smooth muscle.[19,20] Common LAMAs used in the treatment of COPD include aclidinium bromide and tiotropium, which have a duration of effect between 12 and 24 hours. Patients should be made aware that these drugs are associated with trouble urinating, dry mouth, and upset stomach.

ICSs are only recommended for use in COPD with other long-acting bronchodilator therapy.[17] ICSs inhibit the release of inflammatory mediators and mitigate IgE synthesis. This reduces the lungs response to allergens, but these medications do not have any bronchodilatory properties. Common ICSs used in combination with bronchodilators include budesonide, mometasone, and fluticasone. ICS may take several hours or days to notice an effect. Patients should be warned not to discontinue ICS use on their own, as some studies have shown an increase in exacerbations upon discontinuation of an ICS.[17] ICSs are associated with an increased prevalence of oral candidiasis, and patients should be counseled to rinse out their mouths and spit out the water after administration of these medications. Other adverse effects of ICS use include increased prevalence of pneumonia, GI upset and cataract development.[17,19,20]

Roflumilast is only recommended for use in patients with COPD who are Group D and have progressed through triple therapy with LAMA, LABA and ICS. These patients must also exhibit an FEV_1 that is <50% of the predicted value.[17] To treat COPD, roflumilast is dosed at 250 mcg once daily for 4 weeks and increased to a dose of 500 mcg once daily depending upon the patient's response. This medication has no bronchodilatory properties. Roflumilast has been known to cause GI upset, headaches, and muscle cramps, and patients should be made aware that this drug may be taken with or without food.[19,20]

A revised look at studies on continuous antibiotic use in patients with COPD suggests that their use may reduce exacerbation rates.[17] This is reflected in the recommendation to begin macrolides in patients who are former smokers and who have attempted triple therapy with LABA, LAMA, and ICS without relief. Azithromycin 250 mg/day or 500 mg three times per week and erythromycin 500 mg two times per week showed a reduction in exacerbations in patients treated with these therapies for one year.[17] Macrolides inhibit protein synthesis by binding the 50S subunit of bacterial ribosomes.[19,20] The most common side effect associated with these medications is GI upset including diarrhea, nausea and vomiting. Patients should also be counseled to look for symptoms including a rapid heartbeat, changes in hearing, and dizziness. These drugs should be taken with food if the patient is experiencing GI upset, and patients should be aware that the use of

antacids two hours before or two hours after is not recommended *(See Table 3).*

Revisions and new information included in the updated GOLD 2018 Report will allow healthcare practitioners to use the most updated information in the care for COPD patients. By exploring this novel research and reviewing how these changes have been incorporated into current guidelines on COPD pathophysiology, diagnosis, treatment, and evaluation, individuals may be better equipped to manage patients with COPD.

Appendix

Table 1 - ABCD Rating		
Exacerbations	mMRC 0 - 1 or CAT < 10	mMRC ≥ 2 or CAT ≥ 10
0 or 1 which did not lead to hospitalization	**Group A**	**Group B**
≥ 2 or ≥ 1 which lead to hospitalization	**Group C**	**Group D**

Table 2 - COPD Severity and Therapy				
Severity:	First-line:	Second-line:	Third-line:	Last-line:
Group A	SABA or SAMA or LABA or LAMA	Alternate bronchodilator		
Group B	LABA or LAMA	LABA and LAMA		
Group C	LAMA	LABA and LAMA	LABA and ICS	
Group D	LAMA or LABA and ICS	LAMA and LABA	LAMA, LABA and ICS	Roflumilast or macrolides

Table 3 - Pharmacotherapy							
	SABA	**SAMA**	**LABA**	**LAMA**	**ICS**	**Roflumilast**	**Macrolides**
Classification	Short Acting $Beta_2$ adrenergic Agonist	Short Acting Muscarinic Antagonist	$Beta_2$ adrenergic agonist	Long Acting Muscarinic Antagonist	Inhaled Corticosteroid	Phosphodiesterase-4 (PDE-4) Enzyme Inhibitor	Antibiotic
Mechanism of action	Activating $beta_2$ adrenergic receptors relaxes bronchial smooth muscle by activating cAMP.	Blocking muscarinic receptors causes bronchodilation by decreasing cGMP. Not selective for specific muscarinic receptors	Activating $beta_2$ adrenergic receptors relaxes bronchial smooth muscle by activating cAMP. Highly lipophilic resulting in long duration of action	Blocking muscarinic receptors causes bronchodilation by decreasing cGMP Antagonizes M_1, M_2, and M_3 muscarinic receptors	Glucocorticoids inhibit the activity of inflammatory mediators	Inhibition of PDE-4 causes an increase in cAMP in inflammatory cells suppressing cytokine release.	Binds the 50S ribosomal subunit and inhibits RNA dependent protein synthesis.
Side-effects	Accelerated heart rate, hypokalemia	Bronchitis	Chest pain	Xerostomia, upper respiratory tract infections, pharyngitis, sinusitis	Respiratory infections, rhinitis, candidiasis	Headache, weight loss, diarrhea	Loose stools, vomiting, diarrhea, skin photosensitivity,
Products	Albuterol, levalbuterol	Ipratropium bromide	Formoterol, salmeterol	Tiotropium	Budesonide, beclomethasone, mometasone, fluticasone	Roflumilast	Azithromycin, erythromycin
Evidence	21	22, 23	24, 25, 26	27, 28, 29, 30	31, 32	18, 33, 34, 35, 36	10, 37

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ARCH
Annual Review of Changes in Healthcare

Benefits and Risk of Aspirin as Primary Prevention of Cardiovascular Disease

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Abstract

The use of aspirin for primary prevention has been a long-debated topic in healthcare. Up to 20% of the United States population takes aspirin daily or every other day with or without a recommendation from a physician. Aspirin has a well-established role in the secondary prevention of cardiovascular disease. However, in the setting of primary prevention, clinicians should balance the potential cardiovascular events prevented with the risk of major bleeding and should be a decision that providers make on an individual basis. The goal of this review article is to summarize and analyze the results of recent studies testing the use of daily low-dose aspirin in the setting of primary prevention.

Recently, new studies have tested the outcomes of aspirin as primary prevention and have added new information to the topic. The ASCEND trial, ARRIVE trial, and ASPREE trial each tested aspirin as primary prevention in a specific risk factor group. The groups studied were for cardiovascular disease including diabetes, high-risk, and elderly patients respectively. In the ARRIVE and ASPREE trials, patients taking daily low-dose aspirin did not differ significantly from placebo in the prevention of composite cardiovascular events but did have a significant increase in bleeding events. In the ASCEND trial a significant reduction in cardiovascular events among diabetes patients was offset by a significant increase in major bleeding.

The role of aspirin in primary prevention should be reevaluated based on the results of these new trials. The 2019 American Heart Association/American College of Cardiology Guideline on the Primary Prevention of Cardiovascular Disease recommends that low-dose aspirin may be considered for primary prevention of cardiovascular disease in adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding. It is also now recommended that low-dose aspirin not be given on a routine basis for the primary prevention of ASCVD among adults >70 years of age. Further studies should evaluate the use of daily low dose aspirin in different high-risk groups and groups without access to primary care.

Aspirin is one of the most widely available and inexpensive drugs used by patients in the United States and most developed countries.[1] In a 2005 survey conducted by the Agency for Healthcare Research and Quality, results showed that about one in five U.S. adults aged 18 and older reported taking aspirin every day or every other day, with or without recommendation from a physician, with over half the respondents being over the age of 65.[1] Among this sample of patients at least age 65 years old, 41% of these patients were using aspirin as primary prevention of cardiovascular disease (CVD) despite not being told they had indicators of heart disease by their health care provider. It is important for both patients and providers to have communication with one another especially when making the decision to take medication.[1]

With the availability of aspirin being so prevalent, inappropriate use of aspirin initiated by providers or patients may subject these patients to an increased risk of adverse effects without offering benefits towards prevention of cardiovascular events.

The use of daily low-dose aspirin does play a significant role in the prevention of cardiovascular events. Previous studies have shown that low-dose aspirin can be beneficial for certain patients in the setting of secondary prevention of stroke, coronary artery disease, and myocardial infarction (MI), and thus multiple guidelines have endorsed this recommendation.[2,3] Secondary prevention is defined as the actions taken to prevent the progression or recurrence of disease or injury after it has already happened, while primary prevention is defined as the actions taken to prevent disease or injury before initialonset.[4] The use of aspirin as primary prevention of CVD without a history of such disease, underlying condition, or other indication, has remained uncertain due to conflicting studies and differences in opinions of risks versus benefit.

The role of aspirin as primary prevention of CVD has been studied heavily over the past few decades. Current recommendations are largely influenced by the 2009 Antithrombotic Trialist Collaboration which found in a meta-analysis of 6 randomized control trials, that in the setting of primary prevention daily low dose aspirin was associated with a 12% reduction in serious vascular events compared to no daily aspirin.[5] Despite numerous studies, the benefits and risks of aspirin as primary prevention still remain uncertain in part due to difficulty balancing the benefits of CVD reduction and increase in bleeding risk and new trials presenting conflicting results.[6]

In 2018, three separate studies titled ASCEND, ARRIVE, and ASPREE trials were published, each testing the use of aspirin as primary prevention in select patient groups with a risk factor for cardiovascular events.[7,8-11] The goals of each of these trials was to ultimately gain a better understanding of the use of aspirin as primary prevention and to assess the safety and tolerability for each of their specific patient populations.

Guideline Review

Aspirin is a mainstay treatment of secondary prevention of MI or stroke according the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of acute coronary syndrome and the American Heart Association/ American Stroke Association guidelines for management of stroke. Each of these guidelines support the efficacy of aspirin therapy and conclude that the benefits outweigh the risks in the setting of secondary prevention (Grade A evidence).[2,3]

The United States Preventive Services Task Force currently recommends that aspirin may have a role in the setting of primary prevention for adults aged 50 to 59 years with a ≥10% 10-year CVD risk may have a benefit with the initiation of daily low-dose aspirin as long as the patient is not at increased risk for bleeding, has a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (Grade B). This group has been shown to have the greatest benefit. The decision to initiate daily low-dose aspirin in adults aged 60-69 who have a 10% or greater 10-year CVD risk is not routinely recommended and should be based on clinical judgement (Grade C).[12]

The 2012 American College of Chest Physicians CHEST guidelines recommend that for primary prevention of CVD, low-dose aspirin in patients aged > 50 years should be used over no aspirin therapy (Grade 2B).[13]

The 2016 European guidelines on cardiovascular disease prevention in clinical practice sponsored by the European Society of Cardiology suggest that individuals without cardiovascular or cerebrovascular disease are not recommended to take daily low dose aspirin for primary prevention (Grade IIIB).[14]

In regards to patients with diabetes, the 2019 American Diabetes Association Standards of Care for Diabetes suggest that daily low dose aspirin may be considered as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk as long as the risks of increased bleeding are discussed (Grade C).[15]

Guidelines are overall conflicting specific to different factors. Individual clinic judgement of risk versus benefit should be considered in all patients.

Mechanism Overview

Aspirin is well defined as an irreversible COX-1 and COX-2 inhibitor.[16] This mechanism leads to decreased platelet aggregation and anti-inflammatory effects secondary to decreased synthesis of thromboxane A2 and prostaglandin, respectively.[16] Serious side effects of this medication include, but are not limited to, gastrointestinal bleeding, ulceration, and cerebral hemorrhage.[16]

ASCEND Trial

Data representing the use of aspirin in primary prevention for diabetic patients is still uncertain and controversial. Diabetes is associated with a 2-4 times greater risk of CVD compared to those without diabetes.[6] Previous primary prevention trials have

shown that aspirin can significantly reduce the incidence of CV events in patients with diabetes but newer studies, such as the Prevention and Progression of Arterial Disease and Diabetes (POPADAD) trial showed that aspirin failed to significantly reduce CV events in patients with diabetes.[6,17] The ASCEND trial has added further information regarding this dilemma.
The goal of the ASCEND trial was to address this need by evaluating the safety and efficacy of aspirin use in diabetic patients without a history of CVD.[7] This trial randomly assigned 15,480 adults in the United Kingdom with diabetes and no evident CVD, to receive daily enteric-coated aspirin 100 mg or placebo.[7] Relevant inclusion criteria included: age of at least 40 y/o, any type of diagnosed diabetes, and no history of CVD.[7] Primary efficacy outcomes measured were nonfatal myocardial infarction, nonfatal ischemic stroke, transient ischemic attack, or death from any vascular damage.[7] Primary safety outcomes measured were first occurrence of major bleeding, including gastrointestinal bleeding, intracranial hemorrhage, sight-threatening bleeding event in the eye, or other bleeding event that required hospitalization or transfusion.[7]

Significant results of this study showed that patients with diabetes who did take daily aspirin had a 12% reduction in serious vascular events compared to placebo ($p=0.01$).[7] The risk of serious bleeding however was 29% higher in the daily aspirin group versus placebo ($p=0.003$).[7] A majority of the serious bleeding episodes included gastrointestinal bleeding. Between the two groups there was no significant difference seen in all-cause mortality.[7] Despite the reduction in cardiovascular events the results of this trial are difficult to interpret due to significantly increased instances of bleeding events.

ARRIVE Trial
The objective of the ARRIVE trial was to assess the efficacy and safety of aspirin compared to placebo in patients with moderate risk of their first cardiovascular event.[8] Moderate risk was defined as having two to four risk factors for males and three to five risk factors for women.[8] These risk factors included: dyslipidemia, current smoker, high systolic blood pressure, receiving medication for high blood pressure, and a positive family history of CVD.[8] Based on these risk factors, subjects were estimated to have a 10-year ASCVD risk score between 10-20%.[8] There were 12,546 participants enrolled in the study, with a median follow-up of 60 months.[8] Over 90% of the participants were from Germany, Poland, and the United Kingdom and each study group had approximately equal baseline characteristics.[8] Patients were randomized to receive either 100 mg aspirin daily or placebo daily.[8] Primary outcomes measured were a composite of time to first occurrence of confirmed myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischemic attack.[8] Hemorrhagic and major bleeding events were monitored for safety.[8]

Results of this study showed that that aspirin did not significantly decrease the risk of composite major cardiovascular events

(p=0.619) or any individual type of cardiovascular event.[8] The ARRIVE trial did show that the aspirin group had a significant increase in gastrointestinal bleeding (p=0.0007).[8] Most of the gastrointestinal bleeding was diagnosed as mild and non-fatal and there was no difference seen in fatal bleeding between the aspirin and placebo group.[8]

The results of the ARRIVE trial suggest that aspirin use does not have a significant effect on the occurrence of cardiovascular events but did increase the risk of gastrointestinal bleeding. It is important to note that the event rate of cardiovascular events was much lower than expected and may have been a contributing factor.[18] The mean estimated 10 year-ASCVD risk score among participants was 17.3% but the actual 10-year rate in this trial was estimated to be 8.43% in the aspirin group and 8.80% in the placebo group, both of which are much lower than expected and suggest that this sample of subjects represents patients in a low to moderate risk of ASCVD. This may have played a role in why little benefit was seen in the aspirin group.[18]

ASPREE Trial

The ASPREE trial was published in the *New England Journal of Medicine* in October 2018. This study was conducted between 2010-2014, with 19,114 participants, aged 70 years of age or older from Australia and the United States.[9] The objective of this study was to determine whether daily use of aspirin provides benefit with the primary end point of disability-free survival.[9]

The ASPREE trial originally aimed at determining whether low-dose aspirin increases healthy life-span (survival free of dementia and disability).[9] It was a randomized, double-blind, placebo-controlled, primary prevention trial of daily 100 mg aspirin in an older, healthy population with an average treatment duration of 4.5 years.[9] The original primary efficacy measured endpoint of the study was death from any cause, incident dementia, or persistent physical disability, which was assessed every 6 months.[9] Secondary outcome measures were major health issues related to aging (all-cause mortality, fatal and non-fatal cardiovascular events, dementia, mild cognitive impairment, physical disability, major hemorrhagic events, and depression), which were also assessed every 6 months.[9] Inclusion criteria for participants in the trial included: age 65 years or older for African American and Hispanic persons, and any person from another ethnic minority group as well as Caucasian persons 70 years or older.[9] Some notable exclusion criteria included: a history of a diagnosed cardiovascular event, a serious illness likely to cause death within the next 5 years, diagnosed atrial fibrillation, a current or recurrent condition with a high risk for major bleeding, current continuous use of aspirin or other antiplatelet drug or anticoagulant for secondary prevention, a systolic blood pressure ≥180 mmHg and / or a diastolic blood pressure ≥105 mmHg, a history of dementia.[9]

The results of this trial suggested that daily low dose aspirin did not prolong disability-free survival among healthy adults and increased the rate of all-cause mortality compared to placebo.

The ASPREE trial had several sub-analyses conducted. Significant sub-studies to cardiovascular risk were observed and one of the published sub-studies focused on the comparison of the aspirin versus placebo on cardiovascular events and major bleeding in healthy elderly. The sub-analysis measured the endpoints of composite fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, and hospitalization for heart failure.[10] In the aspirin group the rate of CVD was 10.7 events per 1000 person-years versus 11.3 events per 1000 person-years in the placebo group (hazard ratio, 0.95; 95% confidence interval [CI], 0.83 to 1.08).[10] This sub-study also analyzed major hemorrhagic events such as upper gastrointestinal bleeding and intracranial bleeding for safety.[10] The rate of major hemorrhage in the aspirin group was measured to be 8.6 events per 1000 person-years and 6.2 events per 1000 person-years, in the placebo group (hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).[10]
These results suggested that the group receiving daily aspirin had an increased risk of major bleeding or hemorrhage without significantly lowering the risk of CVD when compared to the placebo group.[10] It should be noted that the rate of cardiovascular events was much lower than anticipated and could account for the lack of difference seen.[10]

The trial investigators went on to conclude that based on their analysis, daily low dose aspirin was associated with a greater all-cause mortality, among healthy older adults compared to those who received placebo.[11] This conclusion was different from what was seen in the ASCEND and ARRIVE trial where no difference in overall mortality was observed. An important note on this conclusion is that the higher rate of death seen in the aspirin group was seen in the population from Australia and cancer-related death was the primary cause of most deaths.[11] No specific cancer type was more prevelant.[11]

Discussion

The ASCEND, ARRIVE, and ASPREE trial each addressed an important individual predictor of CVD which includes diabetes, high risk, and old age, respectively. Each of these groups are potentially a higher risk for cardiovascular events and the need for preventative therapy, such as aspirin may be beneficial. Previous studies have not had definitive results as to what patient populations benefit the most from primary prevention with aspirin therapy, and to what extent the benefits outweigh the risk of severe bleeding.[6,9-11] Each of the trials discussed in this article investigated whether aspirin use as primary prevention would provide a significant benefit in cardiovascular outcomes. In the ASCEND trial, patients with diabetes did show a significant benefit in reduction of cardiovascular events but was offset by a significant increase in incidences of bleeding.[7] The ARRIVE trial did not show a benefit in cardiovascular events but did increase the risk of gastrointestinal bleeding.[8] Lastly, the ASPREE trial showed there was no benefit of aspirin therapy in patients >70 years old or >65 if black or Hispanic, but again, increased the risk of bleeding.[9-11] All three studies showed patients had a significant increase in bleeding across all

aspirin groups. How a clinician balances the potential benefits and risks of aspirin therapy is still a gray area and the results of these studies suggest that aspirin therapy may not be appropriate for some groups and should be a more selective treatment option for patients based on individual past medical history.

Studies examining aspirin in the setting of primary prevention have been an ongoing dilemma for decades.[6] With significant changes in healthcare technology and the healthcare system, this further confounds the results of studies. Successful treatment of many different comorbidities such as hypertension and dyslipidemia has generally improved the overall health of patients and in some instances reduced the event rate of CVD outcomes.[6,8] This was a suggested cause for the lower event rate seen in the ARRIVE and ASPREE trial. In the ASCEND, ARRIVE, and ASPREE trials a significant number of patient were on statin therapy with those percentages being 75%, 43%, and 34% respectively.[7,8-11] In previous primary prevention trials patients on statin therapy were associated with up to a 25% decrease in risk of major CV events for every 1 mmol/L decrease in LDL without an increased risk of bleeding.[18]
Ongoing advances in healthcare have continuously affected primary prevention trials throughout the years of study and increases the difficulty of designing and conducting trials.[8] The benefits of treating comorbidities, new therapies, and access to healthcare has influenced the incidence rate and confounded the true benefit of daily aspirin therapy in primary prevention.[18] However, the combination of recent modern-day trials does provide meaningful information about the place of therapy for aspirin in primary prevention. These trials include patients in modern day healthcare systems, including the U.S and various parts of Europe, that that have effective management of comorbidities and access to healthcare resources. The results of these studies reflect outcomes that are more realistic of today's healthcare society versus the past where healthcare access and options were more limited. These studies suggest that treatment with aspirin may not be beneficial or needed in patients without prior CVD and managed comorbidities.
Results of these trials have influenced new recommendations from the AHA and ACC regarding primary prevention with the use of aspirin. In March 2019 the ACC/AHA Guideline on the Primary Prevention of CVD was released. This updated guideline now recommends that low-dose aspirin not be administered on a routine basis for primary prevention of ASCVD among adults >70, or for adults of any age who are at an increased risk of bleeding. The role for aspirin in primary prevention may be considered in select higher ASCVD adults aged 40-70 years who are not at increased bleeding risk.[19] Further studies will need to address different high-risk populations and other factors to truly determine the benefits and risks of aspirin therapy.

Aspirin is a widely available drug for the general public and improper use poses a risk to many consumers. Low dose aspirin is often marketed with the thought of being heart healthy and rarely associated with many of the serious side effects by the common

layperson. This poses a risk for patients who do not communicate or follow-up with a primary healthcare provider regularly as they may start potentially unnecessary therapy that increases the risk of bleeding events and hospitalization without offering benefit. Aspirin has been an extremely effective and affordable medication for decades and will likely continue to be used for secondary prevention of stroke and MI. However, in the setting of primary prevention without a history of CVD, the risk versus benefit of using aspirin needs to be weighed closely. Other effective treatments for comorbidities and risk factors should be considered to reduce the risk of CVD first. Patients and providers should be educated about the risks and benefits of aspirin therapy and patients should consult a healthcare provider when making the decision to use this medication.

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