ISSN 2575-8128

Established 2017 Volume 5, Issue 1

ARCH
annual review of changes in healthcare

May 12, 2021

Table of Contents

The Annual Review of Changes in Healthcare (ARxCH)

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

Online journal is available at: https://www.thearxch.com/

Notice and Disclaimer

ARCH
Annual Review of Changes in Healthcare

Antibiotic Resistance in 2020

Cassandra Kuhn, PharmD Candidate 2021[1]
[1]*University of Findlay College of Pharmacy*

Abstract

Antibiotic resistance has become a growing issue in the past decade. With more and more bacteria becoming increasingly resistant, healthcare workers are finding it more and more difficult to treat certain bacterial resistant infections. Several factors contribute to this issue which may include a lack of profitability of antibiotics and lack of new mechanisms of action being discovered. The FDA and WHO are attempting to combat this problem, but despite their efforts, there are still too few new novel antibiotics. With COVID-19 emerging in the last year, the uncertainty around increasing antibiotic resistance has grown even more.

In January 2020, the World Health Organization (WHO) published a warning about the global threat of antibiotic-resistant organisms and the lack of new antibiotics being developed.[1] Dr. Tedros Adhanom Ghebreysus, the director-general of WHO said, " Never has the threat of antimicrobial resistance been more immediate and the need for solutions more urgent."[1] Reasons for the lack of new antibiotics entering the market includes declining private investment and lack of innovation.[1] Smaller companies have been leading the research and development of new antibiotics while larger enterprises are exiting the field.[1] Antibiotics are not as desirable to produce to larger companies because unlike chronic conditions which require medications that are taken for years, acute infections last only a few weeks. This means that antibiotics have a low profitability for drug makers. In addition, newer antibiotics entering the market do not differ greatly from existing antibiotics.[1] While new antibiotics on the market may have broader coverage, they have very similar mechanisms of action to antibiotics already on the market. For example, one of the recently approved antibiotics, Zerbaxa ® (ceftolozane/tazobactam) is a combination drug that includes a cephalosporin plus a beta lactamase inhibitor, both of which are not novel mechanisms of action.[2]

Mechanisms of Resistance

Gram-negative bacteria, specifically Gram-negative bacilli, are notorious for developing resistance in the past several years.[1] Gram-negative bacteria have an outer membrane, a thin layer of peptidoglycan, and an inner membrane, all of which are used as a barrier to resist antibiotic penetration and permeability.[2] Another way that Gram-negative bacilli acquire resistance is by horizontal gene transfer. This allows the bacteria to produce drug efflux permeases and antibiotic-modifying enzymes.[2] It also allows the bacteria to bypass targets and mutate or modify ribosomes.[2]

Beta-lactamases are especially known for causing resistance to beta-lactam antibiotics. Extended spectrum beta-lactamases (ESBLs) provide bacteria resistance to penicillins and cephalosporins, and carbapenamases provide resistance to carbapenems.[2] Currently, carbapenems are considered the "last line" of defense against highly resistant organisms.[1] There is high concern for drugs that produce ESBL and carbapenemases. Specifically, there is a gap in activity against a beta-lactamase called NDM-1 (New Delhi metallo-beta-lactamase 1).[1] Bacteria that produce this beta-lactamase are resistant to a broad range of antibiotics, including carbapenems.[1]

WHO has published a list of "priority pathogens" that pose the greatest threat to humans.[3] The list includes organisms that are of critical, high, and medium priority. The ranking is based on which organisms have the most resistance to antibiotics.[3] Pathogens in the critical priority ranking include *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae.[4] These gram-negative rods are becoming increasingly resistant to broad-spectrum antibiotics (including carbapenems and third-generation cephalosporins) and are a major threat to

patients who are hospitalized, in nursing homes, or patients who require invasive devices such as a pacemaker, ventilator, or catheter.[3] High priority pathogens include *Enterococcus faecium*, *Helicobacter pylori*, Salmonella species, *Staphylococcus aureus*, Campylobacter species, and *Neisseria gonorrhoeae*.[4] Medium priority pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and Shigella species.[4] The priority pathogens list was created in order to help increase research and development for new antibiotics that target these specific pathogens. Tuberculosis is not included in the list of priority pathogens because it has its own dedicated programs.[4] Tuberculosis resistance has been growing in recent years and is listed as a global priority for research and development.[4] Tuberculosis causes 1.8 million deaths per year, making it the number one infectious disease killer in the world.[4]

WHO and the Food and Drug Administration (FDA) have taken measures to attempt to increase the research and development of new antibiotics.[1] WHO, along with the Drugs for Neglected Disease Initiative (DNDi), have formed the Global Antibiotic Research and Development Partnership (GARDP).[1] GARDP is a non-profit research and development organization that aims to accelerate the development of new antibiotics that target drug-resistant bacteria.[1] GARDP's goal is to deliver five new treatments by 2025.[1] The organization is also working with partners in over 20 other countries to grant access and affordability to treatments to those in need.[1] In 2012, the Generating Antibiotics Incentives Now (GAIN) Act was signed into law as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) which aimed to strengthen drug development efforts for bacteria that were growing increasingly resistant.[2] The GAIN Act created a designation for antibiotics called qualified infectious disease products, or QIDP, if it meets certain criteria.[2] Antibiotics qualify for QIDP designation if they treat serious or life-threatening infections caused by emerging pathogens or specific multidrug resistant pathogens specified by the FDA.[2] In the past decade, 12 new antibiotics have been approved using the QIDP designation, treating infections such as complicated urinary tract infections, hospital-acquired pneumonia, ventilator-associated pneumonia, acute bacterial skin and soft tissue infections, traveler's diarrhea, and complicated intra-abdominal infections.[2]

Fortunately, several new antibiotics are currently in the pipeline. Of the 50 antibiotics in the pipeline as of January 2020, 32 target WHO priority pathogens.[1] However, only a few are active against multi-drug resistant Gram-negative bacteria.[1] The preclinical pipeline looks more promising with over 250 agents being researched to treat WHO priority pathogens.[1] However, these drugs still need to show safety and efficacy and will most likely not be available for several years.[1]

Another promising development in research and drug development is the use of artificial intelligence (AI). In February of 2020, a paper was published that described how AI had been used to discover a new potential antibiotic.[5] Researchers collected data of over 2,000 unique compounds and trained a neural network to find molecules

that stop *E. coli* growth.[5] The model then went through over 6,000 molecules to identify compounds that target *E. coli*, and it correctly predicted antibacterial activity in 51 compounds.[5] Specifically, a molecule called c-Jun N-terminal kinase inhibitor SU3327 was identified by the AI and had very promising activity.[5] In mice, *E. coli*, *Clostridium difficile, Mycobacterium tuberculosis,* and pan-resistant *Acinetobacter baumannii* were susceptible to the newly discovered compound.[5] The drug was effective against every organism that it was tested against aside from *Pseudomonas aeruginosa*.[6] Furthermore, after 30 days, *E. coli* had not developed resistance to the compound while the bacteria began to develop resistance to ciprofloxacin within 3 days.[6] Researchers named the compound "halicin" after Hal, the AI system in the movie *Space Odyssey 2001*.[5] Halicin's structure is unlike typical antibiotics, which means that AI could be very important in discovering new classes of antibiotics in the future.[6]

In the age of the COVID-19 pandemic, antibiotic resistance continues to be an issue, and the pandemic brings forth additional resistance and infectious disease issues. Hospitalized COVID-19 patients may be receiving unneeded antibiotics, and for several weeks, azithromycin and hydroxychloroquine were being used, which is now considered by the CDC to be an inappropriate treatment for COVID-19.[7] Antibiotics are not recommended for COVID-19 patients unless evidence suggests that there is an underlying bacterial infection.[7] Using antibiotics when they are not needed can lead to resistance and potentiate the already existing antibiotics resistance issue. Additionally, hospital admissions increase the risk of acquiring and transmitting healthcare-associated infections which tend to be more resistant and may increase antibiotic use.[7] The pandemic has also led to interruptions in care such as patients not receiving vaccinations on time. Furthermore, wide use of biocidal agents can select for more resistant strains and contribute to antibiotics resistance.[7]

Overall, antibiotic resistance is a global issue that needs the attention of medical professionals, especially pharmacists. Pharmacists can have a crucial role in helping to be stewards of antibiotics by using them appropriately and avoiding overuse.

References

1) Lack of New Antibiotics Threatens Global Efforts to Contain Drug-resistant Infections [Internet]. World Health Organization. World Health Organization; 2020 [cited 2021Jan19]. Available from: https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections
2) Pontefract BA, Ho HT, Crain A, et al.. Drugs for Gram-Negative Bugs From 2010–2019: A Decade in Review [Internet]. OUP Academic. Oxford University Press; 2020 [cited 2021Jan19]. Available from: https://doi.org/10.1093/ofid/ofaa276
3) WHO Publishes List of Bacteria for which New Antibiotics are Urgently Needed [Internet]. World Health Organization. World Health Organization; 2017 [cited 2021Jan19]. Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
4) 2019 Antibacterial Agents in Clinical Development: an Analysis of the Antibacterial Clinical Development Pipeline [Internet]. World Health Organization. World Health Organization; 2019 [cited 2021Jan19]. Available from: https://www.who.int/publications/i/item/9789240000193
5) Burki T. A New Paradigm for Drug Development [Internet]. The Lancet Digital Health. Elsevier; 2020 [cited 2021Jan18]. Available from: https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30088-1/fulltext
6) Trafton A. Artificial Intelligence Yields New Antibiotic [Internet]. MIT News. Massachusetts Institute of Technology; 2020 [cited 2021Jan19]. Available from: https://news.mit.edu/2020/artificial-intelligence-identifies-new-antibiotic-0220
7) Getahun H, Smith I, Trivedi K, et al. Tackling Antimicrobial Resistance in the COVID-19 Pandemic [Internet]. World Health Organization. World Health Organization; 2020 [cited 2021Jan19]. Available from: https://www.who.int/bulletin/volumes/98/7/20-268573/en/

ARCH
Annual Review of Changes in Healthcare

Novel Drug Review of Approved 2020 Breast Cancer Agents

Oscar E. Freyre, PharmD. Candidate 2021[1]
[1]*University of Findlay College of Pharmacy*

Abstract

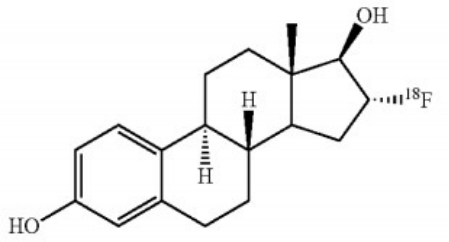
Annually, The Food and Drug Administration's Center for Drug Evaluation and Research publishes a report containing the latest drugs approved. In this review, the following breast cancer agents; Cerianna™ (fluoroestradiol F-18), Trodelvy (sacituzumab govitecan-hziy), and Tukysa (tucatinib), are evaluated for their drug properties including dosing and administration, absorption, distribution, metabolism, excretion, and adverse effects & warnings. In addition to their pharmacological parameters, review of the National Comprehensive Cancer Network (NCCN) Breast Cancer clinical guidelines assess how these agents may impact current clinical practice.

The Food and Drug Administration's Center for Drug Evaluation and Research annually publishes a report containing the latest drugs approved.[1] This report provides a list of novel agents with links to their drug trial snapshots and press releases.[1] In 2020 there were 40 newly approved drugs, three of which are the following breast cancer agents; Cerianna™ (fluoroestradiol F-18), Trodelvy (sacituzumab govitecan-hziy), and Tukysa (tucatinib).[1] These newly approved agents may add to the arsenal of treatment options to be used throughout the different stages and specific tumor characteristics of breast cancers.

Background

For women between the ages of 20-59 years old, breast cancer is the leading cause of cancer death.[2] Breast cancer is estimated to occur in about one-in-eight women as a result of endocrine, genetic, environmental, and lifestyle factors.[2] In 2019, there were 62,930 non-invasive breast cancer cases among women and 271,270 cases of invasive breast cancers that resulted in 42,260 deaths.[2] Prevention, early detection, breast cancer conserving surgery, and mastectomy are fundamental to the treatment of breast cancers, however, later stages require additional pharmacologic treatment regimens specific to tumor characteristics (e.g. hormone receptor positive [HR(+)], human epidermal growth factor receptor 2 positive [HER2(+)], and triple negative breast cancer [TNBC]).[2] The objective of this article is to describe characteristics of Cerianna™, Trodelvy™, and Tukysa™ while considering their potential use in clinical practice guidelines for the treatment of breast cancers.

Cerianna™ (fluoroestradiol F-18)



Cerianna™ is a parenteral radiopharmaceutical agent approved for the detection of estrogen-receptor-positive (ER+) lesions with the use of positron emission tomography (PET) scans in patients with recurrent or metastatic breast cancers.[3,4] Cerianna™ is only useful for the detection of estrogen receptors and is not effective for the detection of progesterone receptors (PR) or human epidermal growth factor receptor 2 (HER2).[3] As a radiopharmaceutical agent, safety precautions must be taken prior to administration. Only experienced and trained providers can administer Cerinna™. They must wear waterproof gloves and radiation shielding.[3] Patients must adequately hydrate before and after receiving Cerianna™.[3]

Dosing & Administration:

For PET imagining, a single bolus dose of 6mCi (222MBq) IV infused over 1-2 minutes, with a maximum amount allowed of 10mL or less.[3,4] Cerianna™ does not require renal or hepatic dose adjustments.[3] PET imagining should commence 80 minutes after Cerianna™ injection.[3]

ADME:

Cerianna™ is highly protein bound and distributes to the hepatobiliary system, is metabolized by the liver, and is eliminated via biliary and urinary excretion.[3]

Adverse Effects & Warnings:

Distortion of sense of taste and injection site pain are adverse effects reported with Cerianna™.[3] Pregnancy and lactation have not been extensively studied but there is still potential for harm of fetal development.[3]

Trodelvy (sacituzumab govitecan-hziy)

Trodelvy™ is a parenteral, topoisomerase inhibitor, Trop-2 antibody that is approved for treatment of adult patients who have received two prior therapies for metastatic disease with triple-negative breast cancer (TNBC).[5] Trodelvy™ should NOT be substituted for or used with other medications containing its active metabolite SN-38 or irinotecan.[5]

Dosing & Administration:

Prior to administration, Trodelvy™ must only be reconstituted with 20mL of 0.9% NaCl for each 180 mg Trodelvy™ vial.[5] The vial must be swirled and not shaken for 15 minutes.[5] Following reconstitution, Trodelvy™ should be diluted with 0.9% NaCl Inj (maximum 500mL) to obtain a concentration between 1.1 mg/mL-3.4 mg/mL.[5] The mixture may then be stored in the refrigerator for up to 4 hours and must not be frozen or shaken.[5] Protect Trodelvy™ from light.[5]

Trodelvy™ consists of a 21-day treatment cycle including weight-based dosing of 10mg/kg on administration days 1 and 8 for a first infusion of 3 hours and subsequent infusions over 1-2 hours.[5] For example, on day 1 the infusion must be given over 3 hours and on day 8 it can be given over 1-2 hours if prior infusions were tolerated.[5] Both must be monitored for at least 30 minutes after infusion.[5]Treatment with Trodelvy™ should be limited to a maximum of 10mg/kg and may be continued until disease progression or intolerable toxicity.[5] Upon completion of administration, the line used should be flushed with 20mL of 0.9% NaCl.[5]

ADME:

Trodelvy™ has an average volume of distribution of 0.045 L/kg.[5] Its half-life is 16 hours.[5] The half-life of its active metabolite free SN-38 is 18 hours.[5] Trodelvy™ has an average clearance rate of 0.002 L/h/kg.[5] The metabolism of Trodelvy™ cannot be concluded due to lack of studies conducted.[5]

Adverse Effects & Warnings:

Trodelvy™ has many adverse effects/warnings which include nausea & vomiting, diarrhea, hypersensitivity, and neutropenia.[5]

Nausea and vomiting occurred in 69% (74/108) and 49% (53/108) of patients respectively during clinical trials.[5] Trodelvy™ is emetogenic and it is recommended to premedicate patients with antipyretics, H1/H2 blockers, and corticosteroids prior to infusion to prevent chemotherapy induced nausea and vomiting (CINV).[5]

Diarrhea occurred in 63% (68/108) of patients during clinical trials.[5] Trodelvy™

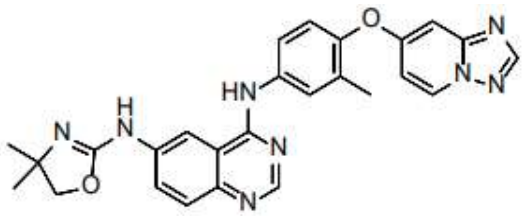
should be withheld for patients experiencing GRADE 3-4 diarrhea and may be resumed when GRADE ≤1.[5] Under negative infectious causes, loperamide can be used to treat diarrhea starting with an initial dose of 4 mg followed by 2 mg with every episode of diarrhea.[5] The maximum allowable dose of loperamide is 16 mg/day.[5]

Hypersensitivity reactions occurred in 37% (151/408) of patients receiving Trodelvy™. Patients must be observed for at least 30 mins after infusion of Trodelvy™.[5] The rate of infusion may be slowed down or interrupted if the patient is experiencing a reaction and promptly discontinued if the reaction becomes life-threatening.[5]

Neutropenia occurred in 54% (220/408) of all patients receiving Trodelvy™ and 6% (24/408) experienced febrile neutropenia.[5]

Dose modifications are needed for many of the side effects associated with Trodelvy™.[5] Health care professionals should consult the package insert to adjust these doses.

Tukysa (tucatinib)



Tukysa™ is an oral tyrosine kinase inhibitor of HER2 approved for the treatment of adult patients with advanced or unresectable metastatic HER2-positive breast cancer who have received one or more anti-HER2 based regimens in the metastatic setting.[7,8] Tukysa is used in combination with trastuzumab and capecitabine.[7,8] This combination includes treatment for patients with brain mestases.[7,8]

Dosing & Administration:

Tukysa™ has a recommended dose of 300 mg taken by mouth twice daily with trastuzumab and capecitabine.[7] Tukysa may be taken with or without food and it is advised that patients separate doses by 12 hours and they should take the medication at the same time each day.[7] It is supplied in 50 mg and 150 mg tablets and it must be stored in its original container.[7] Once opened, Tukysa™ must be used within 3 months.[7] Treatment with Tukysa™ continues until disease progression or intolerable toxicity. [7] Tukysa tablets must be swallowed whole and not chewed, crushed, or split when administered.[7] Capecitabine is contraindicated in severe hepatic impairment (CrCl <30 mL/min) and therefore the use of Tukysa™ cannot be continued.[8]

ADME:

Tukysa™ achieves peak plasma concentration at ~2 hours with a volume of distribution of 1670L with 97.1% protein binding. Tukysa™ is cleared at a rate of 148L/h, metabolized by CYP2C8, and excreted mainly through feces.

Adverse Effects & Warnings:

Tukysa™ carries adverse effects and warnings which include diarrhea, hepatotoxicity, and embryo-fetal toxicity.[7]

Diarrhea occurred in 81% of patients treated with Tukysa™.[7] Severe diarrhea may

cause acute kidney injury, dehydration, hypotension, and even death.[7]

Hepatotoxicity occurred in 8% of patients treated with Tukysa™.[7] Monitoring parameters for hepatotoxicity include: ALT, AST, and bilirubin.[7] For severe hepatotoxicity, it is recommended to reduce the dose or discontinue permanently.[7]

Embryo-fetal toxicity can result in fetal harm when Tukysa™ is used in the treatment of pregnant patients. It is advised that both male and females use appropriate contraceptives for at least 1 week after the last dose.[7] It is important to advise pregnant females and females with reproductive potential about the possible risks of fetal harm while being treated with Tukysa™.[7]

Discussion

As of 2020, The FDA approved the reviewed drugs Cerianna™, Trodelvy™, and Tukysa™ as novel agents for the diagnoses and treatment of certain breast cancers. Because clinical guidelines for breast cancer are ever-changing, it is necessary to consider how these novel agents may impact current clinical practice.

Cerianna™ may have an impact on staging and diagnosing of breast cancer. Alongside with the use of PET scans, Cerianna™ can help determine the hormone receptor status of breast cancer.[3] It must be noted that Cerianna™ can only determine estrogen receptor status and does not include diagnoses of progesterone receptor or human epidermal growth factor 2 receptor status.[3] According to NCCN guidelines, staging is needed to determine treatment regimens. [9] During staging, tumor size (T), number of lymph nodes involved (N), spread of cancer (M), and estrogen, progesterone, or HER2 status is gathered as information to characterize the cancer.[9] Primary treatment for breast cancer is lumpectomy or total mastectomy followed by hormone therapy or chemotherapy.[10] The use of hormone therapy vs chemotherapy is dependent on the breast cancer characteristic, (T/N/M/Receptor status).[9] Therefore, using Cerianna™ to determine the hormone status can help with determining approriate therapeutic regimens for patients.[10]

Trodelvy™ is a later stage agent for the treatment of triple-negative breast cancer for patients that have received two prior therapies for metastatic disease.[5] Trodelvy™ functions as a topoisomerase inhibitor, Trop-2 antibody.[5] Per NCCN 2020 treatment guidelines, Trodelvy™ has been included for the treatment of TNBC.[10] The use of Trodelvy™ is listed as an alternative agent only after the use of a platinum agent and a taxane agent for metastatic disease.[10]

Tukysa™ acts as a tyrosine kinase inhibitor of HER2-positive.[7] Current NCCN guidelines list pertuzumab + trastuzumab + docetaxel (category 1) as the recommended first line regimen for metastatic HER2-positive breast cancer.[10] Tukysa™ has been included in the NCCN guidelines as an "other" recommended regimen including tucatinib + trastuzumab + capecitabine (category 1).[10]

Conclusion

The Food and Drug Administration annually releases a report of novel agents that are introduced to the market. This report provides information on new medications For the purposes of breast cancer, Trodelvy™, Tukysa™, and Cerianna™ were recently approved by the FDA. Development of new agents is important to continue to to help treat and diagnose cancer.

References:

1) New Drug Approvals for 2020 [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2020 Jan [cited 8 Sep, 2020]. Available from: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020
2) Boster B, Patel NK, Michaud L. Breast Cancer. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. Pharmacotherapy: A Pathophysiologic Approach, 11e. McGraw-Hill; Accessed September 08, 2020. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=239762187
3) CERIANNA™ (fluoroestradiol F 18) Injection [package insert on the Internet]. White Oak (MD). U.S. Food and Drug Administration; 2020 [updated 2020 May; cited 2020 Sep 09]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212155s000lbl.pdf
4) Cerianna. In: Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier Inc. 2020 [cited 2020 Sep 09]. Available from: https://www.clinicalkey.com/pharmacology/monograph/5223?n=CERIANNA
5) TRODELVY™ (sacituzumab govitecan-hziy) injection [package insert on the Internet]. White Oak (MD). U.S. Food and Drug Administration; 2020 [updated 2020 Apr; cited 2020 Sep 11]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761115s000lbl.pdf
6) Trodelvy. In: Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier Inc. 2020 [cited 2020 Sep 11]. Available from: https://www.clinicalkey.com/pharmacol - ogy/monograph/5215?n=TRODELVY
7) TUKYSA™ (tucatinib) tablets [package insert on the Internet]. White Oak (MD): U.S. Food and Drug Administration; 2020 [updated 2020 Apr; cited Sep 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf
8) Tukysa™. In: Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier Inc. 2020 [cited 2020 Sep 12]. Available from: https://www.clinicalkey.com/pharmacology/monograph/5213?n=TUKYSA
9) Invasive Breast Cancer. NCCN Guidelines for Patients. Plymouth Meeting (PA). National Comprehensive Center Network. 2020. [updated 2020; cited 2020 Sep 15]. Available from: www.NCCN.org
10) Breast Cancer. NCCN Clinical Practice Guidelines in Oncology. Plymouth Meeting (PA). National Comprehensive Cancer Network. 2020. [updated 2020 July 5; cited 2020 Sep 15]. Available from: www.NCCN.org

ARCH
Annual Review of Changes in Healthcare

Survey of Ohio Pharmacists' Perception of a PharmD/MBA Degree

Matthew Gecks, PharmD Candidate 2021[1]
Devon Taylor, PharmD Candidate 2021[1]
Brandon Rhoades, PharmD Candidate 2021[1]
Devin Rogers, PharmD Candidate 2021[1]
Akesha Edwards, PharmD, PhD.[1]
[1]University of Findlay College of Pharmacy

Abstract

Telehealth is referred to as the remote interactions between health care providers and patients The purpose of this study is to gather information on the perception of pharmacists about dual PharmD/MBA degrees. Findings from this study would contribute to identifying 1) if there is a need for Colleges of Pharmacy to enhance offerings in their curricula related to business and 2) if certain pharmacy occupations favored candidates with a PharmD/MBA over just a PharmD. Surveys were emailed to all Ohio licensed pharmacists (n = 20,553). 711 pharmacists responded (response rate of 3.5%) to the survey which asked pharmacists about their perceptions of the benefits of a PharmD/MBA dual degree. Only 108 pharmacists had an MBA or an additional business degree, such as Healthcare Administration, Finance, or Accounting (15.2%). Attitudes toward the credibility of pharmacists with an MBA were neutral (60.0%) and about one third of them viewed pharmacists with an MBA as more credible than those without an MBA (35.9%). When asked to rate on a scale of 1-5 how much an MBA has or would have helped their career, in their opinion, the most likely Pharmacy professionals to rate the MBA as more useful (4-5) had careers in Academia (mean 3.375, n=32), Independent Community (mean 3.524, n=63), Industry (mean 3.636, n=11), and Managed Care (mean 4.563, n=16). Obtaining an MBA with a PharmD can be a difficult task and may not be perceived as useful to every pharmacist. However, there are groups of people that value a PharmD/MBA which corresponds to more use in their respective area of pharmacy. Business concepts are important in pharmacy practice and a dual degree could help progress more niche areas of pharmacy practice.

Business concepts are critical in the operations of a pharmacy. Pharmacists use business topics daily to run their outpatient stores, prepare inventory, and work with insurance companies. The purpose of this study was to assess how useful a Master of Business Administration (MBA) degree would potentially be to a practicing pharmacist. We hypothesized that most pharmacists would perceive an MBA degree to be beneficial to their professional career.

Pharmacy is moving forward as a profession with advancements as a primary provider in some states to help provide better care for patients.[1] Pharmacists can also obtain an MBA to help advance their profession by becoming more educated in healthcare related business. Additional education in business topics can assist pharmacists in making more informed decisions in activities such as formulary decision making, budgeting, IT services and leadership. MBA courses can also help a pharmacist communicate business concepts between key stakeholders.

Pharmacists should be able to understand, communicate and apply business techniques in pharmacies. Common business-related topics found in MBA curriculums usually include classes such as accounting, leadership, finance, marketing, human resources, operations, and other electives depending on the focus.[2] Previous analyses of the use of certain business topics in pharmacy have confirmed that business skills affect pharmacists everyday responsibilities.[3] Some topics, such as accounting, may only be beneficial for select pharmacists such as those in management positions, owning their own business, or other specialized career paths. Pharmacists in these career paths may utilize more business topics in a more direct manner and would likely have a higher perceived value of an MBA.

A concern has risen about the ability for pharmacy students to understand the value and use of business topics in pharmacy practice.[4] Business concepts are necessary in pharmacy curriculums and are included in the Pharmacy Curriculum Outcomes Assessment (PCOA) as well as other pharmacy accreditation standards. However, this base knowledge may not be enough to prepare students for application as a practicing pharmacist. Most students have reported not experiencing or experiencing only a few business topics during their Introductory Pharmacy Practice Experiences (IPPE) and Advanced Pharmacy Practice Experience (APPE) rotations.[4]

Studies have been conducted that compare student knowledge of business concepts pre-and post-pharmacy business courses that have found a large increase of knowledge in several business concepts.[5] A study by Rollins et al. showed that a pharmacy course with pharmacy students rated their knowledge of business topics as "adequate" after finishing only the required courses.[5] While business classes are important to understand as a pharmacist, it should not come at the cost of replacing clinical knowledge that is critical to pharmacists.[1]

Similar studies have been conducted to examine pharmacist knowledge of business topics with the impact of a PharmD/MBA dual degree.[6] One study by Chummey et al. focused on comparing pharmacy graduates with dual degrees to those without. The study found that the dual degree graduates had a higher average GPA than both pharmacy majors and business majors by about 0.1 and 0.15 respectively, and a higher first year compensation than other pharmacists by about $27,000.[6] Another study by Daly et al. found that 85% of the respondents believed the dual degree helped in career advancement and 90% believed that the dual degree made them more competitive in the job market.[7] Finally, Alkhateeb et al. assessed pharmacists who practiced in specialized career settings such as pharmaceutical marketing and management.[8] Alkhateeb et al. found that an MBA was considered to be beneficial but was not preferred over healthcare associated business degrees.[8]

This study investigates the perceived value of a PharmD/MBA dual degree among practicing pharmacists regardless of their background and practice setting. The study seeks to answer what populations of Ohio licensed pharmacists believe an MBA/PharmD dual degree is beneficial when working in the field.

Methods

This study received prior approval by the University of Findlay's Institutional Review Board. Surveys were emailed to 20,553 pharmacists in the state of Ohio. Participants were selected to be included in this study if they were licensed and actively practicing in the state of Ohio.

Pharmacists were invited to participate in this survey via an introductory email which contained a link to the study survey. Implied consent was given by accessing the link and completing the survey. The survey contained a total of 20 questions which collected demographic information as well as information pertaining to the main research question. A variety of different questions were asked including formats such as multiple choice, fill in the blank, and rating scales of 1-5, with one being "never" and five being "always". No identifiable information was collected from study participants. Questions covered content such as how much business-related content pharmacists have been exposed to over their career and what type, pharmacist perceptions of an MBA, and the benefit and importance in pharmacy of having an MBA. Participants had the option of participating in a drawing for a $100 gift card. Questions were either close ended using yes or no, multiple choice, or of a rating scale format. Surveys were initially sent in December 2019. Reminder emails were sent to non-responders three weeks later.

Results

A total of 715 pharmacists responded to the survey. Demographics are reported in Table 1. When asked about business qualifications, 108 pharmacists (15.2%) reported that they had an MBA or other type of business degree, while 604 pharmacists (84.8%) reported that they did not; there

were 3 non-responders. Male pharmacists were more likely than female pharmacists to have an MBA ($p < 0.001$). Outside of the pharmacy curricula, 337 pharmacists (47.3%) took additional business classes or pursued other continuing education opportunities while 379 pharmacists (53.2%) reported that they did not consider an MBA or taking additional classes.

Pharmacists were asked, *"How often do you think business-related skills are used in the role of the pharmacist"*, on a rating scale of 1-5, with one being "never" and five being "always". One hundred and sixty (22.4%) of them reported that they thought these skills were "always" used, 297 study participants (41.6%) answered with the score of four, 184 pharmacists (25.8%) answered with the score of three, 58 pharmacists (8.1%) responded with a score of two, and 15 pharmacists (2.1%) responded with the lowest rating of "never." The mean score for this question was 3.74 (see Table 2).

Pharmacist opinions were gathered on the ability of an MBA to improve patient outcomes using a similar rating scale with one being "never improves patient outcomes" and five being "always improves patient outcomes." A score of three was the highest chosen rating (30.4%). The mean for this question was 2.55 (see Table 3). *"How much do you feel business classes have helped in your career"* was also rated on a scale of 1-5. Of the 676 study participants that responded to this question, 111 persons (16.4%) answered with the lowest rating of one (not much), 107 persons (15.8%) responded with a rating of two, 248 persons (36.7%) answered with a rating of three, 113 persons (16.7%) answered with a rating of four and 97 persons (14.3%) answered with the highest rating of five (see Table 4). Study participants were also asked to rate if they thought having an MBA benefited or would have benefited their pharmacy career. On a scale of 1-5 with one meaning "not beneficial" and five meaning "extremely beneficial". Most pharmacists responded with a rating of four (n=189, 26.5%), 150 participants (21.1%) responded with a rating of three, 131 participants (18.4%) answered with a rating of five, 126 participants (17.7%) responded with the lowest possible rating and 116 participants (16.3%) responded with a rating of two. For this question, persons in academia (mean score 3.375, n=32), independent community (mean score 3.524, n=63), industry (mean score 3.636, n=11) and managed care (mean score 4.563, n=16) settings responded with higher ratings of four to five. Pharmacists from hospital and community chain settings had the lowest mean scores for this question, with a mean score of 2.949 (n=234) and 2.885 (n=165) respectively (see Table 5 and Table 6).

When asked "*What is your impression of a pharmacist with an MBA"*, 29 respondents (4.1%) said "less credible", 256 respondents (35.9%) said "more credible", and 428 respondents (60.0%) were "neutral." Pharmacists ranked the most beneficial aspect of a business degree as content related to Leadership skills (n=195, 27.5%) followed by Finance (n=124, 17.5%) and then Information and Technology

(n=93, 13.1%). See Table 7 for complete information related to all possible topics.

As shown in Table 8, the most cited reason for not being able to obtain an MBA was time (n=202, 28.4%). Lack of value or benefit was the second most common reason (n=196, 27.5%,) followed by cost (n=113, 15.9%).

From the survey, 365 (51.3%) respondents answered "no" when asked if additional business education was necessary in the progression of pharmacy as a profession. Respondents were also asked to rate the likelihood of them recommending a dual PharmD/MBA degree to current pharmacy students on a scale of 1-5, with one being "will never recommend" and five being "will always recommend." As shown in Table 9, the most selected rating was three (n=211, 29.6%), followed by four (n=175, 24.5%), two (n=142, 19.9%), one (n=104, 14.6%), and then five (n=82, 11.5%).

Table 1. Demographics of Respondents

	Number of Participants (n = 715)	Percentage
Ethnicity		
American	1	0.1%
American Indian or Alaska Native	1	0.1%
Asian	33	4.6%
Black / African-American	11	1.5%
German	1	0.1%
Greek	1	0.1%
Hispanic or Latino	5	0.7%
Indian non-American	1	0.1%
Mixed	4	0.6%
Native Hawaiian or Pacific Islander	2	0.3%
Prefer not to answer	2	0.2%
White	641	89.7%
Did not answer	12	1.7%

Age			
	22-30	109	15.2%
	31-40	179	25.0%
	41-50	135	18.9%
	51+	286	40.0%
	Did not answer	6	0.8%
Years of Practice			
	0-5 years	113	15.8%
	6-10 years	105	14.7%
	11-15 years	86	12.0%
	16-20 years	56	7.8%
	21-25 years	69	9.7%
	26-30 years	78	10.9%
	31+ years	185	25.9%
	I do not currently practice pharmacy	20	2.8%
	Did not answer	3	0.4%
Gender			
	Male	322	45.0%
	Female	385	53.8%
	Other	6	0.8%
	Did not answer	2	0.3%

Table 2. How Often Respondents Think Business Skills Are Used as a Pharmacist

Response*+	*Number of Participants* (n = 715)	Percentage of total
1	15	2.1%
2	58	8.1%
3	184	25.8%
4	297	41.6%
5	160	22.4%
Did not Answer	1	0.1%

*1 = Never, 5 = Always
+Mean Score = 3.74

Table 3. Answers to "Do You Think Having an MBA Would Improve Patient Outcomes?"

Response*+	*Number of Participants* (n = 715)	Percentage of Total
1	153	21.4%
2	199	27.9%
3	217	30.4%
4	106	14.8%
5	39	5.5%
Did not Answer	1	0.1%

*1 = Never, 5 = Always
+Mean Score = 2.55

Table 4. How Business Classes Have Benefited Respondents in Their Careers

Response*+	*Number of Participants* (n = 715)	Percentage of Total
1	111	15.5%
2	107	15.0%
3	248	34.7%
4	113	15.8%
5	97	13.6%
Did not Answer	29	4%

*1 = Not Much, 5 = Very Much
+Mean Score = 2.97

Table 5. Respondents' Opinions on How Much an MBA Helped/Would Help Pharmacy Career

Response*+	*Number of Participants* (n = 715)	Percentage of Total
1	126	17.7%
2	116	16.3%
3	150	21.1%
4	189	26.5%
5	131	18.4%
Did not Answer	3	0.4%

*1 = Not beneficial, 5 = Extremely Beneficial
+Mean Score = 3.12

Table 6. Comparison of Responses to How Much an MBA Helped/Would Help Pharmacy Career Among Areas of Pharmacy Practice

Area of Practice	*Number of Participants* (n = 715)	Percentage of Total	Mean Score
Academia	32	4.5%	3.375
Ambulatory Care	11	1.5%	3
Community Chain	165	23.1%	2.88
Community Independent	63	8.8%	3.52
Hospital	234	32.7%	2.95
Industry	11	1.5%	3.64
LTC	18	2.5%	3
Managed Care	16	2.2%	4.56
PBM	11	1.5%	3
Other Responses	151	21.1%	-
Did not Answer	3	0.4%	-

Table 7. Most Beneficial Aspect of a Business Degree

Aspect	*Number of Participants* (n = 715)	Percentage of Total
Accounting	45	6.3%
Business Development	88	12.3%
Communication	60	8.4%
Economics	44	6.2%
Finance	124	17.3%
Information Technology	93	13.0%
Leadership	195	27.3%
Marketing	29	4.1%
Other	31	4.3%
Did not Answer	6	0.8%

Table 8. Reasons for Not Obtaining an MBA

Reason	*Number of Participants* (n = 710)	Percentage of Total
Lack of Value / No Need	196	27.5%
Money	113	15.9%
Age/Retirement/Near Retirement	23	3.2%
Lack of Interest	5	0.7%
Time	202	28.4%
Already Have MBA (or working on MBA) or Other Master's Degree	92	12.9%
Effort or Additional Work	67	9.4%
Other	12	1.7%

Table 9. Likelihood of Recommending a Business Degree to Future Pharmacists

Response*+	*Number of Participants* (n = 715)	Percentage of Total
1	104	14.6%
2	142	19.9%
3	211	29.6%
4	175	24.5%
5	82	11.5%
Did not Answer	1	0.1%

*1 = Will Never Recommend, 5 = Will Always Recommend
+Mean Score = 2.98

Discussion

Obtaining an MBA with a PharmD can be a difficult, but not insurmountable task. The skills provided from an MBA can translate to many jobs a pharmacist could receive. Dual PharmD/MBA degrees may also improve the communication, leadership, and time management skills of pharmacists especially when talking with non-medical leadership. Though traditionally not all pharmacist roles consider an MBA as necessary, our results do show that pharmacists believe it to be beneficial for certain specialized practice settings.

Our survey found that leadership skills are one of the main reasons a pharmacist would consider an MBA degree. This may be because leadership is critical to the role of a pharmacist and can be more broadly applied to more pharmacy professions. Communication and Leadership skills were cited by pharmacists in our study as two of the most beneficial aspects of a business degree. Knowledge of the Business/Finance field was also included among the top reasons for considering a dual MBA/PharmD degree. An MBA could further prepare an individual for managerial roles in addition to the therapeutics intensive pharmacy curriculum. Content related to economics, finance, accounting, and technology use, along with business knowledge, are important tools that an MBA will give to help prepare pharmacists for a business-related role in pharmacy.

According to the results of this study, the career path where an MBA would be perceived to be most helpful is in academia. According to our survey, independent pharmacy owners believe that they would benefit from a dual MBA/ PharmD degree. Additionally, pharmacy residencies, such as the OhioHealth PGY1/PGY2/MS Health-System Pharmacy Administration Residency, allow for pharmacists to obtain dual degrees after they graduate. A dual degree along with this type of specialized residency may help increase a pharmacist's success in managerial positions.

Time and money were two of the biggest factors as to why pharmacists would not obtain an MBA. An efficient time to acquire an MBA would be while pursuing a pharmacy degree. Instead of taking pharmacy electives or general credits focused in other areas, that time and money could be spent on obtaining an MBA. It was hypothesized that most of the pharmacists who would perceive that having an MBA was beneficial would-be pharmacists who already have an MBA. This could have led to bias in the findings from participants favoring their degrees or from simply having an increased response rate from persons with a greater interest in the subject.

Some recommendations for the future of business education in the pharmacy curriculum could be increasing the credit hours designated for business courses. The majority (52.7%) of pharmacists in our study group reported not receiving any business coursework in their entire career. Therefore, this may be beneficial to future pharmacists. Continuing education requirements related to business topics in

pharmacy would also be something to consider by State Boards of Pharmacy. Two hours of CE credit are required for law and 2 hours are required for Medication / Patient Safety every two years for pharmacist licensing in Ohio. Similarly, two hours could be added for business topics.

There is a use for an MBA/PharmD dual degree, but this is within very specific areas of pharmacy practice. It is not for everyone, but this would be a great route to pursue for those who would like to become better leaders and/or pursue managerial roles.

References

1) Mossialos E, Courtin E, Naci H, et al. From "retailers" to health care providers: transforming the role of community pharmacists in chronic disease management. Health Policy. 2015 May; 119(5):628-39.
2) Cullen A. Using the case method to introduce information skill development in the MBA curriculum. Journal of Business & Finance Librarianship. 2013 Jun 14;18(3):208-32.
3) Davies MJ, Fleming H, Jones R, et al. The inclusion of a business management module within the master of pharmacy degree: a route to asset enrichment? Pharm Pract (Granada). 2013;11(2):109-17.
4) Rollins BL, Gunturi R, Sullivan D. A Pharmacy Business Management Simulation Exercise as a Practical Application of Business Management Material and Principles. AJPE. 2014; 78(3): Article 62.
5) Rollins BL, Broedel-Zaugg K, Reiselman J, et al. Assessment of pharmacy students perceived business management knowledge: Would exclusion of business management topics be detrimental to pharmacy curricula? Curr Pharm Teach Learn. 2012;4(3):197-201.
6) Chumney EC, Ragucci KR, Jones KJ. Impact of a Dual PharmD/MBA Degree on Graduates Academic Performance, Career Opportunities, and Earning Potential. AJPE. 2008;72(2): Article 26.
7) Daly C, Tierney S, O'Brien E, et al. Career Progression of the Pharmacy/MBA Professional: Characterization and Perceptions of the Combined Degree. AJPE. 2017; 81(4): Article 72
8) Alkhateeb F, Clauson K, Latif D, et al. Availability and perceived value of masters of business administration degree programs in pharmaceutical marketing and management. AJPE. 76(4): Article 64.

ARCH
Annual Review of Changes in Healthcare

Investigational Agents in the Treatment of Eosinophilic Esophagitis

Allison Burdick, PharmD Candidate 2022[1]
Kenedee Gallimore, PharmD Candidate 2026[1]
John Kurth, PharmD Candidate 2021[1]
[1]***University of Findlay College of Pharmacy***

Abstract

Eosinophilic Esophagitis (EoE) is a chronic, allergic disease of the esophagus that is characterized by increased esophageal eosinophils caused by allergens. If untreated, EoE precipitates esophageal remodeling that can lead to structural esophageal changes and difficulty eating. Although there are currently no FDA approved therapies for the treatment of EoE, therapies approved for other inflammatory conditions such as topical corticosteroids have a strong recommendation in the current guidelines. Dietary strategies are also currently being utilized, but have shown to be unfeasible in clinical experience. Although not yet approved, new treatment options are being developed to enhance the quality of life in patients suffering from EoE. This article features novel therapeutic approaches to treating EoE, including investigational agents RPC4046, dupilumab, antolimab, and benralizumab.

Eosinophilic Esophagitis (EoE) is a chronic, allergic disease of the esophagus that is characterized by esophageal symptoms and eosinophils, a type of white blood cell that causes injury and inflammation.[1-3]If left untreated, EoE can precipitate esophageal remodeling, such as strictures and narrowing that are harmful to the esophagus.[4-6] EoE is known to be triggered by common food allergens which complicate the use of dietary strategies as a form of treatment.[3] At this time, there are no US Food and Drug Administration (FDA) approved therapies for the treatment of EoE.[7] However, commonly used agents include proton pump inhibitors (PPI) and topical corticosteroids to avoid complications of the precipitating allergen.[5,7]

EoE was first described in 1978, but did not receive a formal pathology and phenotype until the early 1990s.[7,8] Since this time, researchers have begun to evaluate the genetic and environmental risk factors of EoE. It has been deemed a disease of both the innate and adaptive immune response and includes many pathways that contribute to its complications. The specific cells that play a predominant role in the pathophysiology of EoE are eosinophils, Th2 cells, thymic stromal lymphopoietin (TSLP), transforming growth factor (TGF)-β1, and interleukin (IL)-13, among others.[5] In previous years, the diagnosis of EoE was determined by an esophageal biopsy showing a peak eosinophil count of 15 or greater intraepithelial eosinophils per high-powered field with at least an eight week PPI trial.[7] In 2017, the need for a PPI trial was removed from the diagnostic criteria due to their recognition as treatment for the disease.[7]

EoE symptoms can develop in all age groups, but it is most common in children and young adults.[3] Some common symptoms include throat pain, dysphagia, choking during meals, food impactions, or not wanting to eat. Patients often learn ways to adapt to their condition by eating slower, eating smaller bites, or drinking an unusually high amount of liquids with meals.[3] In addition to the biopsy criteria, patients must also be showing symptoms of esophageal dysfunction. The final criteria to be diagnosed with EoE involves ruling out other disorders that may cause similar symptoms as EoE. These disorders include GERD, Celiac disease, Crohn's disease, and infection. Many patients who have EoE also have comorbid inflammatory conditions such as allergies, asthma, and dermatitis.[3] Having these diseases increases the chances for someone to develop EoE.[6] Endoscopic examinations, though not necessary for diagnosis, can be useful to establish presence of EoE precipitated abnormalities such as linear furrowing, concentric rings, white exudates, small-calibre esophagus, linear superficial mucosal tears, and Schatzki ring (a circular band of tissue that forms at the bottom of the esophagus which makes it more difficult to swallow).[1]

CURRENT GUIDELINES

The American Gastroenterological Institute and Joint Task Force on Allergy-Immunology Practice Parameters published clinical guidelines in 2020 giving recommendations on the treatment of EoE. Since there is little data studying EoE, the guidelines do not have high quality of evidence for their recommendations.[7] Many of the recommendations have very low quality of evidence or have a conditional recommendation.[7]

NON-PHARMACOLOGIC RECOMMENDATIONS

Notably, the elemental diet, 6-food elimination diet and allergy testing-based elimination diet carry a conditional recommendation.[7] The elemental diet consists of amino acid-based formulas.[4] This treatment option is undesirable to patients due to taste, nutritional concerns, practical implementation, and cost.[7] The elemental diet has considerably harmful consequenses including interference with development of oral motor skills in children, the potential need for gastrostomy tube, and social isolation due to dining restrictions. There is insufficient data regarding the harmful effects of an elemental diet and more research should be conducted.[7]

Additionally, the 6-food elimination diet consists of removing the six most common food allergens from the diet and then reintroducing them gradually over time. These common allergens are dairy, eggs, nuts, soy, wheat and seafood. Extrapolated data from ten studies reported a histologic response rate of 68% of those who were able to adhere to this diet, yet patients who were unable to adhere to this technique were not included in the primary analysis.[7] Practically, eliminating 6 common foods can be challenging for patients, and more data is needed to reflect the desirability of this technique. Furthermore, it can be difficult to determine the presence of relapse as it may be evident in pathology but the patient may not experience symptoms.[7] The allergy testing-based elimination diet is very similar to the 6-food elimination diet but includes allergy testing to help guide the treatment. While there may be a potential role for these dietary treatments, the risk of potential de novo IgE-mediated allergy upon reintroduction of the common food allergen, as well as risks associated with sequential endoscopies are a concern.[7]

PHARMACOLOGIC RECOMMENDATIONS

Proton-pump inhibitors were the mainstay of treatment in EoE for some time.[3] Twenty-three observational studies that evaluated the histologic response to PPIs showed that PPIs failed to induce histologic remission in about two-thirds of patients, compared with more than 85% of patients in the placebo groups. This caused the committee to lower the recommendation to conditional.[7]

The only treatment intervention for EoE that carries a strong recommendation is topical glucocorticosteroids.[7] Two formulations have been studied in

EoE, including fluticasone or budesonide swallowed from an inhaler and a mixed budesonide slurry composed of nebulizer solution.[4] Topical glucocorticosteroids induced remission in two-thirds of patients compared to less than 15% of patients on placebo from eight double-blind studies that enrolled 437 patients for a duration of 8 weeks. [9]

NOVEL ORAL THERAPIES

Currently, there are three novel corticosteroids that utilize different formulations that are benefical in EoE. In December of 2020, TAK-721, budesonide oral suspension (BOS) received acceptance of its new drug application from the FDA and was granted priority review.[10] BOS was created to avoid the patient burden of mixing the slurry themselves which includes pouring the medication into a cup, adding a sweeter such as Splenda and mixing the solution until it is thickened. This noval oral suspension would eliminate the need for this process. Furthermore, BOS was shown to be safe long term and efficacious with the most common adverse events being respiratory complications, gastrointestinal symptoms, and candidiasis.[11]

Budesonide orodispersible tablet (BOT) was also shown to be safe and effective in a randomized clinical trial.[12] Due to these findings BOT was recently approved by the European Medicines Agency but has not yet been submitted for approval in the U.S.[4] A fluticasone propionate orally disintegrating tablet (APT-1011) is currently undergoing a phase 3 clinical trial and has shown promising results in a randomized clinical trial with no significant difference in adverse events from placebo.[4,13]

NOVEL BIOLOGIC THERAPIES

While these novel treatments are showing promise, investigators have moved towards developing biologic agents for the treatment of EoE. Dupilumab is a fully human monoclonal antibody that targets the alpha subunit of the IL-4 receptor and was granted breakthrough therapy designation from the FDA in late 2020 for EoE.[14] This antibody inhibits signaling of IL-4 and IL-13.[14] Both of these interleukins are crucial for developing Th2 cells that contribute to the inflammatory response in EoE.[5] Dupilumab has already received FDA approval for other atopic inflammatory diseases such as asthma, atopic dermatitis and rhinosinusitis with nasal polyposis.[15,16] In a phase 3 trial, 81 patients aged 12 years and older with EoE received weekly subcutaneous injections, either 300 mg of dupilumab or placebo for a duration of 24-weeks.[17] In the dupilumab group, 64% of patients achieved eosinophilic response compared to 8% in the placebo group.[14] Patients receiving dupilumab had significant signs of improvement including comfortable swallowing as early as 4 weeks that only continued to improve throughout the trial.[14] Investigators found reduced severity of the disease by measuring esophageal tissue changes with grade and stage scores. Dupilumab had scores of 0.761 and 0.753, respectively, compared to 0.001 and 0.012 in the placebo group.[14] Safety was also

evaluated with the overall rate of adverse effects being 86% for dupilumab compared to 82% for placebo.[14] Adverse events reported most often were injection site reactions and upper respiratory tract infections.[14,17]

Similarly, RPC4046 is a humanized monoclonal antibody that targets IL-13 which is overexpressed in EoE that leads to esophageal remodeling. A pilot study of an IL-13 antibody in 23 adults showed a reduction of esophageal eosinophil counts and EoE-related gene expression.[18] This led to a phase 2 trial of RPC4046 that showed 50% of patients achieved histological remission.[18] Adverse events were reported in both the treatment groups and placebo group including mild headache, upper respiratory infection, arthralgias, diarrhea, and nausea.[18,19] A phase 3 trial has not yet begun but will be needed to better show the significance of RPC4046 in the treatment and management of EoE.

Aditionally, Antolimab is an antibody that targets Siglec-8, a receptor resulting in inhibition of mast cells and apoptosis of eosinophils. [20,21] Prior to the research for EOE, antolimab was studied in the ENIGMA trial where antolimab was given to patients with eosinophilic gastritis and gastroenteritis for a duration of four months.[21] In a subgroup analysis, 13 of the 14 patients who also had EoE achieved histological remission. [4] The most common adverse event was an infusion related reaction that occurred more commonly in the first infusion session.[21] Currently, antolimab is in a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 trial including 300 EoE patients. The trial includes two different treatment regimens (1.0 mg/kg monthly or 1.0mg/kg first month then 3.0 mg/kg monthly) as well as a placebo group, for a duration of six months and is estimated for completion by May 2022.[20]

A multicenter, randomized, double-blind, parallel-group, placebo controlled phase 3 trial was launched in December 2020 to investigate benralizumab, a monoclonal antibody that targets IL-5 receptor alpha.[22] By targeting IL-5, the body's antibody-dependent cellular cytotoxicity (ADCC) is intensified to induce apoptosis of eosinophils.[23] Benralizumab has previously been shown effective in the treatment for asthma and platelet-derived growth factor receptor alpha (PDGFRA)-negative hypereosinophilic syndrome.[22,24] In a subgroup analysis of PDGFRA-negative hypereosinophilic syndrome patients, two patients had concomitant EoE. In 24 weeks, biopsies showed no eosinophils in these patients.[22] Although benralizumab has not yet been exclusively studied in EoE, the promising biopsy results of these two patients indicates their potential use and warrants further investigation.

In conclusion, EoE is a chronic condition that, if left untreated, can lead to complications such as esophageal remodeling and abnormalities. Currently, the highest recommended available treatment option included in the guidelines are topical glucocorticosteroids. While topical glucocorticosteroids directly treat the

symptoms and excess of eosinophils present in EoE, new biologic antibodies provide a more targeted approach to therapy. By inhibiting the interleukins IL-4, IL-5, and IL-13, these medications can help prevent complications from the origin of the disease. Similarly, by targeting the inhibitory receptor Siglec-8, apoptosis of eosinophils can be induced even before they make it to the esophagus. Treatment options for EoE continue to be investigated for the goal of receiving an FDA approval for the treatment of EoE.

References

1) Carr S, Watson W. Eosinophilic esophagitis. Allergy, Asthma Clinical Immunology [Internet]. 2011 Nov 10 [cited 2021 Jan 30];7;1-8. Available from: https://aacijournal.biomedcentral.com/articles/10.1186/1710-1492-7-S1-S8
2) Legrand F, Klion A. Biologic therapies targeting eosinophils: current status and future prospects. J Allergy Clin Immunol Pract [Internet]. 2015 Jan 13 [cited 2021 Jan 29];3(2):167-74. Available from: https://www.ncbi.nlm
3) Ko E, Chehade M. Biological therapies for eosinophilic esophagitis: where do we stand? Clinical Reviews in Allergy & Immunology [Internet]. 2018 Jan 25 [cited 2021 Jan 30];55:205-16. Available from: https://link.springer.com/article/10.1007/s12016-018-8674-3
4) Beveridge C, Falk G. Novel therapeutic approaches to eosinophilic esophagitis. Gastroenterology & Hepatology [Internet]. 2020 Jun [cited 2021 Jan 29];16(6):294-301. Available from: https://www.gastroenterologyandhepatology.net/archives/june-2020/novel-therapeutic-approaches-to-eosinophilic-esophagitis/
5) Greuter T, Hirano I, Dellon E. Emerging therapies for eosinophilic esophagitis. The Journal of Allergy and Clinical Immunology [Internet]. 2019 Nov 6 [cited 2021 Jan 30];145(1):38-45. Available from: https://www.jacionline.org/article/S0091-6749(19)31474-5/fulltext
6) Choudhury S, Baker S. Eosinophilic esophagitis: the potential role of biologics in its treatment. Clinical Reviews of Allergy & Immunology [Internet]. 2019 Jun 7 [cited 2021 Jan 31];59:150-59. Available from: https://link.springer.com/article/10.1007%2Fs12016-019-08749-6
7) Hirano I, Chan E, Rank M, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. AGA [Internet]. 2020 May 1 [cited 2021 Jan 30];158(6):1776-86. Available from: https://www.gastrojournal.org/article/S0016-5085(20)30265-1/fulltext
8) Attwood S, Furuta G. Eosinophilic esophagitis: historical perspective on an evolving disease. Gastroenterology Clinics of North America [Internet]. 2014 Mar 24 [cited 2021 Jan 30];43(2):185-99. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4035232/
9) Rank M, Sharaf R, Furuta G, et al. Technical review on the management of eosinophilic esophagitis: A report from the AGA institute and the joint task force on allergy-immunologu practice parameters [Internet]. 2020 May 1 [cited 2021 Jan 30]; 158(6): 1789-810. Available from: https://www.gastrojournal.org/article/S0016-5085(20)30266-3/fulltext?referrer=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F
10) Osaka, J. U.S. food and drug administration accepts new drug application for review, grants priority review for takeda's TAK-721 (budesonide oral suspension) for the treatment of eosinophilic esophagitis. Takeda [Internet]. 2020 Dec 15 [cited 2021 Jan 31]. Available from: https://www.takeda.com/newsroom/newsreleases/2020/u.s.-food-and-drug-administration-accepts-new-drug-application-for-review-grants-priority-review-for-takedas-tak-721-budesonide-oral-suspension-for-the-treatment-of--eosinophilic-esophagitis/
11) Dellon E, Katzka D, Collins M, et al. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. AGA [Internet]. 2017 Mar [cited 2021 Jan 30];152:776-86. Available from: https://scholarworks.iupui.edu/bitstream/handle/1805/14546/Dellon_2017_budesonide.pdf?sequence=1&isAllowed=y
12) Summary of product characteristics. Jorveza, INN-budesonide. European medicines agency [Internet]. 2020 [cited 2021 Jan 30]. Available from: https://www.ema.europa.eu/en/documents/overview/jorveza-epar-summary-public_en.pdf
13) ClinicalTrials.gov. Efficacy and safety APT-1011 in subjects with eosinophilic esophagitis (EoE) (FLUTE-2) (FLUTE-2). [Internet]. 2020 Feb 24 [cited 2021 Jan 30] Available from: https://clinicaltrials.gov/ct2/show/NCT04281108
14) Antrim A. New dupilumab study shows improvement in eosinophilic esophagitis signs, symptoms. Pharmacy Times [Internet]. 2020 Nov 4 [cited 2021 Jan 29]. Available from: https://www.pharmacytimes.com/news/dupilumab-pivotal-data-shows-improvement-in-eosinophilic-esophagitis-signs-symptoms
15) Lexi-Comp Online [database on the Internet]. Hudson (OH): Lexi-Comp, Inc. 1978-2015 [cited 2021 Jan 29]. Available from: http://online.lexi.com/crlsql/servlet/crlonline
16) DUPIXENT (dupilumab) injection, for subcutaneous use. The U.S. Food and Drug Administration. [Internet]. [cited 2021 Jan 30]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf

17) ClinicalTrials.gov. Study to Determine the efficacy and safety of dupilumab in adult and adolescent patients with eosinophilic esophagitis (EoE) [Internet]. 2018 Aug 16 [cited 2021 Jan 30] Available from: https://clinicaltrials.gov/ct2/show/NCT03633617?term=dupixent&draw=4
18) Hirano I, Collins M, Assouline-Dayan Y, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients With eosinophilic esophagitis. AGA [Internet]. 2019 Feb 1 [cited 2021 Jan 30];156(3):592-603. Available from: https://www.gastrojournal.org/article/S0016-5085(18)35208-9/fulltext?referrer=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F
19) Celgene to present new data on investigational compounds at UEGW and ACG congresses. Celgene [Internet]. 2016 Oct 13 [cited 2021 Jan 31]. Available from: https://ir.celgene.com/press-releases-archive/press-release-details/2016/Celgene-to-Present-New-Data-on-Investigational-Compounds-at-UEGW-and-ACG-Congresses/default.aspx
20) Allakos announces the initiation of antolimab (AK002) clinical studies. Allakos [Internet]. 2020 Mar 4 [cited 20201 Jan 21]. Available from: https://investor.allakos.com/news-releases/news-release-details/allakos-announces-initiation-antolimab-ak002-clinical-studies
21) Dellon E. Efficacy and safety of AK002 in adult patients with active eosinophilic gastritis and/or eosinophilic gastroenteritis: primary results from a randomized, double-blind placebo-controlled phase 2 trial (ENIGMA Study) (late-breaking abstract) [abstract 36]. Presented at: ACG 2019 Annual Scientific Meeting and Postgraduate Course [Internet]. 2019 Oct 29 [cited 2021 Jan 30]. Available from: https://www.eventscribe.com/2019/ACG/fsPopup.asp?efp=RUxTQkhWU1g2NDI1&PresentationID=635867&rnd=0.8240249&mode=presinfo
22) Kuang F, Legrand F, Makiya M, et al. Benralizumab for PDGFRA-Negative hypereosinophilic syndrome. The New England Journal of Medicine [Internet]. 2019 Apr 4 [cited 2021 Jan 30];380:1336-46.
23) First patients dosed in phase III trials evaluating fasenra in hypereosinophilic syndrome, eosinophilic esophagitis and eosinophilic granulomatosis with polyangiitis. Pharmiweb [Internet]. 2020 Dec 16 [cited 20021 Jan 29]. Available from: https://www.pharmiweb.com/press-release/2020-12-16/first-patients-dosed-in-phase-iii-trials-evaluating-fasenra-in-hypereosinophilic-syndrome-eosinophilic-esophagitis-and-eosinophilic-granulomatosis
24) Agache I, Rocha C, Beltran J, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: a systematic review for the EAACI Guidelines- recommendations on the use of biologicals in severe asthma. Allergy [Internet]. 2020 Feb 16 [cited 2021 Jan 30];75:1043-57. Available from: https://onlinelibrary.wiley.com/doi/10.1111/all.14235

ARCH
Annual Review of Changes in Healthcare

Recent Advances in Post-Operative Pediatric Opioid Guidelines

Megan LoFaso, PharmD Candidate 2022[1]
Jace Swingle, PharmD Candidate 2022[1]
[1]***University of Findlay College of Pharmacy***

Abstract

Over the past few decades, the United States has been experiencing an opioid epidemic. Unfortunately, children and adolescents are not exempt from the effect this has had on our country. Lack of guidance in prescribing leading to improper or over prescribing can be associated with pediatric overuse and abuse. This article seeks to provide a review of *Guidelines for Opioid Prescribing in Children and Adolescents After Surgery,* a recently published guideline compiled using data from a multitude of published articles focused on pediatric opioid prescribing and the effects these agents have on children. These guidelines provide a gateway to continue research and development of specific guidelines to improve the practice of opioid prescribing after surgery.

Introduction

Over the past few decades, the United States has experienced a dramatic increase in the prescribing of opioids leading to an increase in opioid related deaths.[1] Currently, the US remains at the forefront of this issue, surpassing Europe by four times in the amount of opioids prescribed in a year.[2-5] What is now famously known as the 'opioid epidemic' has affected individuals of all ages, killing 8,986 children and adolescents aging from 0 to 19 years old, which is an increase of 286.2% between the years of 1999 and 2016.[1]

In recent years many efforts have been made to raise awareness of this opioid epidemic, educate providers on safe prescribing practices, and make patients mindful of the potential risks that the overuse of opioids pose.[6] However, much of these efforts have been directed towards the adult population. There has been little research about appropriate opioid prescribing in pediatric patients, especially those requiring surgical procedures.[7] Recent studies have suggested that the adolescent use of opioids can lead to adult misuse.[8-10] With these findings it has become increasingly important to guide opioid prescribing for pediatric patients. The Journal of the American Medical Association is the first to tackle this by publishing *Guidelines for Opioid Prescribing in Children and Adolescents After Surgery.*[7]

Review of Guideline

The study leading to the guideline development was completed by The American Pediatric Surgical Association Outcomes and Evidence-based Practice Committee as well as other professionals specializing in opioid stewardship. Guideline development was based on three prime questions related to opioid misuse, diversion, effective non-opioid regimens and patient/parent education. Kelly-Quon et al. conducted a search which surveyed a total of 14,574 articles for inclusion.[7] These were then narrowed down to 217 articles for analysis by searching topics such as opioid misuse in the pediatric population.[7] Articles that were excluded from the formulation of the guidelines included studies limited to neonatal intensive care, animal and experimental studies.[7]

The authors utilized the surveyed articles to come up with 20 guideline statements pertaining to safe opioid prescribing. These were broken down into 3 major categories: (1) Opioid Misuse, Heroin Use, Diversion, and Conversion to Long-term Use, (2) Perioperative Nonopioid Regimens, and (3) Patient and Family Education.[7]

The first category discusses the impact that the prescribing of opioids to adolescents has on their future behaviors. The trend begins with the prescribing of opioids as most adolescents who misuse opioids obtain them from a prescribing physician.[11-14] Of the adolescents that are prescribed opioids, 3.1% report opioid misuse.[15] While this is a decrease from recent years it is a drastic increase compared to pre-opioid epidemic levels. Additionally, of the adolescents who misuse opioids, a significant number of them will develop future opioid dependence which may include a heroin addiction.[16-17]

The National Survey on Drug Use and Health has reported that 39.2% of opioid misuse cases result from diversion.[18] In the *Guidelines for Safe Opioid Prescribing* by Nationwide Children's Hospital it is noted that the over prescribing of opioids in adolescents is a major contributor to the act of diversion.[19] According to McCabe et al, if approached, 94% of patients will divert medication.[20] Sources show that proper education on the effects of opioids and consequences of diversion can help slow this event.[13]

According to Kelly-Quon et al, pain regimens containing non-opioid alternatives such as acetaminophen, NSAIDs (ketorolac, etc), and steroids are reasonable options for specific postoperative periods.[21,22] This is most feasible in certain general, otolaryngology, and urology surgeries due to their incision size, amount of dissection, and overall invasiveness.[22-30] If adequate pain management is not met with non-opioids, it is recommended that the non-opioid options be optimized followed by an addition of the lowest tolerable dose of an opioid agent.[23,26] It is preferred that these non-opioids be optimized enterally, however, the use of intravenous non-opioids can also be utilized to minimize opioid usage.[7]

It should be noted that if opioid use is required, the FDA states that the use of tramadol and codeine should be avoided in adolescents less than 18 years of age.[31] Tramadol and codeine can induce fatal respiratory depression in patients undergoing tonsillectomy and adenoidectomy, especially under the age of 12 years.[32-33] These agents should also be avoided in obese patients less than 18 years old with obstructive sleep apnea, severe lung disease, or at other risk for pulmonary obstruction.[32-33]

It is important to note that with the lack of formal guidelines in the major pediatric journals, many institutions have established their own protocols on pediatric opioid prescribing. Nationwide Children's Hospital in Columbus, Ohio, a nationally ranked pediatric institution, released their *Guidelines to Safe Opioid Prescribing* in December 2016.[19] This protocol recommends prescribing opioids only when

absolutely necessary at the lowest tolerable dose for the shortest duration possible similar to the recommendations of Kelly-Quon et al.[7,19] Also noted by both sources is the importance of patient/family education on the proper use and disposal of unused medications.[7,19]

Education should begin before the day of surgery in order to decrease the anxiety that the patient and family may be experiencing.[34] This education should continue often and through discharge, providing the family unit with adequate time for questions and information digestion.[35-37] Special consideration should be made for parents caring for young children as parental understanding of pain management regimens has been linked to reduced parental/patient anxiety leading to a decrease in the patient's preoperative and post-operative pain.[38] According to Kelly-Quon et al, the recommended counseling points in the patient and caregiver education include common side effects, how to properly take the medication, proper storage as well as appropriate disposal.[10] Follow-up is also recommended to assess the patient's well-being as well as proper medication disposal if needed. Follow-up on disposal is important because it is estimated that 30% of caregivers do not dispose of opioids properly due to forgetfulness or poor understanding of the importance of proper disposal.[39]

In conclusion, *Guidelines for Opioid Prescribing in Children and Adolescents After Surgery* by Kelly-Quon et al. provides recommendations consistent with the recommendations of the FDA and current providing practices as evidenced by the protocol from Nationwide Children's Hospital. While the authors provide some examples of medications that can be utilized in the decrease of opioid prescribing in certain surgeries, they do not provide any dosing recommendations for these medications. In addition, the authors provide guidance on the practices to prevent opioid use, overuse, and misuse. However, the authors do not provide readers with the appropriate dosing of opioids in the pediatric population or the algorithm used to arrive at the prescribing of such medications. Further studies must be conducted in order to fill in the literature gap for pediatric opioid prescribing. These guidelines set the stage for researchers to continue to evaluate and assess opioid prescribing practices in the pediatric population and continue to combat the opioid epidemic in the United States.

References

1) Gaither JR, Shabanova V, Leventhal JM. US national trends in pediatric deaths from prescription and illicit opioids, 1999-2016.JAMA Netw Open. 2018;1(8):e186558.
2) Guy GP, Jr., Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. MMWR - Morbidity & Mortality Weekly Report. 2017 7 07;66(26):697–704. PubMed PMID: 28683056; English. [PubMed: 28683056]
3) Washington DUDoVA, US Department of Defense, The Management of Opioid Therapy for Chronic Pain Working Group. The Management of Opioid Therapy for Chronic Pain Working Group. VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. 2010.
4) Group UoWPPS. University of Wisconsin Pain & Policy Studies Group. Global Opioid Consumption, 2015. Madison, WI: University of Wisconsin Pain & Policy Studies Group; 2015.
5) Chou R 2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain: what are the key messages for clinical practice? [Review]. Pol Arch Med Wewn. 2009 7-8;119(7–8):469–77. PubMed PMID: 19776687; English. [PubMed: 19776687]
6) Overton HN, Hanna MN, Bruhn WE, Hutfless S, Bicket MC, Makary MA; Opioids After Surgery Workgroup. Opioid-prescribing guidelines for common surgical procedures: an expert panel consensus.J Am Coll Surg. 2018;227(4):411-418.
7) Kelley-Quon LI, Kirkpatrick MG, Ricca RL, Baird R, Harbaugh CM, Brady A, Garrett P, Wills H, Argo J, Diefenbach KA, Henry MCW, Sola JE, Mahdi EM, Goldin AB, St Peter SD, Downard CD, Azarow KS, Shields T, Kim E. Guidelines for Opioid Prescribing in Children and Adolescents After Surgery: An Expert Panel Opinion. JAMA Surg. 2021 Jan 1;156(1):76-90
8) Hu M-C, Griesler P, Wall M, Kandel DB. Age-related patterns in nonmedical prescription opioid use and disorder in the US population at ages 12-34 from 2002 to 2014. Drug Alcohol Depend. 2017;177:237-243.
9) Banerjee G, Edelman EJ, Barry DT, et al. Non-medical use of prescription opioids is associated with heroin initiation among US veterans: a prospective cohort study. Addiction. 2016;111(11):2021-2031
10) Kelley-Quon LI, Cho J, Strong DR, et al. Association of nonmedical prescription opioid use with subsequent heroin use initiation in adolescents.JAMA Pediatr. 2019;e191750.
11) US Department of Health and Human Services SAMHSA, Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health 2017 (NSDUH-2017-DS0001). Published 2019. Accessed October 7, 2020.
12) Osborne V, Striley CW, Nixon SJ, Winterstein AG, Cottler LB. Sex differences in patterns of prescription opioid non-medical use among 10-18 year olds in the US. Addict Behav. 2019;89:163-171.
13) McCabe SE, West BT, Boyd CJ. Motives for medical misuse of prescription opioids among adolescents.J Pain 2013;14(10):1208-1216.
14) Brands B, Paglia-Boak A, Sproule BA, Leslie K, Adlaf EM. Nonmedical use of opioid analgesics among Ontario students. Can Fam Physician. 2010; 56(3):256-262.
15) Sung H-E, Richter L, Vaughan R, Johnson PB, Thom B. Nonmedical use of prescription opioids among teenagers in the United States: trends and correlates.J Adolesc Health. 2005;37(1):44-51.
16) Cerdá M, Santaella J, Marshall BDL, Kim JH, Martins SS. Nonmedical prescription opioid use in childhood and early adolescence predicts transitions to heroin use in young adulthood: a national study.J Pediatr. 2015;167(3):605-12.e1, 2.
17) Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Patterns of prescription drug misuse among young injection drug users. J Urban Health. 2012;89(6):1004-1016.
18) US Department of Health and Human Services SAMHSA, Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health 2017 (NSDUH-2017-DS0001). Published 2019. Accessed October 7, 2020.
19) Nationwide Children's Hospital [Internet]. Columbus (OH): Nationwide Children's Hospital; Dec 2016. Guidelines for Safe Opioid Prescribing; [cited 21 Jan 2021]; [4 pages].
20) McCabe SE, West BT, Teter CJ, Ross-Durow P, Young A, Boyd CJ. Characteristics associated with the diversion of controlled medications

among adolescents. Drug Alcohol Depend. 2011;118(2-3):452-458.
21) Kelly LE, Sommer DD, Ramakrishna J, et al. Morphine or Ibuprofen for post-tonsillectomy analgesia: a randomized trial. Pediatrics. 2015;135 (2):307-313.
22) Mattos JL, Robison JG, Greenberg J, Yellon RF. Acetaminophen plus ibuprofen versus opioids for treatment of post-tonsillectomy pain in children. Int J Pediatr Otorhinolaryngol. 2014;78(10):1671-1676.
23) Riad W, Moussa A. Pre-operative analgesia with rectal diclofenac and/or paracetamol in children undergoing inguinal hernia repair. Anaesthesia. 2007;62(12):1241-1245.
24) Kuzma J. Randomized clinical trial to compare the length of hospital stay and morbidity for early feeding with opioid-sparing analgesia versus traditional care after open appendectomy. Clin Nutr. 2008;27(5):694-699.
25) Kashefi P, Mirdamadi M. Preemptive analgesia with ibuprofen and acetaminophen in pediatric lower abdominal surgery.J Res Med Sci. 2005;10 (4):222-226.
26) Viitanen H, Tuominen N, Vääräniemi H, Nikanne E, Annila P. Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. Br J Anaesth. 2003;91(3):363-367
27) Sutters KA, Miaskowski C, Holdridge-Zeuner D, et al. A randomized clinical trial of the effectiveness of a scheduled oral analgesic dosing regimen for the management of postoperative pain in children following tonsillectomy. Pain. 2004;110(1-2):49-55.
28) Bolton P, Bridge HS, Montgomery CJ, Merrick PM. The analgesic efficacy of preoperative high dose (40 mg x kg(-1)) oral acetaminophen after bilateral myringotomy and tube insertion in children. Paediatr Anaesth. 2002;12(1):29-35.
29) Moir MS, Bair E, Shinnick P, Messner A. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. Laryngoscope. 2000;110(11):1824-1827.
30) Dawson GS, Seidman P, Ramadan HH. Improved postoperative pain control in pediatric adenotonsillectomy with dextromethorphan. Laryngoscope. 2001;111(7):1223-1226.
31) United States Food and Drug Administration (FDA). FDA drug safety communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Published 2017. Accessed November 18, 2019.
32) Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. 2017.
33) Food and Drug Administration (FDA). Tramadol: drug safety communication - FDA evaluating risks of using in children aged 17 and younger. 2015.
34) Wisselo TL, Stuart C, Muris P. Providing parents with information before anaesthesia: what do they really want to know? Paediatr Anaesth. 2004;14(4):299-307.
35) Kankkunen P, Vehviläinen-Julkunen K, Pietilä A-M, Halonen P. Is the sufficiency of discharge instructions related to children's postoperative pain at home after day surgery? Scand J Caring Sci. 2003;17(4):365-372.
36) Lim SH, Mackey S, Liam JLW, He H-G. An exploration of Singaporean parental experiences in managing school-aged children's postoperative pain: a descriptive qualitative approach.J Clin Nurs. 2012;21(5-6):860-869.
37) Sharek PJ, Wayman K, Lin E, et al. Improved pain management in pediatric postoperative liver transplant patients using parental education and non-pharmacologic interventions. Pediatr Transplant. 2006;10(2):172-177.
38) Fortier MA, Kain ZN. Treating perioperative anxiety and pain in children: a tailored and innovative approach. Paediatr Anaesth. 2015;25(1): 27-35.
39) Kain ZN, MacLaren JE, Hammell C, et al. Healthcare provider-child-parent communication in the preoperative surgical setting. Paediatr Anaesth. 2009;19(4):376-384.

ARCH
Annual Review of Changes in Healthcare

Opicapone: A New FDA Approval to Reduce Pill Burden in Parkinson's Disease

Matthew Buchfellner, PharmD Candidate 2022[1]
[1]*University of Findlay College of Pharmacy*

Abstract

Treatment developments for Parkinson's Disease patients have continued to grow since its first diagnosis as a neurological syndrome in 1817. The options for these patients has improved over that time and with it has come an increasing responsibility for pharmacists to know the most up to date guidelines and newer medications to treat Parkinson's Disease when one of these patients is presented to them. Future guidelines may incorporate opicapone, a newly developed once daily pill, as a viable treatment option for Parkinson's Disease patients.

Parkinson's Disease is a progressive and chronic neurodegenerative disorder that is characterized by motor symptoms such as resting tremor, bradykinesia, and rigidity, as well as non-motor symptoms such as mood disorders, sleep disturbances and cognitive impairment. In the United States each year an estimated 50,000 people are diagnosed with Parkinson's Disease and about one million Americans currently have the disease.[1] Progression of Parkinson's Disease and the emergence of worsening symptoms may differ from patient to patient following diagnosis.[1] There is no cure for Parkinson's Disease; the goals for treatment are to improve quality of life and manage symptoms of the disease.[2] The critical role of the pharmacist in the care of this patient population is utilizing their pharmacological knowledge to improve the quality of the lives of patients living with Parkinson's.

The Canadian guideline for Parkinson's Disease of 2019 reflects the substantial changes in the literature on the treatment of the disease over the last 10 years.[2] This guideline reflects the substantial changes in the literature on the treatment of the disease over the last 10 years, with the most up to date evidence. According to that guideline, the goals of treatment for Parkinson's includes maintaining activities of daily living, limiting adverse effects of pharmacological treatment, and most notably includes cultivating patient independence and quality of life.[2] The quality of life for Parkinson's patients, particularly those that are stages 3 and above, is considerably low due to the severe debilitation that comes with advanced disease.[2] These patients can no longer move as they normally would and subsequently require constant support and monitoring.[2] Both the stiffness in the legs that make it impossible to stand or walk and the hallucinations and delusions that could result make it necessary to use medications to manage the disease.[3]

The pathophysiology of Parkinson's Disease involves a loss of function of a number of neurotransmitters, but most notably a deficiency of the neurotransmitter dopamine. Dopamine is the essential coordination neurotransmitter and enables neurons in the brain to communicate and control movement; in Parkinson's patients this chemical imbalance causes loss of fine motor movement and motor symptoms as well as non-motor symptoms such as depression.[4] Because of this, pharmacological management of Parkinson's Disease includes dopamine replacement therapy or treatments that can increase the amount of dopamine in the brain. The formulation carbidopa and levodopa is the mainstay of treatment. While this therapy reduces symptoms, it tends to become less effective over time leading to the development of "off" periods where symptoms are not controlled effectively and the quality of life for patients rapidly decreases in correlation with disease progression.[4] Additionally, patients needing carbidopa and levodopa therapy may need to manage these periods by taking this medication every two to four hours in some cases, with a maximum dosage limit of 800 milligrams of levodopa per day.[4]

The later stages of Parkinson's Disease see more of these "off" periods, and as such medications have been developed to

manage these periods and prolong disease progression as much as possible.[4] One such dopamine preserving medication is the COMT (catechol-o-methyl transferase) inhibitor, which blocks the ability of enzymes that normally break down levodopa, thereby extending its effect in the body.[4] The problem, however, is that COMT inhibitors as they existed before the year 2020 had to be co-administered with carbidopa and levodopa in order to achieve clinical effect, sometimes every two to four hours. This, in turn, led to a higher pill burden for those patients that needed additional therapy to carbidopa and levodopa, with an added pill to take each time. A series of reports from the U.S. Food and Drug Administration published in 2016 in which Parkinson's Disease patients were surveyed for their perspectives and what is most critical to them in treatment considerations revealed the three biggest downsides of treatment were the pill burden of their daily lives, the periods of "off-time" that they experienced, and the limited treatment options that existed for their disease.[5] Some of these concerns were addressed in the recent FDA approval of a COMT inhibitor that patients take once daily at bedtime instead of up to six times daily with carbidopa and levodopa.

On April 24th, 2020, opicapone (brand name: Ogentys) was approved for use by the Food and Drug Administration (FDA) in the United States.[6] Previously, this medication had been approved and used in Europe and Japan, after first being synthesized in 2017.[4] The medication comes in 50 and 25 milligram capsules, with a recommended dosage of 50 mg given once daily at bedtime. A dose adjustment to 25 mg once daily at bedtime should be recommended only in cases of patients with moderate hepatic impairment.[6] The medication should be taken at bedtime due to the reported side effect of sedation that is uncharacteristic of the traditional COMT inhibitors.[6] Potential advantages of opicapone may include no dose adjustments for renal deficiency and no geriatric dose considerations.[6]

Opicapone does show promise as a potential therapy for Parkinson's, but it is not without its limitations and side effects. This medication, like other existing COMT inhibitors, is contraindicated in patients already taking monoamine oxidase (MAO) inhibitors or in patients experiencing pheochromocytoma, paraganglioma, or a catecholamine secreting neoplasm.[6] Furthermore, opicapone contains additional precautions for cardiovascular effects, somnolence, hypotension, and dyskinesia.[7] Dyskinesia, the involuntary movements that often occur with Parkinson's Disease medications, is the most common adverse reaction leading to discontinuation of opicapone.[6] Opicapone, like other COMT inhibitors, must be added to existing regimens of carbidopa and levodopa, because it functions chiefly to enhance the effect of levodopa in the body. Futhermore, data has indicated that the incidence of dyskinesia is less than that with the other COMT inhibitors. According to the BIPARK-1 trial, the most common side effect reported with this medication is dyskinesia, with 20% of patients reporting the effect.[8] This was seen to be less than its predecessor entacapone in BIPARK-1, in which 25% reported tardive dyskinesia.[8]

Two twelve-week multinational phase 3 clinical trials testing the safety and effectiveness of opicapone as compared to placebo and to another COMT inhibitor entacapone (Comtan) was the basis for FDA approval.[9] These two trials, known as BIPARK-1 and BIPARK-2, demonstrated that individuals treated with opicapone had a significantly greater reduction in the time that they spend in "off" periods.[8] In BIPARK-1, a patient population receiving opicapone was compared to a patient population receiving entacapone, in which a COMT inhibitor was given each time levodopa was given.[8] Specifically, researchers aimed to assess the percentage of people that woke up in the morning without pain and assessed the time to first period of no pain as a UPDRS III score.[8] Data reported that the patient population receiving opicapone had less pain and less waking up in the morning with pain, and was overall statistically non-inferior to entacapone; opicapone treatment resulted in a numerically greater reduction in off-time (opicapone, −121.9±17.0; entacapone, −105.7±16.3 minutes; P = 0.46) and a significant reduction in UPDRS III score (opicapone, −4.6±0.8; entacapone, −2.4±0.8; P=0.04 versus entacapone).[8]

In the subsequent study BIPARK-2, the primary endpoint was a change from the "off" state of pain to the "on" state of no pain in comparing opicapone to placebo.[9] The results indicated that patients receiving opicapone had a statistically significant time decrease from pain to no pain.[9] The adjusted treatment difference vs. placebo was significant for the 50-mg/d opicapone group (treatment effect, -54.3 [95% CI, -96.2 to -12.4] minutes; P = 0.008), but was not statistically significant for the 25-mg/d opicapone group (treatment effect, -37.2 [95% CI, -80.8 to 6.4] minutes; P = 0.11).[9] The data from these trials was presented at the American Neurological Association's 2020 Virtual Meeting and might be a starting point for new guidelines for Parkinson's Disease being created with opicapone listed as a viable treatment option.[10]

As mentioned earlier, it is important to note that opicapone, like the classical COMT inhibitors, does not replace carbidopa and levodopa therapy, and must be added to existing medication regimens containing this medication.[11] It is critical for the pharmacist to be able to understand how to be able to apply this clinical knowledge to improve the care of a Parkinson's patient, and to put the role of new medications like opicapone into perspective. In this way, opicapone's use or future function in the guidelines is add-on therapy to patients having "off" periods of pain with maximized or near maximized carbidopa and levodopa.[12] A major advantage of opicapone is its propensity to be given once daily at bedtime. In the future, for patients not adequately controlled on carbidopa and levodopa, clinicians may choose to add on opicapone once daily instead of a different COMT inhibitor to be given each time levodopa is given.[13] The pharmacist's potential role of being able to help reduce the pill burden with once daily opicapone may help improve the quality of life of Parkinson's patients in the United States.

References

1) Bial Pharmaceuticals [Internet]. Trofa, Portugal: Bial; 2021. FDA approves Opicapone; 2020 [cited 2021Jan15]. Available from: https://www.bial.com/com/media/news/fda-approves-opicapone/
2) Grimes D, Fitzpatrick M, Gordon J et al. CMAJ. Canadian Guideline for Parkinson Disease; 2019 [cited 2021Jan15]. 191: E989-1004.
3) Parkinson's Foundation [Internet]. New York (NY): Parkinson's Foundation; 2021. Stages of Parkinson's; 2021 [cited 2021Jan15]. Available from: https://www.parkinson.org/Understanding-Parkinsons/What-is-Parkinsons/Stages-of-Parkinsons
4) Wexler, M [Internet]. Parkinson's News Today. Bionews Services LLC. Pensacola (FL): 2020. New Data Support Effectiveness of Ongentys for Parkinson's 'Off' Periods; 2020 [cited 2021Jan15]. Available from: https://parkinsonsnewstoday.com/2020/10/06/new-data-support-effectiveness-of-ongentys-for-parkinsons-off-periods/?cn-reloaded=1
5) U.S. Food and Drug Administration [Internet]. Silver Spring (MD): 2020. The Voice of the Patient: Parkinson's Disease; 2016 [cited 2021Jan15]. Available from: https://www.fda.gov/media/124392/download
6) Neurocrine Biosciences Inc. [Internet]. San Diego (CA): 2020. OGENTYSTM (opicapone) capsules for oral use; 2020 [cited 2021Jan15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212489s000lbl.pdf
7) Lexicomp [Internet]. Hudson (OH). Wolters Kluwer. 2020. [cited 2020Jan10]. Available from: http://online.lexi.com
8) Lew M, Hauser M, Isaacson S, et al. Efficacy of Opicapone Compared to Entacapone in Parkinson's Patients with Motor Fluctuations and ON Hoehn & Yahr ≤ 2.5: A Post Hoc Analysis of BIPARK-1; April 14th, 2020 [cited 2021Mar17]. Available from: https://n.neurology.org/content/94/15_Supplement/4429
9) Lees AJ, Ferreira J, Rascol O, et al. BIPARK-2 Study Investigators. Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol. 2017 Feb 1;74(2):197-206.
10) American Neurological Association [Internet]. Annals of Neurology; 2020: 145th Annual Meeting American Neurological Association; 2020 [cited 2021Jan15]. Available from: https://2020.myana.org/sites/default/files/docs/2020/wiley_abstract_supplement-final.pdf
11) U.S. Food and Drug Administration [Internet]. Silver Spring (MD): 2020. Drug Trials Snapshots: OGENTYS; 2020 [cited 2021Jan15]. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-ongentys
12) Cision Ltd. [Internet]. Chicago (IL). 2020. Neurocrine Biosciences Presents Phase III Data Analysis Demonstrating that Opicapone Added to Levodopa Resulted in a Significant and Sustained Increase in ON Time without Troublesome Dyskinesia in Parkinson's Disease Patients with Motor Fluctuations; 2019 [cited 2021Jan15]. Available from: https://www.prnewswire.com/news-releases/neurocrine-biosciences-presents-phase-iii-data-analysis-demonstrating-that-opicapone-added-to-levodopa-resulted-in-a-significant-and-sustained-increase-in-on-time-without-troublesome-dyskinesia-in-parkinsons-disease-patients-with-300843924.html
13) Pharmacist's Letter [Internet]. Therapeutic Research Center; 2021. Clarifying the Role of Ogentys and Kynmobi for Parkinson's Disease; 2020 [cited 2021Jan15]. Available from: https://pharmacist.therapeuticresearch.com/Content/Articles/PL/2020/Dec/Clarify-the-Role-of-Ongentys-and-Kynmobi-for-Parkinson-s-Disease

ARCH
Annual Review of Changes in Healthcare

Evaluation of Aromatherapy in the Management of Generalized Anxiety Disorder Symptoms

Sarah Kepple, PharmD Candidate 2022[1]
Dana Song, PharmD Candidate 2022[1]
[1]***University of Findlay College of Pharmacy***

Abstract

Anxiety is the most common psychiatric disorder in individuals across the world. It affects everyone differently in terms of symptoms and severity, but the focal points are characterized by an excessive feeling of worry or impending doom. Anxiety can be managed pharmacologically with selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). There are non-pharmacologic practices, however, that people can utilize that date back to the Ancient Egyptians. However, there are non-pharmacologic practices dating back to the Ancient Egyptians that people can also utilize. Aromatherapy is a holistic medicine practice that utilizes scents to stimulate sensations for the management of certain conditions. There are many essential oils on the market for the management of anxiety. This article will discuss anxiety, pharmacologic therapies for anxiety, holistic medicine, and the uses and benefits of aromatherapy on anxiety symptoms.

Introduction

What is Anxiety?

Anxiety is a natural response and normal part of the human brain, where a person may occasionally experience disruptions in daily life. It is an adaptive response that allows for perception of a stressful event. However, anxiety disorders are psychiatric conditions that involve extreme fear or worry.[1] Simply put, it is due to an overactive fear response. This differs from normal feelings of anxiety in a way where constant anxiety becomes debilitating, persistent psychological and physical symptoms.[1] It affects the person's ability to function by making it difficult for the person to get out of bed, go to school, or function in society.[1] Situation anxiety is more severe, but temporary. These last no more than 2-3 weeks at a time. When an anxiety disorder becomes long-term, it starts to affect other health aspects and can evolve into cardiovascular, cerebrovascular, GI, and respiratory disorders.[1] There are several forms of anxiety, including generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, obsessive compulsive disorder, specific phobias, selective mutism, and more. These disorders can be hereditary, but can sometimes develop through other factors ranging from gender, brain chemistry, personality, life events, and more.[1]

Anxiety disorders are one of the most common mental disorders in the United States. The US national prevalence data shows that nearly 40 million people (roughly 18%) experience anxiety disorders.[2] Around 8% of children and adolescents experience anxiety symptoms before the age of 21.[2] Despite the disorders being treatable, only one third of those experiencing anxiety disorders actually receive treatment.[1,2]

There are several risk factors involved with anxiety disorders. First, females have a higher chance of developing an anxiety disorder compared to men.[2,3] There is a 2:1 female to male ratio for anxiety disorders. This disorder is most commonly seen in the young adult to middle-aged group (21-45 years of age).[2,3] The most common psychiatric comorbidity seen with anxiety is depression.[1,2] A patient who presents with anxiety disorders may be diagnosed with depression as well. When coupled with other ongoing issues such as social issues, financial problems, medical illnesses, family history of anxiety and depression, and lack of support from families or friends, this may increase the risk factors for an individual developing an anxiety disorder.[3] Like chronic comorbid conditions, such as diabetes or allergies that are passed through familial generations, anxiety is the same way.[2] Medical illnesses may arise from anxiety disorders and these may lead to cardiovascular, neurologic, endocrine, metabolic, gastrointestinal, and other illnesses. [4]

Generalized anxiety disorder (GAD) is a common mental health anxiety disorder that leads to excessive, uncontrolled worry in an individual that interferes with the normal everyday functioning.[2,3] GAD occurs for at least 6 months and causes significant

distress and impairment in social, occupational, or other important areas of function.[5] The individual may have uncontrolled worry about different events with heightened tension. This can range from pure GAD, where the individual has no comorbidities, or typical GAD, where the individual usually presents with other comorbid conditions in addition to GAD. The presentation of GAD can vary amongst patients, but generally involves difficulty concentrating, restlessness, fatigue, muscle tension, sleep disturbances, and/or irritability.[5]

In fear of a threat, the locus ceruleus acts as an alarm and activates the release of norepinephrine.[4] Since norepinephrine stimulates sympathetic nervous system responses, an anxious person will experience increased heart rate, panic, and increased blood pressure. Additionally, excessive norepinephrine causes an increase in glutamate release, an excitatory neurotransmitter that causes further sympathetic responses.[4] The increased levels of circulating glutamate results in more feelings of panic and anxiety. Therefore, the flight-or-fight response becomes continuously activated.[4]

In order to develop an effective plan for management of anxiety, several factors must be considered. These factors include severity, chronicity of symptoms, age, medication history, comorbidities, history of prior family response, patient preferences, cost, and the goal of anticipated effects. The anxiety goals of therapy are to reduce the severity and duration of anxiety symptoms, improve day-to-day functions, induce remission, prevent functional impairment, and improve quality of life.[4] As such, anxiety symptoms could be managed either by non-pharmacological treatments and/or pharmacological treatments.[4]

First-Line Therapies in Anxiety Management

Pharmacological Interventions

The treatment for each type of anxiety may differ slightly in terms of first-line of treatment. However, the treatments generally consist of either antidepressants, benzodiazepines, or buspirone. Alternative medications may be used for breakthrough anxiety.

There are two main groups of antidepressants: selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[4] The first-line for long-term management of anxiety disorders include either SSRIs or SNRIs depending on the patient.[4] Antidepressants reduce psychic symptoms compared to other classes for anxiety, but could take at least four weeks, or longer, for patients to see the full effect.[4] Psychic symptoms include apprehension, worry, hallucinations, and more.[4,6] SSRIs can have different adverse reactions that either do or do not subside with time. Some examples of adverse reactions that do not typically subside with SSRIs include sexual dysfunction and anticholinergic symptoms (drowsiness, dry eyes/mouth, constipation, etc).[4,6]

With these medications used to treat anxiety, patients can develop withdrawal upon discontinuation.[4] In addition, patients might experience undesirable side effects from these medications that, while helping the condition, could lead to additional emotional or physical problems.[6] For these reasons, some patients may want to look for a more natural approach to managing their anxiety symptoms. Patients may also want to choose to incorporate natural therapies into their regimen to complement current pharmacologic or non-pharmacologic therapies.

Non-Pharmacologic Interventions: Cognitive Behavior Therapy

Today, most non-pharmacological therapies for managing anxiety are centered on cognitive behavior therapy.[4,7] During this therapy, many relaxation techniques are used and taught to the patient for them to utilize when experiencing anxiety symptoms. With generalized anxiety disorder, patients experience feelings of excessive worry or impending doom. As a result, the individual has decreased problem solving abilities, attention disturbances, and decreased ability to effectively manage stressful or negative situations.[7] The overall goal of this therapy is to replace worrisome thoughts and provide the patients with coping strategies and techniques. A study conducted by Gould et al. determined that cognitive behavior therapy and pharmacologic interventions are equally effective in the management of generalized anxiety disorder.[8] Other nonpharmacologic treatments are available to patients with generalized anxiety disorder, including music therapy, meditation, and aromatherapy, which will be discussed in this article.

Essential Oils and Aromatherapy

History

Essential oils were founded by the ancient Egyptians around 3500 BC through the cultivation of plants for medicinal and religious practices.[9] The popularity of essential oils expanded throughout Asia and Europe, and became an integral component of Indian Ayurvedic medicine and many holistic therapies practiced by the Greeks.[9] Holistic medicine is defined as a whole-body approach to health care and is a combination of traditional medicine and complementary/alternative medicine (CAM).[9] This practice focuses on the link between physical health and the overall well-being of an individual in the prevention and treatment of disease. It takes into account the psychological, emotional, social, spiritual, and environmental states of an individual to gain a clear picture of the patient.[9] Problems arise when one or more of these components are out of balance. As a result, the holistic approach helps bring equilibrium to these unbalanced components.[9] Holistic medicine is practiced by many people and is an integral component of different cultures.[9]

While essential oils were popular and used since 3500 BC, the term "aromatherapy" was not coined until the year 1937 after a French chemist and perfumer, Rene Maurice Gattefosse, severely burned his hand.[9] He did not have any medications to treat this injury and

decided to treat the wound with pure, undiluted lavender oil. After doing so, the chemist claimed the pain immediately subsided and promoted healing with no evidence of infection or scarring.[9] This led to him conducting more experiments on the uses and effects of essential oils from nature when treating patients.[9] Aromatherapy has continued to evolve in both understanding and popularity since the early 1980s as more people have become interested in natural medicine and environmental concerns.[9] Today, many people utilize these essential oils.

Postulated Mechanisms of Aromatherapy

Aromatherapy works through the sense of smell and skin absorption of essential oils to stimulate certain sensations.[10] Several products can be used for aromatherapy, such as diffusers, inhalers, bathing salts, and topical applications (creams, diluted oils through roller-bottles, etc).[10] Essential oils have been used for symptom management of different conditions, such as asthma, insomnia, anxiety, depression, pain, inflammation, arthritis, or endocrine system conditions (erectile dysfunction, menstrual pain, or menopause) to name a few.[10] In addition to being used in different conditions, there are many essential oils available on the market.

Particular smells associated with some essential oils help reduce anxiety in individuals.[11] However, this is still an unclear mechanism and is still a hypothesis, therefore, more research needs to be completed on this.

Aromatherapy Agents, Uses, and Delivery

The following list details the different essential oils and their potential effects:[12]

- Valerian: May help promote sleep and calms the nerves by eliciting a mildly sedating effect.[12]
- Jatamansi: Utilized in Ayurvedic medicine to help calm the mind and encourage sleep. Some studies have also shown that it may relieve symptoms of depression by decreasing the number of GABA (inhibitory) neurotransmitters and monoamine oxidase receptors in the brain.[12]
- Lavender: The most popular essential oil for anxiety symptoms. The mechanism behind the effect is unclear, but is thought to have an impact on the limbic system (the memory and emotion complex of the brain).[12]
- Jasmine: Inhalation may promote a general sense of well-being without causing sleepiness.[12]
- Holy basil (Tulsi): Has a spicy, mint aroma due to the presence of eugenol, which may help treat physical and mental stress.[12]
- Sweet basil: Contains phenol compounds that are thought to calm the mind and relieve stress. It has been shown to be less sedating than diazepam, a common medication in the treatment of anxiety.[12]
- Bergamot: May help improve mood and anxiety symptoms.[12]
- Chamomile: May contain relaxing and sedating properties. There is not much understanding behind the

effects of inhaling the scent, but it has shown promising benefits in mild-moderate general anxiety disorder when taken orally.[12]
- Rose: May help relax the senses in pregnant patients during labor when administered via a footbath.[12]
- Vetiver: May promote relaxation.[12]
- Ylang ylang: May promote relaxation.[12]
- Frankincense: May ease anxiety symptoms.[12]
- Clary sage: May ease tension and help control cortisol levels in women.[12]
- Patchouli: May relieve symptoms of anxiety, depression and stress.[12]
- Geranium: May help decrease diastolic blood pressure and anxiety symptoms in pregnant patients during labor.[12]
- Lemon balm: May help relieve symptoms of mild-moderate generalized anxiety disorder and promotes sleep when taken via capsules.[12]
- Marjoram: May help ease headaches.[12]
- Fennel: May help relieve anxiety symptoms related to menopause.[12]

In addition to using these oils as single agents, they may also be combined with other oils to elicit multiple effects or more symptom management.[12] For example, the combination of ylang ylang with lavender and bergamot may help to lower stress levels by decreasing blood pressure, heart rate, and serum cortisol levels (the main hormone that contributes to stress).[12]

The delivery of these agents mentioned above include inhalation, oral, and injections.[13] These different delivery actions produce similar effects on the brain, where 5-HT and dopamine (DA) are affected.[14] In numerous studies that used rose oil, a physiological and psychological relaxation and anxiolytic effect was seen in primigravida women.[15] Another study reported that rose geranium oil produced an anxiolytic effect in mice after an acute intraperitoneal injection.[16]

Studies Evaluating the Effectiveness of Aromatherapy

The placebo effect is a common rationale given for the mechanism of essential oils. A study by Ahmad et al evaluated the use of relaxation promoting essential oils, namely lavender, in pharmacy students via a randomized-single-blind placebo controlled trial. The students that were enrolled in the study were male and did not have a previous diagnosis of anxiety or depression, but were to undergo aromatherapy twice daily for three weeks during final exams. The researchers concluded that there was no benefit from aromatherapy when compared to placebo.[17]

Although the ratio for anxiety diagnosis is twice as many in females compared to males, there is still a greater bias towards using male subjects when looking at anxiolytic drug therapies.[2,3] Only a few studies looked at both sexes when comparing the medications. Differences in male and female physiology is apparent especially in steroid hormones. Hormones affect anxiety greatly, as sex hormones are

one of the main causes between anxiety differences in male and female. Studies show that high levels of estrogen reduce anxiety levels in female rodents.[18] Additionally, human males and females differ greatly in their olfactory bulb. This difference in the olfactory molecules and receptors results in dissimilarities between the male and female response.[18,19] As a result of both sexes displaying different responses to essential oils, it may be more beneficial if future studies looked at both sexes in order to determine a more comprehensive mechanism of action.

In a Portuguese study, there were 50 subjects enrolled to receive 6 different types of aromatherapy massages.[20] There was a statistically significant found ($p<0.001$) reduction in heart and respiratory rates. However, due to being an uncontrolled and small study, it may be underpowered.[20] In the study, 39/50 were female and the average age was 30 and 35 years of age, men and women respectively.[20] Medications and tobacco use were not excluded so it may have played a part in their anxiety reduction.[20] In order to reduce this potential bias, the researchers tried to take this consideration into account by timing their aromatherapy massages.[20] In the discussion, the researchers addressed that some of the limitations of the study may stem from the lack of standardized concentrations and formulations of essential oils. There was also a lack of sample calculations, control group, and large sample size. Despite showing benefit in aromatherapy use, more studies would need to be conducted in order to show benefit from use.[20]

Discussion

Based on the following methods and treatments available, it may benefit individuals suffering from anxiety to try more natural products when evaluating the side effect profiles of traditional pharmacologic therapies, cost of both pharmacologic and non-pharmacologic therapies, convenience-of-use, and time.

With aromatherapy, patients may experience a quick response to ease anxiety symptoms. Aromatherapy can be delivered via different methods that an individual can keep on themselves (bracelets, necklaces, roll-bottles, inhalation sticks, etc) or stationed throughout their place of residence (diffusors, candles, etc).

There is limited data and research available on aromatherapy benefits or effectiveness, so it should not replace pharmacologic medications. When completing a MeSH search in PubMed, there was limited data and research conducted on aromatherapy. When using search words “aromatherapy AND anxiety,” only 9 results appeared between 2012 and 2021. For this reason, there were not major conclusive studies showing benefits for aromatherapy use in anxiety. In certain cases, some individuals may benefit from essential oil alone. In others, however, there may be limited to no benefit of using essential oils. This does not disregard the use of essential oils completely. Regardless, if essential oils work well for one person, this may not be the case for everyone. If a person experiencing anxiety prefers to take a more natural approach to anxiety

management, aromatherapy is a possible option, but the individual should always consult with their physician regarding its use.

In conclusion, more studies should be conducted to evaluate the effectiveness, safety, and mechanism of action of aromatherapy on patients with psychiatric conditions, such as anxiety and depression.

References:

1) Anxiety and Depression Association of America [Internet]. Silver Spring: ADAA; c2010-20 [updated 2020; cited 2021 Jan 5]. Available from: https://adaa.org/understanding-anxiety
2) Generalised anxiety disorder and panic disorder in adults: management. NICE clinical guidelines. 2011 Jan;1-42.
3) Anxiety.org [Internet]. Newport Beach: Consumer Brands; c1999-2021 [cited 2021 Jan 5]. Available from: https://www.anxiety.org/
4) Melton ST, Kirkwood CK. In: Pharmacotherapy: A Pathophysiologic Approach, 11e. New York, NY: McGraw-Hill; 2020.
5) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Washington DC. 2013.
6) Lexicomp [Internet]. Alphen aan den Rijn (NL): Wolters Kluwer. c2021. [cited 2021 Jan 7]. Available at: http://online.lexi.com/action/home
7) Cottraux J. Nonpharmacological treatments for anxiety disorders. Dialogues Clin Neurosci. 2002 Sep;4(3):305-19.
8) Gould RA, Otto MW, Pollack MH, et al. Cognitive behavioural and pharmacological treatment of generalized anxiety disorder: a preliminary metaanalysis. Behav Ther. 1997;28:285–305.
9) FGB Natural Products. History of Essential Oils. 2016. Felton Grimwade & Bosisto's. Available from: https://www.fgb.com.au/content/history-essential-oils
10) Perry N, Perry E. Aromatherapy in the Management of Psychiatric Disorders. CNS Drugs. 2012 Aug 29;20(4):257–280.
11) Cooke B, Ernst E. Aromatherapy: A systematic review. Br J Gen Pract. 2000;50:493–496.
12) McDermott A. Try This: 18 Essential Oils for Anxiety. Healthline 2017. Available from: https://www.healthline.com/health/anxiety/essential-oils-for-anxiety
13) Zhang N, Yao L. Anxiolytic effect of essential oils and their constituents: a review. J. Agric. Food Chem. 2019;67:13790-808.
14) Oliveira-Pinto AV, Santos RM, Coutinho RA, et al. Sexual dimorphism in the human olfactory bulb: Females have more neurons and glial cells than males. PLoS One. 2014;9(11):e111733
15) Mohebitabar S, Shirazi M, Bioos S, et al. Therapeutic efficacy of rose oil: A comprehensive review of clinical evidence. Avicenna J Phytomed. 2017;7(3):206–13.
16) Abouhosseini TM, Hajizadeh MA, Maggi F, et al. Anxiolytic and antidepressant activities of Pelargonium roseum essential oil on Swiss albino mice: Possible involvement of serotonergic transmission. Phytother Res. 2018;32(6):1014–1022.
17) Ahmad R, Naqvi AA, Al-Bukhaytan HM, et al. Evaluation of aromatherapy with lavender oil on academic stress: A randomized placebo controlled clinical trial. Contemp Clin Trials Commun. 2019 Mar 15;14:100346.
18) Meziane H, Ouagazzal AM, Aubert L, et al. Estrous cycle effects on behavior of C57BL/6J and BALB/cByJ female mice: Implications for phenotyping strategies. Genes, Brain Behav. 2007;6(2):192– 200. .
19) Kang N, McCarthy EA, Cherry JA, et al. A sex comparison of the anatomy and function of the main olfactory bulb-medial amygdala projection in mice. Neuroscience. 2011:172(1):196– 204.
20) Domingos TDS, Braga EM. Massage with aromatherapy: effectiveness on anxiety of users with personality disorders in psychiatric hospitalization. Rev Esc Enferm USP. 2015 Jun;49(3):453-9.

ARCH
Annual Review of Changes in Healthcare

Review of the National Action Plan for Combating Antibiotic-Resistant Bacteria

Paige Willms, PharmD Candidate 2025[1]
[1]*University of Findlay College of Pharmacy*

Abstract

Improved sanitations systems, better hygiene, vaccines, and the use of antibiotics and other medications, have reduced the number of deaths caused by bacterial infections. Unfortunately, as our practices to reduce bacterial infections improve, the bacteria's defenses improve just as quickly. Bacteria can develop resistance to the antibiotics that are used to kill them. To help combat antibiotic-resistance, a national plan has been put in place. This paper reviews the updates that have been made in the 2020-2025 plan as well as the components of the plan that are still being used.

Antibiotics have been used to treat patients since the 1940s. Soon after the new treatment was developed, resistance from bacteria began being observed.

Due to years of overprescribing, and overuse in agriculture and other industries antibiotic resistance has become a serious issue. Antibacterial resistance happens when bacteria develop the ability to become resistant to the medication designed to kill them. Once the bacteria have developed this trait, they are then able to pass this information to other bacteria. Eventually enough bacteria become resistant to a certain antibiotic that it is no longer useful in certain individuals.[1]

Resistant infections are difficult and sometimes impossible to treat. In most cases, antibiotic-resistant infections require extended hospital stays, additional follow-up doctor visits, and costly and toxic alternatives.[1] The Centers for Disease Control and Prevention (CDC) reports that antibiotic resistant bacteria are responsible for more than 2.8 million infections and 35,000 deaths a year in the Unites States.[2]

As this issue grows, crucial steps must be taken to combat antibiotic resistance so that we do not return to a pre-antibiotic era where small infections could be deadly. The National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) aims to help decrease the amount of antibiotic resistance.

The Executive Order 13676 established the Federal Task Force on Combating Antibiotic-Resistant Bacteria to identify actions to implement the National Strategy.[3] Based on the 2014 U.S Government's National Strategy for CARB, the first National Action Plan was released in 2015 by the Federal Task Force. The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), also established by Executive Order 13676, is composed of both Federal and non-Federal subject-matter experts in human and agricultural heath.[3]

In midst the COVID-19 pandemic, this plan has been updated to better assess and control antibiotic resistance.[2] In October 2020, the updates to the National Action Plan were released. This plan will range from 2020-2025 and then will likely be readjusted to better assess our standing on the issue in the future.[2] The 2020-2025 plan builds on the original plan released in 2015 by expanding evidence-based activities that have been shown to stop the spread of antibiotic resistance, such as increasing infection prevention and control and improving the way antibiotics are used.[4]

The new plan features the same main goals with updated objectives. The plan can be broken down into five main goals. The first goal is to slow the emergence of resistant bacteria and prevent the spread of resistant infections.[3] Bacteria and fungi resistance is inevitable, but it is important to slow this process to minimize the effects on

human and animal health.[3] One way to achieve this is through primary prevention of infections through infection control and other interventions.[3] Also, using antibiotics in humans and animals only when needed rather than as a preventative measure will greatly help to reduce the likelihood of bacteria developing resistance.[3]

The Task Force on CARB anticipates challenges of trying to accomplish the goal of slowing and preventing the spread of resistant infections.[3] The Task Force anticipates having difficulties changing behaviors to ensure that the optimal infections control practices and appropriate prescribing are taking place.[3] Changing the way our healthcare systems have operated in the past is a challenge that will not be conquered overnight. Nonetheless, these efforts are vital to prevent future complications. Another issue will be identifying and scaling up the best practices across spectrums of care and ensuring their continuity while coordinating these practices across One Health. One Health is a collaborative and transdisciplinary approach with the goal of achieving optimal health outcomes by recognizing the interconnection between people.[3]

Additionally, engaging all relevant stakeholders could be another potential difficulty.[3] The objectives of the CARB plan explain plans to expand on national, regional, and state capacity for detecting, containing, and preventing antibiotic-resistant infections.[3] Additional education and training to help to change current practices efforts are also being made.

The next goal that is outlined is to strengthen national One Health surveillance efforts to combat the resistance. Antibiotic resistances are no doubt a One Health issue because it affects the health of humans, animals, plants, and the environment.[3] Efforts to track the resistant organisms mass scale surveillance. This requires the collaboration of many U.S. Government agencies to track and report cases of resistance.[3] This plan not only brings these agencies together but sets standards for practices and deadlines to invoke results.[3] There are many challenges that come from trying to strengthen the national infrastructure for surveillance of antibiotic use and resistance. Encouraging local, State, and private partners and stakeholders to collect and share data across the human, animal, plant, and environmental sectors is not an easy feat.[3] Enhancing training and testing capacities will require laboratories to maintain ongoing support for staff, continuously maintaining testing equipment, and advancing testing methodologies.[3] It is essential to find cost effective ways to collect and transmit the obtained data as well as practices that are time efficient. Four objectives have been put into place to help offset these perceived complications.

The third goal is to advance development and use of rapid and innovative diagnostic tests for identification and

characterization of resistant bacteria.[3] New diagnostic tests are urgently needed to detect antibiotic resistance and to improve surveillance, the control of infections, and treatment decision-making by providers. The major issue to this is introducing new diagnostics that lack research on their appropriate use in clinical and veterinary care and a lack of point-of-care antibiotic resistance diagnostics in outpatient settings.[3] There also needs to be a development of an incentive program to promote validation, adoption, and appropriate use of new and currently available diagnostics. The high cost of developing new diagnostics with the limited return on the investment is a huge difficulty that this plan hopes to not only address but to overcome by increasing education and showing the importance of these developments as well as to find ways to incentivize developments.

The fourth goal is to accelerate basic and applied research and development for new antibiotics, other therapeutic, and vaccines. While surveillance and management are extremely important aspects of the plan, the development of better therapeutics are equally important. Tracking the issue allows us to know where we stand, but if we want to stay ahead of the issue it is important that new therapies are being created to help decrease current and possible future resistance. Research can help to improve our understanding of the many factors that contribute to the emergence, spread, and persistence of antibiotic resistance and can support new strategies or preventing and mitigating infections.[3] Improving on existing therapies is also important. Research on alternative to antibiotics, including bacteriophages, monoclonal antibodies, immune modulators, and phytochemicals, suggests that these products can help prevent and treat infections in humans and animals without promoting antibiotic resistance.[3] Effective vaccines that prevent infection are another alternative to the use of antibiotics. Other research and innovative products like biotherapeutics including microbiome-based products, prophylactic monoclonal antibodies, and decolonizing agents, could expand the range of strategies and help reduce the impact of antibiotic resistance.[3] The discovery of new classes of antibodies with activity against gram-negative bacteria is also very challenging.[3] Not only is it hard to find all these break throughs, but there is also the lag time to consider. The time that it takes for these discoveries to be made and then to be applied to development of new therapies and then to be distributed in medical practices. This involves more research and more education before the real impacts of the research finding can be felt. The main focuses of this goal are just as trying to increase the amount of research so that we can hopefully find new and better way of navigating through this impediment.

The last goal is to improve international collaboration and capacities for antibiotic-resistance prevention,

surveillance, control, and antibiotic research and prevention.[3] As outlined in the National Biodefense Strategy, the U.S. Government Global Healthy Security Strategy, and in accordance with the U.S Government's engagement through the Global Health Security Agenda, the U.S. Government works to enhance the capacities of governments, civil society, academia, and the private sector in partner countries and the international community to address the emergence, spread, and impact of antibiotic resistance.[3] To do this it is crucial to be able to rapidly detect and contain antibiotic-resistant pathogens.[3] Enhancing the global efforts as well as establishing a well-functioning internal network to detect and respond to antibiotic resistance is a lofty task. This requires an alignment of many resources in the U.S and the rest of the world.[3] Accomplishing this goal is extremely important so that all other efforts are not in vain. It is to be noted that the problem of antibiotic resistance is a threat to the humans, animals, plants, and the environment everywhere not just the United States. "Microbes don't respect borders. They don't respect political boundaries. They don't respect political ideology. So, whatever our borders and national ideologies are, we need to work together; otherwise, it's going to take a terrible toll." States Martin Blaser, MD, chair of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB).[2]

Although it is evident that the plan falls short in some areas even with the updates, the existence of this plan is an extremely important start. "Having a National Action Plan for CARB is important both symbolically and functionally," said David Hyun, MD, senior officer with the Pew Charitable Trusts' antibiotic resistance project. "When the first plan came out in 2015, it sent an important signal that the US recognized and is working to combat the growing threat of antibiotic resistance, and by issuing an updated plan, the U.S. is sending a clear message that the fight against superbug remains a national priority."[2]

The National Action Plan for CARB does not specifically address the need for incentives to fix the financial model for antibiotics, which is widely seen as a roadblock to bringing innovative new antibiotics to market.[2] The plan will be reassessed at its completion in 2025 which will allow an opportunity to adjust the current goals and objective to better decrease the emergence and spread of antibiotic-resistant infections and to better address issues like the current financial model.[3]

Within five years the previous portion of the CARB plan was also able to accomplish several objects. By working together on local, state, territorial and international levels the U.S Government has established the nation-wide Antibiotic Resistance Laboratory Network (AR Lab

Network).[3] New programs were developed to improve antibiotic usage in healthcare. Biopharmaceutical accelerator, CARB-X, was initiated to help develop and approve new diagnostic and treatment options.[3] Moving forward into the next five-year plan it will be interesting to see what progress is made on the updated plan objectives.

References:

1) About Antibiotic Resistance [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2020 [cited 2021Jan31]. Available from: https://www.cdc.gov/drugresistance/about.html
2) Chris Dall | News Reporter | CIDRAP News | Oct 12 2020. Feds release new national antibiotic resistance plan [Internet]. CIDRAP. 2020 [cited 2021Jan30]. Available from: https://www.cidrap.umn.edu/news-perspective/2020/10/feds-release-new-national-antibiotic-resistance-plan
3) Federal Task Force on Combating Antibiotic-Resistant Bacteria, 2020. National Action Plan for Combating Antibiotic-Resistant Bacteria [Internet]. Washington (DC): Department of Health and Human Services; 2020 [cited 2021 March 22]. Available from: https://www.hhs.gov/sites/default/files/carb-national-action-plan-2020-2025.pdf
4) U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (National Action Plan) [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2020 [cited 2021Jan30]. Available from: https://www.cdc.gov/drugresistance/us-activities/national-action-plan.html

ARCH
Annual Review of Changes in Healthcare

The Prominent Role of Telehealth during the COVID-19 Pandemic

Elaine Ng, PharmD Candidate 2026[1]
Jessica Singh, PharmD Candidate 2026[1]
[1]*University of Findlay College of Pharmacy*

Abstract

Telehealth is referred to as the remote interactions between health care providers and patients through a variety of audio or video platforms. Over the past years, it has become quite useful in clinical health care, professional health care education, and public health administration. There are multiple technologies that provide telehealth such as videoconferencing, streaming media, store-and-forward imaging, and other wireless communications. Telehealth includes remote clinical services with other non-clinical services such as health administration meetings, medical education, and health worker training.

In the past, American rural areas had a more profound need for telehealth due to limited medical specialities and extended travel times to clinics.[1] Remote methods of communication ensure that patients have access to special health care services that may not physically be accessible to them. This type of communication presents the importance of telehealth in modern health care.[2]

Companies, such as Teladoc® and MeMD®, provide a variety of medical services. Teladoc, one of the first telehealth providers in the United States, includes "pediatric services, nonemergency medical issues, dermatological conditions, mental health consultations for issues such as depression and addiction, and sexual health consultations."[3] Teladoc® has its own physicians that can send prescriptions to pharmacies and analyze lab results.[3] Whereas, MeMD® follows a different approach. MeMD® allows users to explain their symptoms and a doctor assesses them within the same consultation.[3] It also offers urgent care services and talk therapy sessions.[3]Most telehealth service companies have similar goals of providing the best quality of health care through remote communications.

The Cruciality of Telehealth

The need for telehealth care increased vastly in 2020 as SARS-CoV-2, the virus that causes COVID-19, spread. COVID-19 is considered a public health emergency so it is essential that individuals follow updated regulations. In-person communication between health care providers and patients needed to be limited due to COVID-19 restrictions such as social distancing. Telehealth technologies play an important role in ensuring these restrictions are followed while attempting to limit the spread of the virus. The public is encouraged to stay home during the pandemic, but this proves difficult for in-person doctor visits not pertaining to COVID-19. Telehealth assists in reducing the risk of "patients infecting others (particularly health care workers)."[4]

Another key benefit of remote health care communication is preserving personal protective equipment (PPE).[5] Remote communications also decrease the risk of transmitting the SARS-CoV-2 virus to others if either the provider or patient carries it. In order to accommodate all patients' circumstances, multiple methods of telehealth can be offered with each method varying vastly in terms of its procedures, policies, and guidelines.[4]

Methods of Telehealth

Different methods of telehealth have been employed over the recent years for many types of health care issues. These methods can be categorized into three main types of remote communication: synchronous, asynchronous, and patient monitoring.

Synchronous telehealth refers to "real-time telephone or live audio-video interaction" between health care providers and patients. This method involves devices

that are able to connect to communication networks.

Asynchronous telehealth methods include "store and forward" formatting, which implies messages, images, or data are submitted to online portals.[5] These submissions are later evaluated and responded to by health care professionals. This type of communication typically occurs through secure networks.

The other main type of telehealth is remote patient monitoring. It allows patients to enter specific health data (weight, blood pressure, blood sugar, etc.) from one location to health care providers. [5] Commonly, health care workers recommend this form of telehealth once a patient is released from care. [5] Remote patient monitoring ensures the patient is maintaining routine care while recovering.[5] All these telehealth methods play a significant role in limiting in-person clinic visits during the COVID-19 pandemic.

The History of Telehealth Before COVID-19

The outbreak of COVID-19 has significantly expanded the application and importance of remote health care systems. The expansion of telehealth and telemedicine have grown exponentially in recent years due to the rapidly improving telecommunications infrastructure, as 98% of Americans now live in areas with 4G LTE service with increased processing speeds across all devices.[6] Because of the increase in quality and availability of internet usage and cloud-based consulting services, the next generation of health care professionals are developing in a digital world in which the past inconveniences of technological efficiency are no longer concerns.[6]

A continuing obstacle regarding the advancement of telehealth includes the reimbursement process, because the Centers for Medicare and Medicaid Services (CMS) guidelines are not standardized across all states. [6] However, even before the onset of COVID-19 telehealth guidelines and policies were as advanced and widespread as they had ever been.[7] The Center for Connected Health Policy released the guide "State Telehealth Medicaid Fee-For-Service Policy: A Historical Analysis of Telehealth: 2013 - 2019" in order to display the trends and growth of telehealth over the past few years.[7] The key findings include that live video is now reimbursed by Medicaid across all states and D.C. compared to 6 states and D.C. in the Spring of 2013.[8] Additionally, the number of states reimbursing for remote patient monitoring has tripled since 2013.[8]

Telehealth has been expanding the past 7 years as exemplified by increased adoption of reimbursement policies for varying forms of telehealth, and it appears to be continuing to grow in the time of COVID-19 with the addition of security measures and privacy reassurance.[9] In times before COVID-19, in which telehealth was not a universally necessary form of health care, telehealth still continued to be widely adopted due to the convenience it offers when coupled with today's technological advancements.[8] However, with the current

pandemic creating the unexpected need to provide health care remotely, former guidelines and policies became inapplicable, and have needed to be modified.[10]

Current Guidelines for Telehealth

The unexpected onset of COVID-19 created a need for a widespread remote form of health care. Due to the sudden need to adjust to unconventional practices, many new but temporary policies and guidelines revolved around telehealth. Many of these policies specifically focused on reimbursement policies, cyber security, temporary expansion, and other flexibilities to further accommodate patients.[11]

The Centers for Medicare & Medicaid Services (CMS) often directs reimbursement policies for various health care practices. Under the newly enacted Coronavirus Preparedness and Response Supplemental Appropriations Act and the 1135 Waiver, telehealth has been covered in a broader spectrum by Medicare and Medicaid Under the 1135 Waiver.[12] Medicare is valid for coverage in terms of office, hospital, and general medical visits that occur by telehealth in the U.S. including from patients' homes.[12] Furthermore, the HHS Office of Inspector General (OIG) will also allow for health care providers to reduce or waive cost-sharing for telehealth visits that are paid for by federal health care programs.[12] Therefore, the CMS concluded that for the duration of the COVID-19 Public Health Emergency, telehealth visits will be regarded the same as in-person medical visits with the same cost and rates.[12]

Beyond more leniency in coverage for telehealth, there is greater expansion in the qualifications of telehealth sites and methods in order to provide health care and services to more people.[12] Patients living in rural areas were significantly impacted by the needed distancing from COVID-19, therefore Federally Qualified Health Centers (FQHCs) and Rural Health Clinics (RHCs) are temporarily considered distant telehealth sites to provide telehealth services to patients remotely.[11] Another significant development in a wider outreach includes the CMS's broadened consideration of what is deemed to be covered telehealth service by Medicare, which now includes emergency departments visits, therapy services, and home visits.[11] Federal health care programs such as Medicare, Medicaid, and the Children's Health Insurance Program (CHIP) have also become more receptive towards changes with cost-sharing.[11] The HHS Office of Inspector General (OIG) has been allowing health care providers to decide whether cost-sharing for virtual care can be reduced or waived.[11]

Beyond Federal health programs, billing and reimbursement for telehealth services have been lowered as well.[11] Certain private insurance plans may reimburse patients for any telehealth service, with most companies covering at least a few telehealth services; however, it depends on the company to decide its policies.[11] Similarly, Medicaid does cover some forms of telehealth practices, but it differs from state to state, with no two states having the exact same reimbursement policies and guidelines.[11] Policies for reimbursement and

billing of telehealth care services have temporarily expanded due to COVID-19, with federal and state government making an effort to remove both territorial and payment barriers in hope to make remote health care accessible and affordable to all.[11] Overall, the lack of standard protocols in reimbursement guidelines between states poses the common issue of uneven coverage for all patients, and this brings to light several other conditions that may limit the advancement and permanence of telehealth.

The Future of Telehealth

The COVID-19 pandemic has had a great impact on the delivery of health care, in which telehealth reimbursement has been covered by health care providers and payers to help limit exposure to the coronavirus.[10] However, the question of whether telehealth will become a standard form of health care and whether temporary mandates will become permanent is up to debate.[10]

Because of the sudden and unprecedented deregulation of telehealth, it is still unclear how the current and future of health care services will be impacted. The question comes down to whether the benefits of telehealth will exceed the current concerns regarding quality of care and security. Some health care providers and experts question how essential medical examinations such as lab work, scans and imaging, or physical exams will be incorporated into telehealth and how the quality of care and patient understanding of their health will be impacted, or the negative impacts if certain medical practices are adopted deficiently.[9]

Furthermore, it is unclear whether current society is willing to adopt telehealth as a central form of health care after the pandemic ends, as cultural acceptance of virtual visits rather than in-person visits has been an unprecedented matter.[5] The concern of technological accessibility and security also arises.[9] Access to the internet and technology is not universal, and familiarity with telecommunications pose barriers to telehealth.[9]

Additionally, there is no standard protocol nor policy for interstate licensure, as Medicare and Medicaid policies for reimbursement differ greatly across all states.[9]

Conclusion

Telehealth has become a crucial part of the healthcare system since the beginning of the COVID-19 pandemic in the United States. Different methods to provide telehealth care to patients allows patients to communicate with their healthcare providers convieniently. Although telehealth technology provides many benefits, the lack of standardized guidelines in security and coverage plans poses a concern of equitable health care for all patients. The sudden onset of the COVID-19 pandemic has led to an unparalleled uptake of telehealth with temporary conditions in which the outcomes have not yet been observed.[9] While telehealth services include benefits, such as limiting the spread of COVID-19 and preserving PPE, they still remain subject to further review and study.

References

1) What is telehealth? How is telehealth different from telemedicine? [Internet]. HealthIT.gov. 2019 [cited 2021Feb1]. Available from: https://www.healthit.gov/faq/what-telehealth-how-telehealth-different-telemedicine
2) Why is telehealth important for rural providers? [Internet]. HealthIT.gov. 2019 [cited 2021Feb1]. Available from: https://www.healthit.gov/faq/why-telehealth-important-rural-providers
3) Roland J, Potter D. 10 Best Telemedicine Companies [Internet]. Healthline. 2020 [cited 2021Feb1]. Available from: https://www.healthline.com/health/best-telemedicine-companies
4) Hoffman DA. Increasing Access to Care: Telehealth during COVID-19. Journal of Law and the Biosciences. 2020; 7(1): 1-15.
5) Using Telehealth to Expand Access to Essential Health Services during the COVID-19 Pandemic [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention. 2020 [cited 2021Feb1]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html
6) Telehealth set for 'tsunami of growth,' says Frost & Sullivan [Internet]. Healthcare IT News. 2020 [cited 2021Feb1]. Available from: https://www.healthcareitnews.com/news/telehealth-set-tsunami-growth-says-frost-sullivan
7) Center for Connected Health Policy. State telehealth medicaid fee-for-service policy [Internet]. CCHPCA. 2020 [cited 2021Feb1]. Available from: https://www.cchpca.org/sites/default/files/2020-01/Historical%20State%20Telehealth%20Medicaid%20Fee%20For%20Service%20Policy%20Report%20FINAL.pdf
8) History of Telehealth [Internet]. AccessMedicine. 2018. [cited 2021Feb1]. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=2217§ionid=187794434
9) Royce T. Will telehealth services become the norm following COVID-19 pandemic? [Internet]. UNC Lineberger. 2020 [cited 2021Feb1]. Available from: https://unclineberger.org/news/will-telehealth-services-become-the-norm-following-covid-19-pandemic/
10) Strazewski L. Telehealth's post-pandemic future: Where do we go from here? [Internet]. American Medical Association. 2020 [cited 2021Feb1]. Available from: https://www.ama-assn.org/practice-management/digital/telehealth-s-post-pandemic-future-where-do-we-go-here
11) Assistant Secretary for Public Affairs (ASPA). Telehealth: Delivering Care Safely During COVID-19 [Internet]. US Department of Health and Human Services. 2020 [cited 2021Feb1]. Available from: https://www.hhs.gov/coronavirus/telehealth/index.html
12) Fact sheet Medicare Telemedicine Health Care Provider Fact Sheet [Internet]. CMS. 2020 [cited 2021Feb1]. Available from: https://www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet

University of Findlay®

Meaningful Lives. Productive Careers.