Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine September/October 2021



COVID Pandemic Resurgence

Overcoming Vaccine Hesitancy, Skepticism, and Hostility

Missouri Physicians Battling COVID

Common Vaccine Concerns and Misconceptions

Collecting on Business Interruption Coverage for COVID Losses

Kansas City University

CLINICAL UPDATES

1 FIRST LITERATURE REPORT

Vaping Associated with Cardiac Arrest in Teenager

Missouri State Medical Foundation congratulates the following medical students as recipients of the MSMA Scholarship

Kansas City University



Marenda Biggs



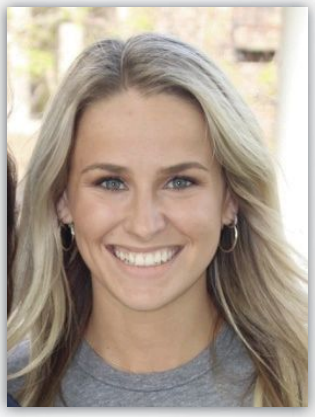
Berina Karisik



Kaitlyn Long



Morgan Mcbride



Jansynn Radford



Jarrett Sappington



Karson Schroeder



William Thomson



Sabrina Wiser

Helping students focus on their medical education for over 50 years, the Missouri State Medical Foundation has benefitted thousands of medical students statewide. We thank the many donors who have committed their energy and resources to fulfilling the Foundation's mission, and we are grateful for their generosity.

For over 20 years, MSMA Scholarships have been funded by the Foundation for students at each of Missouri's medical schools. The Foundation has also facilitated the creation of scholarship funds through a matching grant program.

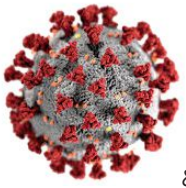
Donations may be sent to: Missouri State Medical Foundation
P.O. Box 1028 | Jefferson City, MO 65102 | www.msma.org/msmf

Not pictured: Dominic Maiuro

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

Volume 118 | Number 5 | September/October 2021 **www.msma.org/missouri-medicine**



COVID-19 REPORT
GUEST EDITOR
Overcoming Vaccine Hesitancy, Skepticism, and Hostility in Missouri
by **Albert L. Hsu, MD** & Robin Trotman, DO 396

PRESIDENT'S FORUM
Missouri Physicians Battling COVID
by **Alexander R. Hover, MD** 401

Download COVID Handout
Common Vaccine Concerns and Misconceptions
by Missouri State Medical Association 404

MEDICAL | LEGAL
Assessing Your Chances of Collecting on Business Interruption Coverage for COVID-19 Losses
by Varsha Gadani, JD & Dominic Castillo, JD 408

PERSPECTIVE
Smokescreen: What the Marijuana Industry Doesn't Want You to Know
by Kevin Sabet, PhD 411

SCIENCE OF MEDICINE | FEATURE SERIES
Clinical Updates Presented by Kansas City University

Pandemic Brings Loss, Hardship, and Challenges; KCU Remains Committed and Dedicated
by W. Joshua Cox, DO & **Laura Rosch, DO** 420

Innovations Through Virtual Reality Simulation
by Robert Tyler, DO, Galina Danilova, MBA, Schoen Kruse, PhD & Angela Pierce, PhD 422

It Is Time for an Oil Change: Polyunsaturated Fatty Acids and Human Health
by Natalie Powell, Suman Chaudhary, MS & Asma Zaidi, PhD 426

Exploring the Influence of a Pandemic on Medical Education
by Mariam Akhtar, MD 431

Osteopathic Manipulative Treatment as an Intervention to Reduce Stress, Anxiety, and Depression in First Responders: A Pilot Study
by Christena Abraham, BS, Shelly N.B. Sloan, MS, Charles Coker, BS, Blair Freed, BS, Matthew McAuliffe, BS, Halden Nielsen, BA, **Tanner Riscoe, BS**, Robert Steele, MS, Andrew Dettwiler, BS, Gia Oberley, BS, Kenneth Zaremski, DO, Kelley Joy, DO, Andi Selby, DO, Ree Wells-Lewis, PhD & Bradley A. Creamer, PhD 435

Management of Obesity Using Telemedicine During the COVID-19 Pandemic
by Angela A. Wang-Selfridge, DO & Jennifer F. Dennis, PhD, MS 442

Integrating Oral Health into Primary Care
by Erinne N. Kennedy, MPH & Linda C. Niessen, MPH 446

SCIENCE OF MEDICINE | FIRST LITERATURE REPORT
1FIRST LITERATURE REPORT
Vaping Associated Cardiac Arrest at School in a Teenager with Anomalous Left Coronary Artery
by **Todd A. Glenski, MD** & Courtney E. Dorris, BS, Gina M. Patel, MD, **Christian M. Taylor, MD** & Nichole M. Doyle, MD 450

SCIENCE OF MEDICINE
The Importance of Maintaining a Low Omega-6 Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies
by James J. DiNicolantonio, PharmD & **James O'Keefe, MD** 453

A Primer on Chimera Associated Receptor T-cells
by Sumalatha Muthineni, MD, Katelyn Zink, PharmD & Suman Kambhampati, MD 460

Retinal Degeneration: Short-Term Options and Long-Term Vision for Future Therapy
by Shabnam Majidi, Judith M. Ogilvie, PhD & Colin A. Flaveny, PhD 466

FROM YOUR ASSOCIATION
One Picture = 1,000 Words 400
Correspondence 416
New Members 417
Missouri Medicine in the News 418
Statement of Ownership 419

momedical @momedicalassn mostatemedicalassociation momedical momedical

MSMA member names in bold

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

www.msma.org/missouri-medicine











About Missouri Medicine

In publication since 1904, the peer-reviewed, award-winning, bi-monthly *Missouri Medicine: The Journal of the Missouri State Medical Association* is indexed by Index Medicus, MEDLINE, Scopus, and PubMed. Complete issues archived at PubMed Central since 2010. Content appears on EBSCO Host Research databases.

With a large and respected editorial board and regular participation by Missouri's six medical schools on eight campuses, *Missouri Medicine* is among the nation's foremost state medical journals.

Articles are frequently cited in impact factor journals and regularly featured in the national media including: *Wall Street Journal*, CSPAN-2, KevinMD, *Outside Magazine*, *Runner's World*, *NBC News*, *General Surgery News, Ophthalmology Times*, and many others. Issues of *Missouri Medicine* are printed on acid-free paper with open access to digital issues available at www.msma.org/missouri-medicine-library.

Copyright & Postal Entry

Missouri Medicine, the Journal of the Missouri State Medical Association, is owned and copyrighted by the Missouri State Medical Association. Published at 113 Madison Street, Jefferson City, Missouri 65101. Printed by Walsworth Publishing, Fulton, Missouri. Periodicals postage paid at Jefferson City, Missouri, and at additional mailing offices. Postmaster: Send address changes to Missouri State Medical Association, c/o Membership Dept., P.O. Box 1028, Jefferson City, MO 65102. Annual subscription is included in membership dues; non-members pay $75.00.

Disclaimer

All articles, editorials, letters, and advertisements published represent the opinions of the authors and advertisers, and do not necessarily reflect the official policy or endorsement of the Missouri State Medical Association or the institution with which the author or product or service is affiliated unless clearly specified. *Missouri Medicine* reserves the right to make the final decision on all content and advertisements.

Missouri Medicine Editor

John C. Hagan, III, MD, FACS, FAAO

Managing Editor

Lizabeth R. S. Fleenor, BJ, MA

Contributing Editors & Publication Committee

Justin M. Albani, MD
Jessica D. Bauerle, MD
Jeffrey G. Copeland, MD
Betty M. Drees, MD
David A. Fleming, MD
Arthur H. Gale, MD
William R. Reynolds, DDS, MD
Charles W. Van Way, III, MD

Editorial Board

Allergy & Immunology: Jacqueline L. Reiss, MD
Anesthesiology: Kathy M. Perryman, MD
Cardiac Surgery: Michael C. Murphy, MD
Cardiology: Jerry D. Kennett, MD
Colon & Rectal Surgery: Jose M. Dominguez, MD
Dermatology: Jon A. Dyer, MD
Emergency Medicine: Randall S. Jotte, MD
Endocrinology: Howard M. Rosen, MD
Family Medicine: Beth E. Rosemergey, DO
Gastroenterology: David H. Cort, MD
General Surgery: Joseph A. Corrado, MD
Hematology & Oncology: Leonid Shunyakov, MD
Hospital Medicine: Lancer G. Gates, DO
Infectious Disease: Hariharan Regunath, MD
Internal Medicine: Fariha Shafi, MD
Internal Medicine/Pediatrics: Stephen T. Keithahn, MD
Medical Genetics: Patricia I. Dickson, MD
Medical Student Section: Imaima Casubhoy, UMKC
Military Medicine: Michael S. Clarke, MD
Neonatology: Joshua E. Petrikin, MD
Nephrology: Gary G. Singer, MD
Neurology: Pradeep K. Sahota, MD
Neurosurgery: Keith M. Rich, MD
Obstetrics & Gynecology: Octavio R. Chirino, MD
Ophthalmology: John B. Holds, MD
Orthopaedics: Gregory R. Galakatos, MD
Otolaryngology: John F. Eisenbeis, MD
Pain Medicine: Anne T. Christopher, MD
Pathology: Louis P. Dehner, MD
Pediatrics: April L. Tyus-Myles, MD
Physical Medicine & Rehabilitation: David J. Haustein, MD
Physician Wellness: Jessica A. Gold, MD
Plastic Surgery: Edmond B. Cabbabe, MD
Preventive Medicine: James H. O'Keefe, MD
Psychiatry: Laine M. Young-Walker, MD
Public Health: Katherine R. Lichtenberg, DO
Pulmonary Medicine: Gary A. Salzman, MD
Radiology: Andrew J. Bierhals, MD
Resident & Fellow Section: Anup Bhattacharya, MD
Retired Physicians: Juan C. Corvalan, MD
Rheumatology: Anne E. Winkler, MD
Sports Medicine: Brian L. Mahaffey, MD
Statistics & Methodology: Christopher R. Carpenter, MD
Toxicology & Addiction Medicine: Evan S. Schwarz, MD
Urology: Elizabeth A. Piontek, MD
Vascular Surgery: Jonathan M. T. Bath, MD
Women Physicians Section: Joanne Loethen, MD
Young Physician Section: Marc Mendelsohn, MD

Editor Emeritus

Donald G. Sessions, MD, 1988-1992
J. Regan Thomas, MD, 1992-2000

Contact

Editor: John C. Hagan, III, MD / drjhagan3@gmail.com / 816-478-1230
Managing Editor: Lizabeth R.S. Fleenor / lfleenor@msma.org / 573-636-5151
Instructions for Authors: www.msma.org/missouri-medicine
***Missouri Medicine* Library: www.msma.org/missouri-medicine-library**
ISSN 0026-6620 / Established 1904 / ©2021 Missouri State Medical Association

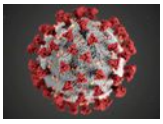


Children's
HOSPITAL & MEDICAL CENTER
OMAHA

When one number connects you to the region's best neonatal and pediatric transport team, **Anything can be.**

1.855.850.KIDS (5437) is your 24-hour link to pediatric specialists for physician-to-physician consults, referrals, admissions and transport.

Education • Research • Advocacy • Care



Overcoming Vaccine Hesitancy, Skepticism, and Hostility in Missouri

by Albert L. Hsu, MD & Robin Trotman, DO

Vaccination and non-pharmacologic mitigation measures (hand-washing, crowd-avoidance, social distancing, mask-wearing) are the fastest way to put this pandemic behind us.

Similar to the 1918 H1N1 "Spanish flu" pandemic, COVID-19 has manifested as twin public health and economic crises. In the U.S., the first wave of COVID-19 migrated from the Northeast and Pacific Northwest to the Sun Belt, and then the Midwest in 2020. During that first wave, we physicians counselled patients and the public that the elderly and immunocompromised were most vulnerable, and physicians promoted non-pharmaceutical interventions like social distancing and masking. Thus, physicians are also learning to live with uncertainty amid constantly-evolving COVID-19 guidance.

From January-April 2021, Missouri had some of the lowest COVID-19 case rates in the nation. Largely due to the rapid emergence of the Delta (B.1.617.2) variant, however, Missouri was among the top five states with the highest rates of new COVID-19 cases in July. Many Missouri counties still have COVID-19 vaccination rates under 30%,[1,2] partly due to widespread vaccine skepticism and misinformation on social media.



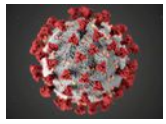
Albert L. Hsu, MD, (left), is an Ob/Gyn and a reproductive endocrinology and infertility subspecialist at the University of Missouri-Columbia and President of the Boone County Medical Society. Robin Trotman, DO, FIDSA, is an infectious disease specialist at CoxHealth in Springfield, Missouri.

Delta Variant

With several new mutations,[3,4] the Delta variant of SARS-CoV-2 appeared first in India, and continues to evolve and spread throughout the U.S. Delta replicates faster, transmits more easily and to more people, and causes higher viral loads. It also results in more "breakthrough" infections among vaccinated populations, and it causes more severe illness in the unvaccinated. Delta is estimated to be 40-60% more transmissible[5] than the initial D614G strain or Alpha variant ("UK," or B.1.1.7 variant), with a basic reproduction number (R_o) of 5-8. For viruses with a R_o of 2.5 spreading in fully-susceptible populations, 10 cycles of transmission results in 9,536 infections. In contrast, viruses with a R_o of 6 result in 60,466,176 infections after 10 cycles of transmission.

By May 2021, India had up to 400,000 cases and up to 4,000 daily deaths. Data from Scotland[6] suggest that those with Delta were twice as likely to be hospitalized as those with Alpha. Even in highly-vaccinated populations such as Iceland, where 96% of women and 90% of men received at least one vaccine dose, there has been a rise in COVID-19 cases, but no concomitant rise in deaths. It is encouraging that, despite breakthrough infections, the vaccine appears highly protective against death from COVID-19.

The consensus of many surveillance studies is that approximately 80-90% of cases, over 95% of hospitalizations, and over 98% of deaths from COVID-19 occur among those unvaccinated against COVID-19. Those reluctant or unwilling to get vaccinated are most vulnerable, leading some to call this Delta storm a "Pandemic of the Willfully Unvaccinated." Vaccine hesitancy, skepticism and hostility, coupled with lack of vaccine availability





The COVID-19 pandemic has now killed more Americans than the 1918 flu pandemic did. As of September 20, 2021, more than 675,000 people in the United States have died from COVID-19, according to Johns Hopkins University. Above, the Oakland Municipal Auditorium in California was converted to a temporary hospital with volunteer nurses from the American Red Cross in 1918 to help with the patient load. Source: University of California.

in many nations, increases the likelihood of further mutations, potentially leading to more dangerous "variants of concern" like Delta.

In Missouri, many recently-hospitalized COVID-19 patients are under 65 years old, with a median age of 52 in the dedicated COVID ICU at one southwest Missouri hospital.[7] In the first wave of COVID-19 in 2020, the elderly and those with comorbidities (diabetes, obesity, chronic lung disease) were most vulnerable to SARS-CoV-2. In contrast, Delta has been unpredictable, landing younger and otherwise-healthy patients in intensive care, with deaths in adults as young as 30. Unfortunately, infectious disease experts can no longer predict who becomes severely ill from COVID-19.

On a macro-level, this is not surprising. We know natural selection exerts pressure on viruses and selects for advantageous mutations to target vulnerable populations: the elderly in 2020, unvaccinated groups (severely immunocompromised, hesitant and skeptical individuals, younger populations) today. The second wave of the 1918 pandemic (winter 2018) was the deadliest wave, hitting younger and healthier patient populations than the first wave (spring 2018).

Confronting Vaccine Hesitancy, Skepticism, and Hostility

With our ICUs filling up, it is hard not to feel upset with those who remain willfully unvaccinated; however, vaccine-shaming, scolding, condescension, and finger-wagging are neither helpful nor productive.[8,9] Well-organized anti-vaccine groups are remarkably successful at swaying public opinion against mask mandates, vaccines, and other mitigation measures to protect us. Some politicians are also suing to block mask mandates in our schools and communities, despite evidence-based public health recommendations.[8]

As physicians, it is important to recognize that some may never accept vaccines; on an individual patient level, it is crucial to actively listen empathetically, to allay vaccine fears, and to express understanding of individual patient concerns.[8-10] Not long ago, we proclaimed that children and young adults had no severe consequences from COVID-19. Our main concern was that they might miss school, or infect vulnerable family members; we did not think they would become terribly ill or end up hospitalized. Emerging data on increased childhood hospitalizations, MIS-C, "long COVID," and myocarditis in athletes

has changed our thinking. At this time, neither of the authors would be comfortable sending our children to indoor camps with unvaccinated youth.

In one author's (ALH) reproductive endocrinology and infertility practice, half his patients (and their partners) remain unvaccinated. Some patients now seek medical exemption waivers for pregnancy or preconception, because of employer mandates for COVID-19 vaccinations. For pregnant patients, he reviews national guidance[12,13] from the American College of Obstetricians and Gynecologists (ACOG), recommending all pregnant and lactating individuals to be vaccinated against COVID-19: "ACOG encourages members to enthusiastically recommend vaccination … emphasizing known [vaccine] safety and increased risk of severe complications associated with COVID-19 infection, including death, during pregnancy." For infertility patients, he quotes national guidelines[10,14] from the American Society for Reproductive Medicine (ASRM) stating "COVID-19 vaccination does not impact male or female fertility or fertility treatment outcomes," so we are to "encourage vaccination for all patients during evaluation and treatment for infertility." ALH will not provide medical exemption waivers for COVID-19 vaccinations to his pregnant or preconception patients.

> **"While not typically part of medical education, we must learn to communicate uncertainty and nuance to patients and the public. We will learn from this pandemic and evolve as doctors, as communicators, as patient advocates, and as humans.**

There is also rampant misinformation[13] about COVID-19 vaccines and infertility. For couples in which the female partner is under 35, infertility is defined as the inability to conceive after one year of regular, unprotected heterosexual intercourse – so COVID-19 vaccines simply haven't been around long enough to determine any (positive or negative) effects of vaccines on fertility. However, SARS-CoV-2 may negatively impact male fertility. After SARS-CoV-2, there is evidence for virions in both semen samples and testicular biopsies,[15-17] as well as reports of men with testicular pain, orchitis, epididymitis, and/or testicular damage.[15] Studies also suggest that hypogonadism, oxidative stress, and disruption of the hypothalamic-pituitary-testicular axis may occur after SARS-CoV-2 infection in men.[15-17] COVID-19 vaccines may actually protect male fertility, by decreasing risks of hypogonadism and testicular damage.[13]

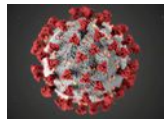
Limitations to Science, as a Persuasive Argument

At the time this was writing, (August 30, 2021), FDA had just formerly approved the Pfizer COVID-19 vaccine (beyond emergency use), with recommendations for a booster (third dose). While these developments reassure many, ASRM[10] and others[8,9] note "for some patients, conveying evidence-based scientific information will not be enough to provide reassurance of the importance of vaccination. Appealing to patients with empathy and personal reassurance can go a long way towards allaying fears and encouraging them to be vaccinated."

Best practices for discussing vaccine hesitancy[18] are to genuinely seek out specific patient concerns through open-ended questions.[9] It is also critical to approach discussions with grace and humility; it has been challenging for us all to keep up with rapidly-evolving information[8] throughout this pandemic. Whatever your personal opinion on vaccines, civility is critical for an open and constructive dialogue, free from "vaccine shaming," bullying, and virtue-signaling.

While a hardcore 10-15% of the population is unlikely to ever receive COVID-19 vaccines, many remain "on-the-fence" with unanswered questions.[17] Given the rise in COVID-19 cases, our Missouri State Medical Association (MSMA) has recommended[19] "consulting your physician for questions about the vaccine," and encouraged "simple acts to help stop the virus: practice social distancing when possible, voluntarily wear a mask in public places, and get tested if you feel sick." This recommendation is partly due to emerging data[20,21] on breakthrough infections in fully-vaccinated individuals.

While COVID-19 vaccines are 95% effective against symptomatic disease from the original wild-type SARS-CoV-2 (and Alpha variant), mRNA



vaccines are less effective[22] in preventing symptomatic infection from Delta. These data are often used by anti-vaccine forces as proof that "those vaccines don't work," however, a low death rate despite a high incidence of infection shows vaccines indeed work. The vaccine will not prevent car accidents in recently-vaccinated persons, and there will indeed be other unintended deaths in vaccinated patients, unrelated to the vaccine. Vaccines do not prevent having someone cough in your face; the best mitigation measures for "someone coughing in your face" are masking and social distancing, which also protected people during the 1918 pandemic. Not much has changed!

Conclusion

We have seen a parade of COVID-19 treatments go by, from hydroxychloroquine to ivermectin, from convalescent plasma to monoclonal antibodies. While some monoclonal antibodies are spectacular, and while steroids help the severely ill, we will not emerge from this pandemic with medical treatments: vaccination and non-pharmacologic mitigation measures (hand-washing, crowd-avoidance, social distancing, mask-wearing) are the fastest way to put this pandemic behind us.

Another important issue is our crumbling public health infrastructure. Without good surveillance, a tiny spark of highly-contagious disease easily becomes an inferno. We have an excellent multi-layered global surveillance system for influenza, which we should replicate for SARS-CoV-2 and its variants. Our wonderful public health partners must also be empowered, not threatened.

The COVID-19 pandemic has created unparalleled medical, social, political, and economic challenges. Constantly-evolving guidelines have resulted in a public that is understandably uncertain, fearful, and suffering from "COVID fatigue." There are many sources[8, 13, 18] of vaccine hesitancy; having a script of responses can be a useful tool to address common questions. In this edition of *Missouri Medicine*, MSMA provides a guide to address common concerns and misconceptions about COVID vaccines. See page 404.

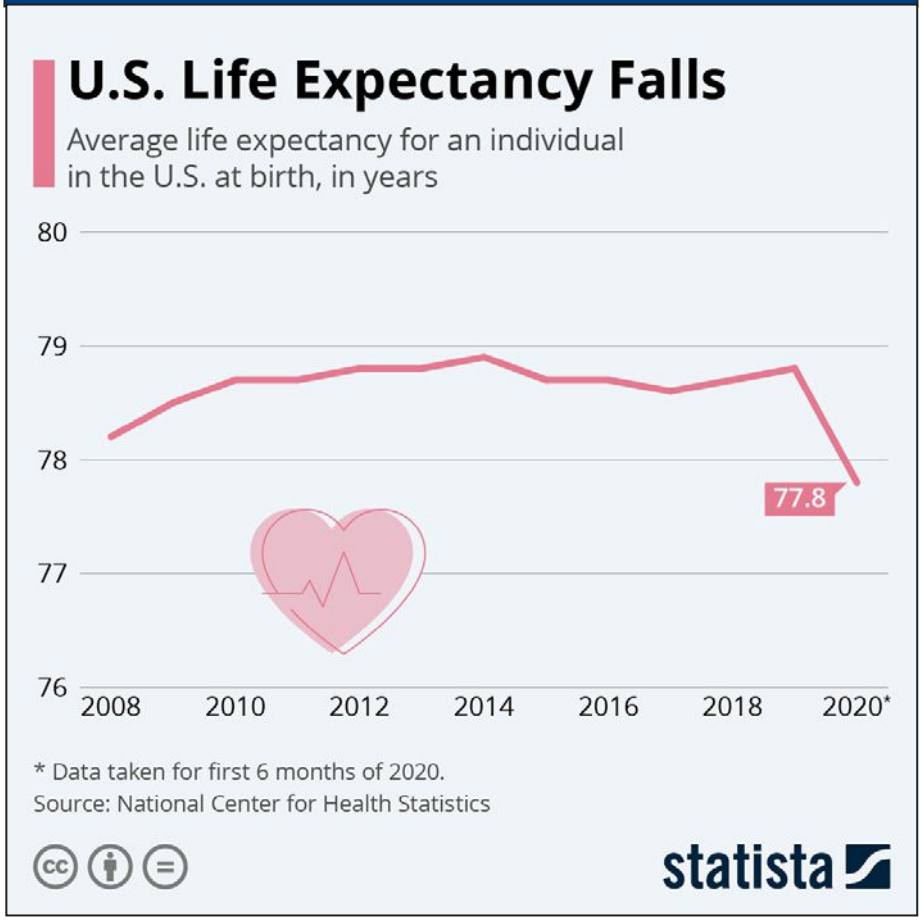
Amid evolving public health guidelines, COVID-19 has helped health care providers develop a finer appreciation of the anxiety, uncertainty, feelings of helplessness, and fears of the unknown, that regularly complicate decision-making for our patients. For those who see things as "black-and-white," and were perhaps overly dependent on algorithms, it has likely been a particularly difficult time. All of us could likely be a little less dogmatic, as we start appreciating the nuances[8] and gray areas in medicine. In learning to live with uncertainty, we should learn that with every plan, we must be flexible, able to absorb new information, and ready to change direction with little notice. While not typically part of medical education, we must learn to communicate uncertainty and nuance to patients and the public. We will learn from this pandemic and evolve as physicians, as communicators, as patient advocates, and as humans.

References

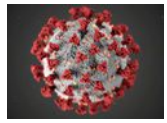
1. "COVID-19 in Missouri" by Missouri State Department of Health and Senior Services (DHSS), at <https://health.mo.gov/living/healthcondiseases/communicable/novel-coronavirus/data/public-health/statewide.php>, accessed 22 August 2021.
a. As of 8/22/21, at least 58 counties (Andrew, Audrain, Barton, Bates, Bollinger, Buchanan, Butler, Carter, Cedar, Chariton, Clark, Crawford, Dallas, Daviess, DeKalb, Dent, Douglas, Dunklin, Grundy, Harrison, Howell, Iron, Jasper, Johnson, Laclede, Lawrence, Lewis, Lincoln, Madison, Maries, McDonald, Mercer, Miller, Moniteau, Morgan, New Madrid, Newton, Oregon, Ozark, Pemiscot, Pike, Pulaski, Putnam, Ralls, Randolph, Ray, Reynolds, Ripley, Schuyler, Scotland, Shannon, St. Clair, Stoddard, Texas, Vernon, Washington, Wayne, and Wright counties) in Missouri had <30% of their populations completing the COVID-19 vaccination series.
2. "COVID-19 Vaccinations in Missouri" by Missouri State Department of Health and Senior Services (DHSS), at <https://covidvaccine.mo.gov/data/>, accessed 25 July 2021.
3. "SARS-CoV-2 Variant Classifications and Definitions" by the US Centers for Disease Control and Prevention, at <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>, updated 20 July 2021, accessed 25 July 2021.
4. "Variants of the Virus" by the US Centers for Disease Control and Prevention, at <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant.html>, updated 28 June 2021, accessed 25 July 2021.
5. "SPI-M-O: Consensus Statement on COVID-19" by United Kingdom, at <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993321/S1267_SPI-M-O_Consensus_Statement.pdf>, dated 2 June 2021.
6. "Delta variant impact on hospitalization revealed" by the University of Edinburgh, at <https://www.ed.ac.uk/news/2021/delta-variant-increases-risk-of-hospitalisation>, published 18 Jun 2021
7. Personal Communication, Dr. Robin Trotman (Cox Hospital in Springfield Missouri) to Missouri Telehealth Network at <https://showmeecho.org/>, Mon 19 July 2021
8. Escandón K, Rasmussen AL, Bogoch II, Murray EJ, Escandón K, Popescu SV, Kindrachuk J. COVID-19 false dichotomies and a comprehensive review of the evidence regarding public health, COVID-19 symptomatology, SARS-CoV-2 transmission, mask wearing, and reinfection. BMC Infect Dis. 2021 Jul 27;21(1):710. doi: 10.1186/s12879-021-06357-4. PMID: 34315427; PMCID: PMC8314268.
9. "Talking about Vaccines" by the US Centers for Disease Control and Prevention, at <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/talk-about-vaccines.html>, updated 27 April 2021, accessed 25 July 2021.

10. "Patient Management and Clinical Recommendations During the Coronavirus (COVID-19) Pandemic. ASRM COVID-19 Task Force Update #16, 23 July 2021 by the American Society for Reproductive Medicine (ASRM) at <https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate16.pdf>, accessed 30 July 2021
11. "ACOG and SMFM Recommend COVID-19 Vaccination for Pregnant Individuals" press release, 30 July 2021 at <https://www.acog.org/en/news/news-releases/2021/07/acog-smfm-recommend-covid-19-vaccination-for-pregnant-individuals>, accessed 30 July 2021.
12. "Making a Strong Recommendation for COVID-19 Vaccination, by the American College of Obstetricians and Gynecologists (ACOG)," at <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care?utm_source=redirect&utm_medium=web&utm_campaign=int>, updated 30 July 2021, accessed 30 July 2021
13. Watson RE, Nelson TB, Hsu AL. Fertility considerations: The COVID-19 disease may have a more negative impact than the COVID-19 vaccine, especially among men. Fertil Steril. Published online 19 Mar 2021: https://www.fertstertdialog.com/posts/fertility-considerations-the-covid-19-disease-may-have-a-more-negative-impact-than-the-covid-19-vaccine-especially-among-men?room_id=871-covid-19
14. "ASRM, ACOG, and SMFM Issue Joint Statement: Medical Experts Continue to Assert that COVID Vaccines Do Not Impact Fertility." American Society for Reproductive Medicine (ASRM) Press Release, 5 February 2021 at <ASRM, ACOG and SMFM Issue Joint Statement: Medical Experts Continue to Assert that COVID Vaccines Do Not Impact Fertility | ASRM>, accessed 30 July 2021
15. Madjunkov M, Dviri M, Librach C. A comprehensive review of the impact of COVID-19 on human reproductive biology, assisted reproduction care and pregnancy: a Canadian perspective. J Ovarian Res. 2020 Nov 27;13(1):140. doi: 10.1186/s13048-020-00737-1. PMID: 33246480; PMCID: PMC7694590.
16. Gonzalez DC, Khodamoradi K, Pai R, Guarch K, Connelly ZM, Ibrahim E, Arora H, Ramasamy R. A Systematic Review on the Investigation of SARS-CoV-2 in Semen. Res Rep Urol. 2020 Dec 1;12:615-621. doi: 10.2147/RRU.S277679. PMID: 33294423; PMCID: PMC7718981.
17. Achua JK, Chu KY, Ibrahim E, Khodamoradi K, Delma KS, Iakymenko OA, Kryvenko ON, Arora H, Ramasamy R. Histopathology and Ultrastructural Findings of Fatal COVID-19 Infections on Testis. World J Mens Health. 2021 Jan;39(1):65-74. doi: 10.5534/wjmh.200170. Epub 2020 Nov 3. PMID: 33151050; PMCID: PMC7752514.
18. Hsu AL, Johnson T, Phillips L, Nelson TB. Sources of Vaccine Hesitancy: Pregnancy, Infertility, Minority Concerns, and General Skepticism. Open Forum Infectious Diseases, https://doi.org/10.1093/ofid/ofab433, 18 August 2021
19. Facebook post by Missouri State Medical Association (MSMA), at <https://www.facebook.com/momedical/photos/pb.499899750048129.-2207520000../4263450280359705/?type=3&theater>, posted 16 July 2021
20. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M, Maor Y, Cohen R, Hussein K, Weinberger M, Zimhony O, Chazan B, Najjar R, Zayyad H, Rahav G, Wiener-Well Y. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021 Jul 7:S1198-743X(21)00367-0. doi: 10.1016/j.cmi.2021.06.036. Epub ahead of print. PMID: 34245907; PMCID: PMC8261136.
21. "COVID-19 Breakthrough Case Investigations and Reporting" by the US Centers for Disease Control and Prevention, at <https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html>, updated 15 July 2021, accessed 25 July 2021.
22. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J, Tessier E, Groves N, Dabrera G, Myers R, Campbell CNJ, Amirthalingam G, Edmunds M, Zambon M, Brown KE, Hopkins S, Chand M, Ramsay M. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021 Jul 21. doi: 10.1056/NEJMoa2108891. Epub ahead of print. PMID: 34289274.

ONE PICTURE = 1,000 WORDS



MM



Missouri Physicians Battling COVID

by Alexander R. Hover, MD

> *"Hi, I'm Dr. Kari Cooper and I am an emergency physician at CoxHealth. I have been treating COVID patients since the beginning of the pandemic and have seen some of the sickest patients of my career in the last 18 months. It has been so incredibly heartbreaking and humbling to see our patients and their families struggling with severe illness, long-term physical and emotional effects, and loss of their loved ones. It is all the more tragic to know that nearly every one of these losses are preventable with an extremely safe vaccination.*
>
> *My colleagues and I have heard the last words of far, far too many people before we place them on a ventilator with the knowledge that a huge number of them will never come off the machine. Far more often than not, those words include regret of not getting the vaccine. Don't be the next person to have this regret. Get vaccinated!*
>
> *If you have concerns, PLEASE talk to your healthcare professionals about them. We can address the myths and will give you honest and verifiable information so you can make a truly informed decision in the best interest of yourself and your family."*

What a powerful and personal message from a frontline physician in hopes of saving lives! This was intended for a public service announcement in our Springfield community. This is just one example of how Missouri physicians, individually and as organized medicine, are responding to the physician's oath: "To dedicate my life to the service of humanity."

Leadership is a responsibility for all of us — either as formal or informal leaders. Often, the work of informal leaders is as critical to their community as that of formal leaders. That is certainly true for the activities of so many physicians around the state battling COVID pandemic.



Alexander R. Hover, Jr., MD, FACP, AGAF, is President of the Missouri State Medical Association for 2021-2022. He is a Gastroenterologist from Ozark, Missouri.

MSMA, as an organization as well as with its individual members, is an important leader in the fight against COVID. Some of MSMA's initiatives in this fight include collaboration with the Missouri Hospital Association, DHSS, and state governments leaders. Your Association has set policy statements, created educational materials dealing with vaccine misinformation, participated in the Governor's Committee on Equitable Vaccine Distribution, requested a mask mandate in 2020, and facilitated distribution of vaccine to independent physician clinics.

One important initiative was advocating for COVID liability — passed in 2021. Also SB 51 and 42 helps keep independent physician offices open to see patients during the COVID pandemic. MSMA supported the mental health parity requirement for insurers as passed in HB 432 which will help mitigate the increasing mental illness related to COVID. Our MSMA lobbyists were able to mitigate the stringent language in HB 271, which would have severely limited the ability of local public health departments to respond to pandemic emergencies, making the final language in HB 271 much less restrictive.

MSMA's work on your behalf requires intense and sophisticated activity at the state legislature and state agencies. Yes, these initiatives do benefit physicians, but

at their core, they are really benefiting Missouri citizens in need of healthcare during the pandemic. Ongoing MSMA work includes our Public Affairs committee meeting to guide sharing of best practices. There is no "finally" to this work.

All around the state, I hear and observe intensive and sustained effort on the public behalf by medical specialties, component medical societies, and individual physicians. I wish I had time to cover this in depth, as I am proud of what Missouri physicians are doing on behalf of their state. My observations remind me that the keys to successful change in public health are rooted in sustained physician commitment, faith in the scientific method, social relationships, and a clear, simple message.

For example, even physicians may be uncertain of the science and therefore reticent about advising patients on the safety of vaccines. Some people distrust government or public health, but most Americans do trust physician and nurse recommendations. The recent University of Chicago Harris/AP-NORC survey reported at least 70% of Americans "trust their doctor or their nurse to do what is right for them."

Helping individual physicians advise their patients is surely a key. Albert Hsu, MD, MSMA member, noted that Boone County Medical Society has been supporting almost weekly educational webinars updating the science for physicians and their messaging for the community. Getting a clear and simple message from a trusted health professional is a solid start.

Based on multiple discussions with local society leaders and experienced informal leaders it seems pretty clear that the strongest predictor of influencing decisions for local governments and public health departments is based on:

1) a record of having worked on prior public health issues such as smoking abatement;

2) having component medical society and MSMA members as part of the public health structure or political governance; and

3) having longstanding personal relationships based on collaboration and trust prior to any crisis.

David Nowak, EVP for the St. Louis Metropolitan Medical Society, provided me with information on its public health policy statements, education, and updates on pandemic initiatives and physician engagement. Direct input into public health decision-making requires time and energy to have physicians directly involved in local governance. Just a few examples include Luis Giuffra, MD, as a member of the St. Louis City Joint Boards of Health and Hospitals; Ravi Johar, MD, and Jay Meyer, MD, as members of the St. Louis County Health Advisory Board; and Sam Page, MD, serving as St. Louis County Executive. The work of these physicians — all MSMA members — and others as part of the St. Louis City and County Health, takes time and effort but ensures that physician guidance is needed in a public health crisis.

The Kansas City Kansas City metro area Chief Medical Officers' Council discussed with their KC Chamber of Commerce on how to support mandatory masking. This is also an excellent source in educating local government administrators on the current overwhelming hospitals resource needs, staff losses due to COVID infection and burnout, delays for time critical diagnosis such as AMI, stroke, and trauma, and the likely burden of long-term post COVID health effects.

Greene County Medical Society has been engaged particularly through our three-decade-old Community Health Advisory Committee, which includes GCMS physicians, local health system representatives, federal disaster planning, and public health and local governments representatives. The longstanding trusted relationship has been the backbone for influencing and collaborating with local government leaders.

Providing mass vaccination clinic support, facilitating a grant to acquire a mobile vaccination unit to vaccinate the difficult-to-reach residents, holding press conferences and policy statements supporting vaccination, and urging masking and social distancing has been some of the continuous activity of the GCMS Executive Committee members. These activities seem to a help ameliorating the COVID Delta variant surge as seen in the in late July and August for Greene County and the region.

The major sacrifice for physicians and other health care professionals has been suffering COVID infection, long-term illness, and even death. Moreover, just the ongoing battle to control the pandemic has been exhausting. I have no way of calculating the number of person hours spent on this altruistic work, hours that could have been spent with family or personal pursuits. Consider also the personal stress on physicians and other health leaders who, not infrequently, are attacked in social media.

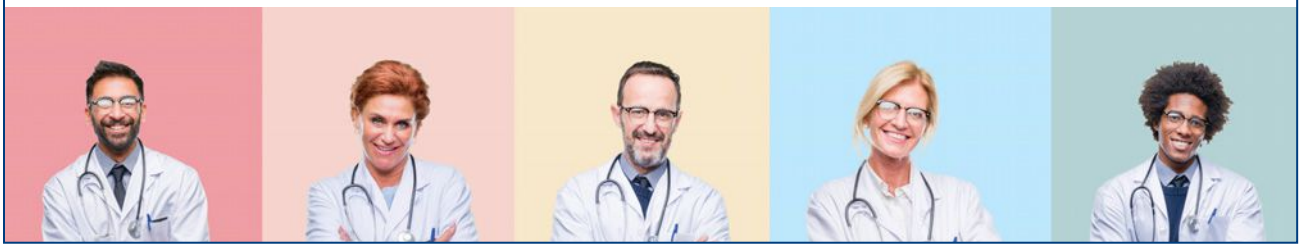
The contribution that we can all make is our prayers for the frontline workers and their families. We can also express our gratitude, support, and respect for our colleagues engaged in public health for our communities. Finally, the duty for all of us is to be knowledgeable regarding vaccination and COVID mitigation. Then we can "do what is right" because that is what our patients expect and trust in us. **MM**

MISSOURI PHYSICIANS HEALTH PROGRAM
The Physician Lifeline: Preserving Physicians' Lives

We make recovery possible for physicians, residents, and medical students.
Our program depends on your generosity. Please consider a donation—

themphp.org / donate

Mail checks to, **The MPHP 1023 Executive Parkway, Suite 16 St. Louis, MO 63141**





Today – Do more of what you love

At Mercy Clinic, we span across four states with a team of more than 2,100 Mercy primary care and specialty care physicians, 600 advanced practitioners. Mercy was named one of the top five largest U.S. Health Systems in 2017 by Truven, an IBM Watson Health Company and we serve millions annually. Mercy includes 44 acute care and specialty (heart, children's, orthopedic and rehab) hospitals, more than 700 physician practices and outpatient facilities, more than 40,000 co-workers and more than 2,000 Mercy Clinic physician in Arkansas, Kansas, Missouri and Oklahoma. Mercy also has outreach ministries in Arkansas, Louisiana, Mississippi, and Texas.

To find out about Physician and Advanced Practitioners openings across the Mercy System please contact:

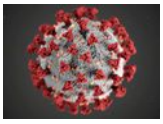
Sara McCleary, Director of Physician Recruitment
Sara.McCleary@mercy.net | 417-556-8963

Or go to **http://www.mercy.net/careers** to search for your specialty opportunities.

Mercy

List of Specialties:

- Anesthesiology
- Cardiology - Electrophysiology
- Cardiology - Interventional
- Cardiology - Non-Invasive
- Critical Care - Intensivist
- Dermatology
- Emergency Medicine
- Endocrinology
- Family Medicine
- Family Medicine - OB
- Gastroenterology
- General Surgery
- General Surgery - Breast Surgery
- Geriatric Medicine
- Gynecology - Urogynecology
- Hematology and Oncology
- Hospitalist
- Infectious Disease
- Internal Medicine
- Maternal-Fetal Medicine
- Med-Peds
- Neonatology
- Nephrology
- Neurological Surgery
- Neurology
- Neurology - Neuroimaging
- Obstetrics and Gynecology
- Obstetrics and Gynecology - OB Hospitalist
- Occupational Medicine
- Oncology - Gynecological
- Oncology - Surgical
- Ophthalmology
- Oral and Maxillofacial Surgery
- Orthopaedic Surgery
- Orthopaedic Surgery - Adult Reconstructive Surgery
- Orthopaedic Surgery - Hand Surgery
- Orthopaedic Surgery - Trauma
- Otolaryngology
- Pain Medicine
- Palliative Care
- Pediatrics
- Pediatrics - Emergency Medicine
- Pediatrics - Hospitalist
- Pediatrics - Ophthalmology
- Pediatrics - Surgery
- Pediatrics - Urgent Care
- Physical Medicine and Rehab
- Plastic Surgery
- Psychiatry
- Psychiatry - Child
- Pulmonary Disease
- Pulmonary Disease - Critical Care
- Radiation Oncology
- Radiology
- Rheumatology
- Sleep Medicine
- Telemedicine
- Trauma Surgery
- Urgent Care
- Urology
- Vascular Surgery



Scan to Download!

Common Vaccine Concerns and Misconceptions



As COVID continues to affect Missourians, your patients, friends, and coworkers may come to you with questions about the vaccine. This guide addresses some of the most common concerns or misconceptions you may encounter.

Reassure patients that it's okay to have questions or concerns. The stress of the pandemic is immense and misinformation about the vaccine is rampant, so feeling fearful or angry is natural. Having an open and honest conversation with a trusted physician or pharmacist may help alleviate your patients' anxiety about receiving the COVID vaccine.

CONCERN

The vaccine will give me COVID.

FACT

The vaccine trains your immune system to recognize and defend your body from COVID, but it will not actually cause a COVID infection. The vaccine does not contain live COVID virus.

MISCONCEPTION

I don't need the vaccine because I've already had COVID.

FACT

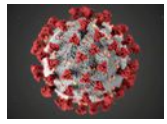
Getting infected with COVID does provide some natural immunity after your infection has run its course. However, this natural immunity decreases over time. Early studies indicate that the immunity provided by the COVID vaccine is longer-lasting than the immunity acquired through infection.

CONCERN

The vaccine will affect my fertility.

FACT

The COVID vaccine will not affect fertility. The American College of Obstetricians and Gynecologists has stated that the COVID vaccine is safe for people who are thinking about becoming pregnant, wanting to become pregnant, are pregnant, or who are breastfeeding.



MISCONCEPTION

99% of people who test positive for COVID survive, and I'm healthy. I don't need the vaccine.

FACT

While it's true that the majority of people who test positive for COVID survive, that's not the whole story. Even among previously healthy patients, long-term side effects in COVID survivors can include chronic fatigue, mild to severe lung problems, joint pain, chronic headaches, cognitive issues, depression, anxiety, loss of smell or taste, and others.

If you're not worried about complications for yourself, consider your family, friends, and coworkers. You don't know what underlying health conditions the people around you might have, and getting the vaccine will help you protect the people who are closest to you.

CONCERN

The vaccine will cause unknown long-term complications.

FACT

According to the CDC, vaccine monitoring has historically shown that side effects generally happen within six weeks of receiving a vaccine dose. For this reason, the FDA required each of the authorized COVID vaccines to be studied for at least eight weeks after the final dose. Millions of people have received COVID vaccines, and no long-term side effects have been detected.

MISCONCEPTION

The vaccine has caused severe side effects and death in a large number of people who received it.

FACT

All vaccines and medicines do carry a small risk of adverse reactions. However, millions of people in the United States have safely received the COVID vaccine under some of the most intense safety monitoring in U.S. history.

The CDC and the FDA are currently monitoring reports that the Johnson & Johnson vaccine may have an increased risk of developing thrombocytopenia syndrome or Guillain-Barre Syndrome. It's important to understand that these reported side effects are still incredibly rare.

It's also important to note that reports of adverse events to the Vaccine Adverse Event Reporting System (VAERS) following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. It simply means that a patient experienced an adverse health event within a certain timeframe after receiving a vaccine. Correlation does not always equal causation.

MISCONCEPTION

Certain blood types/skin colors are less susceptible to COVID, so I don't need to get the vaccine.

FACT

No blood type, skin color, or other physical characteristic has been found to decrease the risk of getting infected with or having complications from COVID.

CONCERN

The vaccine won't protect me against COVID variants.

FACT

The vaccine is effective against COVID variants. A June 2021 study from the U.K. found that the Pfizer vaccine is 96% effective against hospitalization from the delta variant after two doses. This is encouraging news!

MISCONCEPTION

The vaccine doesn't work anyway. People are still getting infected.

FACT

The vaccine works. Many people are still getting infected in Missouri because around half of Missourians still have not received the COVID vaccine. In July 2021, around 97% of people hospitalized in the United States due to COVID symptoms were unvaccinated.

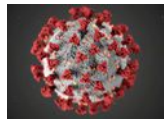
While unlikely, people who have been vaccinated can still get COVID. However, people who are vaccinated but become infected with COVID are much less likely to experience severe symptoms or require hospitalization.

CONCERN

The vaccine is made of aborted fetal tissue.

FACT

The Pfizer and Moderna vaccines were developed without the use of fetal tissue and do not contain fetal tissue. The Johnson & Johnson vaccine did use fetal cell lines (cells grown in a lab, not aborted fetal tissue) in the production of its vaccine. This is a complex ethical issue. In short, if you're concerned about fetal tissue being used in the production of vaccines and have the option to choose, opt to receive the Pfizer or Moderna vaccines.



CONCERN

The vaccine will alter my DNA.

FACT

The mRNA in the Pfizer and Moderna vaccines never enters the nucleus of the cell where your DNA is located. The mRNA causes your cells to make protein to stimulate the immune system, and then the mRNA quickly breaks down — without interacting with your DNA at all.

MISCONCEPTION

We can't trust the vaccine because its development was rushed and it hasn't been approved by the FDA.

FACT

Researchers have been studying and working with mRNA vaccines for decades. The companies who created the current COVID vaccines put their vaccines through rigorous clinical trials involving tens of thousands of volunteers.

The FDA requires the companies to follow up with volunteers for up to two years after getting the vaccine to make sure the vaccines are safe and effective. Because of how prevalent COVID is, it only took a few months for the clinical trials to collect enough data to make an initial evaluation. The FDA, as well as an independent panel of vaccine experts, closely scrutinized the data from those trials and deemed the current vaccines in the U.S. safe and effective for emergency use. Similar independent panels in several other countries are in agreement.

MISCONCEPTION

The pandemic will be over soon anyway, so I don't need to get the vaccine.

FACT

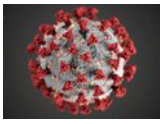
The unfortunate fact is this: things will not be "normal" again until we achieve herd immunity against COVID. As another enormous wave of COVID cases sweeps across Missouri in the summer of 2021, nearly a year after the first wave of COVID cases first devastated the state, it is clear that the virus is still very much a threat. Many more people around Missouri must get vaccinated in order to decrease the transmission rate of COVID and get us back to our normal lives.

Missouri State Medical Association
www.msma.org | heidi@msma.org

MISSOURI PHARMACY ASSOCIATION
www.morx.org | ron@morx.com

Scan to Download!

Sources: Centers for Disease Control and Prevention, Mayo Clinic, Johns Hopkins University, Cleveland Clinic



Assessing Your Chances of Collecting on Business Interruption Coverage for COVID-19 Losses

by Varsha Gadani, JD & Dominic Castillo, JD

Based on the litigation so far, businesses will have to overcome a few hurdles in order to collect on their insurance policies for COVID-19 losses.

Introduction

The COVID-19 pandemic has significantly changed day-to-day life, and it has had a considerable impact on businesses. Many businesses have struggled to survive, and some ultimately had to close their doors for good, so it's no surprise that businesses are turning to their insurance policies in hopes of covering their losses. Specifically, many businesses are hoping to collect on their business interruption coverage, but some have experienced claim denials, leading to costly litigation. This article examines litigation trends relating to businesses' attempts to collect on their business interruption coverage for COVID-19 losses.





This article was written by Varsha Gadani, JD, (left), Senior Associate, and Dominic Castillo, JD, (right), Associate, of Husch Blackwell's Austin, Texas office. Husch Blackwell represents a full spectrum of healthcare providers and other businesses in regulatory compliance and litigation matters and serves as outside legal counsel to the Missouri State Medical Association. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are encouraged to consult their own attorney concerning their specific situation and specific legal questions.

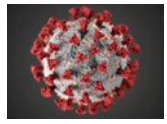
Business Interruption Insurance

All-risk property insurance policies cover all risks of loss except for risks that are expressly and specifically excluded.[1] Often, these policies will include coverage for business income and civil authority. Business income coverage pays the actual loss of business income due to necessary suspension of operations caused by direct loss to property resulting from a covered cause of loss.[2] Civil authority coverage typically covers the actual loss of business income and necessary expenses caused by an action of a civil authority that prohibits access to the covered property in certain instances due to a covered cause of loss.[3] Traditionally, these cover business profits or fixed costs of operating the business, temporary relocation and costs associated with moving the business operation, and extra expenses to keep an operation running beyond normal fixed costs.

Coverage under an all-risk property insurance policy generally requires direct physical loss or damage to property. Causation plays a major role in linking the business loss with a physical damage or loss. The requirement of a direct physical loss is a customary limitation for business interruption coverage. Typically, the mere loss of use of the business operations by itself is insufficient to support a direct physical loss, and rather, it requires either a direct or proximate cause that leads to the loss.[4]

All-risk policies will usually either explicitly include or exclude covered perils. One very common exclusion is the exclusion against viruses and diseases. Many policies expressly exclude viruses and bacterium or include a requirement of direct physical loss caused by a virus or other communicable disease.

Consequently, the policy's terms, including specific exclusions, will dictate whether a claim will



be successful. In order to assess whether a claim will be covered, the specific policy, including exclusions, should be reviewed, as further discussed in the analysis of recent litigation. Even if the exclusion against viruses is not in the policy, recent cases demonstrate that the direct physical loss hurdle is difficult to surmount when attempting to link the causation required to enforce a typical business interruption policy.

Business Interruption Litigation

Recent litigation shows that businesses have been largely unsuccessful when attempting to collect on their business interruption coverage for COVID-19 losses. The two main reasons for this are because policies often have exclusions for viruses, and businesses have struggled to show that COVID-19 caused a direct physical loss.

Denied Claims Upheld Because No Physical Loss

Recent attempts to collect under business interruption or civil authority coverage have generally resulted in judgment in favor of insurance companies.

In a recent case, the 8th Circuit found that loss of use of a property did not rise to the level of direct physical loss, as required by the policy. In this case, Oral Surgeons, P.C., a provider of oral and maxillofacial surgery services, was forced to stop performing procedures from late March until May of 2020 when Iowa entered a state of emergency as a result of the COVID-19 pandemic, when restrictions were placed on dental practices.[5] Oral Surgeons' claim for lost business income was denied because the court found there was no "direct physical loss" to Oral Surgeons' property.

Oral Surgeons' policy specifically required a "direct physical loss" to trigger business interruption coverage. The 8th Circuit followed precedent that stated mere loss of use is insufficient to be considered a "direct physical loss."[6] The court rejected Oral Surgeons' claim and held that the policy "clearly does not provide coverage for . . . loss of use . . . absent a showing of direct physical loss or physical damage.[7]

Similarly, in Texas, an iconic barbecue restaurant, Terry Black's Barbecue, LLC, unsuccessfully attempted to collect under its commercial property insurance policy's business interruption coverage.[8] Terry Black's argued that the civil authority's closure order in conjunction with the presumed presence of COVID-19 on the premises caused direct physical damage. Direct physical loss was not defined in the policy, and the court found physical loss to be unambiguous.

The court, applying the ordinary meaning, stated that a physical loss must be "some distinct, demonstrable, physical alteration of the property," as opposed to economic losses.[9] The court held that no direct physical loss was found because COVID-19 does not produce any physical damage to property under the ordinary sense of the word. Additionally, the closure by the civil authority on its own is insufficient to cause any tangible physical alteration of the property. Instead, it merely precluded Terry Black's from operating its restaurant.

These jurisdictions are not alone in the interpretation of what constitutes a "direct physical loss" or "damage to property." For instance, an Ohio court applied the Merriam-Webster definition of physical damage to exclude any intangible or incorporeal damages (including COVID-19), and it found that civil authority closures alone do not constitute direct physical damage.[10] Cases in California,[11] Iowa,[12] and Georgia[13] have also followed this line of interpretation that a business has not met the "direct physical loss" requirement of typical business interruption and civil authority policy provisions if the business only alleges that COVID-19 or a civil authority's action restricts a business' ability to operate and the business fails to demonstrate tangible physical damage or alteration.

Potentially Viable Arguments

Missouri has seen a nuanced split on the "direct physical loss" requirement related to COVID-19 closures. A couple Missouri businesses have survived summary judgment,[14] where the insurer has requested for the court to make a determination based on the pleadings and prior to a trial.

In one case, a hair salon franchise, Studio 417, filed a claim under its all-risk property insurance policy, which covered everything except risks specifically and expressly excluded.[15] The insurer moved for summary judgment. In the motion for summary judgment, the insurer argued that Studio 417 did not allege any direct loss of actual, permanent, or physical loss of the property. The court disagreed, finding persuasive Studio 417's argument that COVID-19 is a physical substance that is active on inert physical surfaces emitted through

the air and making the property unsafe and unusable resulting in direct physical loss of the premises.

Studio 417 also sought relief under the civil authority coverage provision. The court determined that because hair salons were completely shut down by the civil authority, Studio 417 had a viable claim to survive the motion for summary judgment. Interestingly, the court distinguished a hair salon's complete prohibition on inviting individuals inside for long periods of time from restaurants that could still serve to-go and take-out food to patrons. The civil authority's prohibition was sufficient to support a plausible allegation that the civil authority coverage provision was triggered.

In another case in Kansas City, a group of dental clinics filed suit against their insurer to collect on COVID-19 losses.[16] Based on the Missouri stay-at-home orders, the dentists had to remain at home and were forced to suspend their business operations, and they argued this caused a "direct physical loss." The policy did not define "direct physical loss," so the court applied the plain and ordinary meaning.

The dentists also argued that it is likely that employees, patients, and visitors were infected with coronavirus, which they argued deprived them of their use of the property and damaged it. They also reminded the court that the policy required direct physical loss, not damage, so the loss of access and functionality constituted physical loss. For purposes of the motion for summary judgment, the court felt the claim was plausible and allowed the dentists' claims to go forward to trial.[17]

Studio 417 and the dentists' claims are still being litigated, so we do not yet know whether their arguments regarding physical loss will be successful and whether their insurers will have to pay out on these claims. The outcome of these cases will be instructive on how Missouri courts view the direct physical loss requirement of business interruption and civil authority provisions in relation to COVID-19.

Of note, a United States Judicial Panel on Multidistrict Litigation centralized 34 cases from six Midwestern states against Society Insurance Company to determine whether COVID-19 caused any direct physical loss of or to property.[18] This case may also be instructive on this issue.

Conclusion

Unfortunately, "all risk" insurance does not actually provide coverage for *all* business risks and interruptions. Based on the litigation so far, businesses will have to overcome a few hurdles in order to collect on their insurance policies for COVID-19 losses. First, businesses should check the terms of their policies for the types of coverage they have and any exclusions from that coverage. Then, a business will likely have to demonstrate a direct physical loss or damage. In many cases, the COVID-19 virus and government-mandated closures are not enough to collect on these policies. This can leave policyholders with enormous losses. Due to the high losses most businesses have already experienced, it would be prudent to analyze chances of success on a claim prior to initiating costly litigation and potentially increasing overall losses.

References

1. *Studio 417, Inc. v. Cincinnati Ins. Co.*, 478 F. Supp. 3d 794, 797 (W.D. Mo. 2020).
2. *Id.*
3. *Id.*)
4. *See e.g.*, *Pentair, Inc. v. American Guarantee and Liability Ins. Co.*, 400 F.3d 613, 616 (8th Cir. 2005).
5. *Oral Surgeons, P.C. v. Cincinnati Ins. Co.*, 2 F.4th 1141 (8th Cir. 2021). Missouri is in the 8th Circuit.
6. *Id.* (quoting and *Pentair, Inc. v. American Guarantee Liability Ins. Co.*, 400 F.3d 613, 614 (8th Cir. 2005)).
7. *Id.* at 1145.
8. *Terry Black's Barbecue, LLC v. State Automobile Mutual Ins. Co.*, 514 F.Supp.3d 896 (W.D. Tex.—Austin Div., Jan. 21, 2021).
9. *Id.*
10. *Brunswick Panini's, LLC v. Zurich American Ins. Co.*, 2021 WL 663675, Case No. 1:20CV1895 (mem. op.) (Mar. 9, 2021).
11. *Barbizon School of San Francisco, Inc. v. Sentinel*, 2021 WL 1222161, Case No. 20-cv-08578-TSH (mem. op.) (Mar. 31, 2021) (holding that a 'detrimental economic impact' that is not accompanied by a distinct and demonstrable, physical alteration of the property is insufficient to support a direct physical loss).
12. *Gerleman Mgmt., Inc. v. Atlantic States Ins.*, 506 F.Supp.3d 663 (S.D. Iowa—Central Div., Feb. 22, 2021) (holding that the coronavirus "does not cause a tangible change to the physical characteristics of property" to trigger coverage under the business interruption provision).
13. *K.D. Unlimited Inc. v. Owners Ins. Co.*, 2021 WL 81660, Civ. Action File No. 1:20-CV-2163-TWT (N.D. Ga. Jan. 5, 2021).
14. Summary judgment is an expedited judgment entered by a court for one party and against another party based on the pleadings without a full trial. A party may move for summary judgment, and the court can grant it if the moving party shows that there is no genuine dispute as to any material fact.
15. *Studio 417, Inc. v. Cincinnati Ins. Co.*, 478 F.Supp.3d 794 (W.D. Mo.—Southern Div. Aug. 12, 2020).
16. *Blue Springs Dental Care, LLC v. Owners Ins. Co.*, 488 F.Supp.3d 867 (W.D. Mo.—Western Div. Sept. 21, 2020).
17. *But see, Zwillo V, Corp. v. Lexington Ins. Co.*, 504 F.Supp.3d 1034 (W.D. Mo.—Western Div. Dec. 2, 2020) (disagreeing with the holding in *Blue Springs Dental Care* that the plain meaning of the direct physical loss does not cover losses related to COVID-19).
18. *In re Soc'y Ins. Co. Covid-19 Bus. Interruption Prot. Ins. Litig.*, 492 F. Supp. 3d 1359 (J.P.M.L. 2020).

MM

Smokescreen: What the Marijuana Industry Doesn't Want You to Know

by Kevin Sabet, PhD

The data is continually examined, but it cannot be clearer that marijuana legalization, commercialization, and normalization has led to negative outcomes to public health, safety, and has served as a breeding ground for corruption.

In 2012, Colorado became the first state in the country to flout federal law and "legalize" the recreational use of marijuana. Since then, some 19 states have also moved to legalize the sale and use of the substance. Despite this, legalization efforts in most states, such as New Hampshire, Minnesota, and Delaware failed to pass in the 2021 legislative session. Of note, in states where marijuana is legal, the overwhelming majority of towns and communities have banned marijuana sales and production. This expansion and normalization of marijuana and its use has led to many harms and the establishment of a for-profit marijuana industry that works diligently to continue its expansion — both at the state and federal level — and to cover up the consequences.

Marijuana commercialization holds many negative ramifications for public health, social justice, and public safety. More people are using marijuana while remaining largely ignorant of its negative consequences and use rates are surging across the United States after decades of declines. In 2018, more than 43.4 million people using marijuana in the past year — a more than 6% increase over the previous year. This alarming increase — especially the increases found among young people and pregnant women, prompted then-U.S. Surgeon General Jerome Adams to issue a first-of-its-kind health advisory on marijuana use.[1]

In states where marijuana is legal, retail and medical licenses far outnumber popular food chains. In Colorado, for example, marijuana retail locations outnumber all McDonald's and Starbucks locations in the state combined.[2] In 2019, there were 1,016 registered retail and medical marijuana locations combined compared with 392 Starbucks and 208 McDonald's.[3] The sheer commonplace numbers of such stores alone promotes and normalizes marijuana use.

Rising THC Potency and Use Levels

While it is true that humans have used marijuana in some form for thousands of years, the marijuana of today looks nothing like the drug of the past. In the 1970s marijuana contained roughly 1-3 percent tetrahydrocannabinol, the main psychoactive component of marijuana.[4] Since then, market demand and a shift in consumption methods — largely driven by the marijuana industry — have led to a newer, much more potent form of the drug. One study found that the average potency of the marijuana plant increased from 8.9% THC in 2008 to 17.1% THC in 2017. Meanwhile, concentrates — a new form of marijuana that are consumed in the form of edibles, tinctures, "dabs," and vaping oils — contained an THC potency of 6.7% in 2008 and 55.7% in 2017.[5]



Kevin Sabet, PhD, serves as president and co-founder of Smart Approaches to Marijuana. He formerly served as a senior drug policy advisor to the Clinton, Bush, and Obama Administrations. His latest book, Smokescreen: *What the Marijuana Industry Doesn't Want You to Know*, was published in April 2021 by Forefront Books.

According to recent data from Colorado, higher potency forms of marijuana are becoming increasingly more popular among young people. The 2020 release of data from the Healthy Kids Colorado Survey found that since 2017, past-month marijuana use has increased 14.8% among those aged 15 or younger has increased 14.8%, 3% among those 16 and 17, and 1.9% among those aged 18 and older. Overall, marijuana use amongst all age groups rose 6.2%.[6]

But when diving deeper into the data, it can be found that Colorado's youth have dramatically increased their use of high potency marijuana. Since 2015, there has been a quintupling of youth use of high potency concentrates and the rate of youth marijuana vaping has doubled.[7] A short brief on the potential health hazards that can result from marijuana use underscores why this increase in use is problematic.

Potential Health Hazards from High Potency Marijuana

Researchers have found marijuana to be an addictive drug.[8] Brain scans of marijuana users show changes in the structure of the brain's reward center to be consistent with addiction[9] and up to 47% of regular users experience withdrawal symptoms when they cease use.[10]

The National Institute on Drug Abuse reports that around 30% of marijuana users have some form of marijuana use disorder and that people who begin using marijuana before the age of 18 are four to seven times more likely to develop a marijuana use disorder compared with those who start later.[11] One recent study on rats found that marijuana vaping may support "conditioned drug-seeking behavior,"[12] a cause for concern as vaporized marijuana gains popularity.

Studies have also found marijuana use can cause severe consequences for mental health. Marijuana is increasingly linked to the onset of psychosis and schizophrenia[13] and shows a more modest association with depression and anxiety.[14] In one of the most comprehensive studies to date on marijuana and psychosis, Di Forti, et al. found that daily marijuana use is associated with an increased likelihood of developing psychosis. What's more, researchers found that daily users of high potency marijuana have four times greater odds for the development of psychosis.[15]

Frequency of marijuana use, as well as higher THC potency, is associated with the most severe impact on mental health, which is evidenced by psychosis, suicidality, reshaping of brain matter, and addiction.[16] The increasing demand for high-potency marijuana products and the coinciding prevalence of marijuana use disorder are indicative of a future maelstrom with unknown consequences for public health, especially as the industry engages in a concerted effort to undermine scientifically proven risks of marijuana use.

Marijuana Commercialization: The Rising Threat

As mentioned earlier, the commercialization of marijuana has the most potential to create a future substance abuse crisis. the adaptability of marijuana gives way to mass-marketed products modeled after popular consumer goods. Marijuana-infused "edibles" come in the form of cookies, candy, ice cream, sodas, and other sweet treats that are particularly appealing to children.[17] Marketing tactics make use of bright colors and catchy names, replicating images or appropriating the names of well-known commercial food products. For example, the brand recognition of "Pop-Tarts," a widely consumed kid-friendly breakfast product, was seized upon by one marijuana producer to market "Pot Tarts." Unfortunately, these products are thought to be contributing to the increased accidental marijuana exposures among children and others.

These kinds of growth tactics by industry are not new. They largely mirror the boom of Big Tobacco in the early 1900s—and not by accident.[18]

Enter the Titans of Addiction-For-Profit

The addiction-for-profit model utilized by Big Tobacco was wildly successful in the United States. By the early to mid 1960s, an estimated 42% of Americans were smokers.[19] However, in 1964 the release of the first ever Surgeon General's Advisory on Smoking and Health was the shot across the bow for the tobacco industry that set the pace

for the next 40 years of deceitful lobbying and marketing tactics by Big Tobacco in an effort to stem the gradual decline in cigarette use. As it stands today, cigarette use is at an all-time low and Big Tobacco has its eyes set on a new product: marijuana.

In 2019, Altria, the maker of Marlboro cigarettes, invested $2 billion into Canadian marijuana company Cronos and spent another $12 billion to become a large shareholder in Juul, which controls about three-quarters of the market for vaping products in the U.S.[20] Soon after, Imperial Brands, one of the largest tobacco companies in the world, invested more than $100 million in another Canadian company to develop marijuana vaping products.[21]

In an effort to further its investment, Altria has officially hired lobbyists to push lawmakers at the federal and state level to legalize recreational marijuana sales and help craft how such sales would unfold.[22]

Altria is not the only addiction giant lobbying on pot, either. Lobbyists for Constellation Brands—the maker of Corona beer—share an office, and meetings, with the lobbyists of Canopy Growth,[23] the giant marijuana firm that hired former House Speaker John Boehner to be their chief lobbyist and make him a multi-millionaire should federal legalization occur.[24]

Alcohol lobbyists working on the marijuana issue claim they can help establish regulations around "the successful sale of age-restricted products," but data show the regulation of underage alcohol consumption has been a failure: more than 70% of teens have consumed at least one alcoholic beverage by the time they reach age 18, children as young as 12 have engaged in underage alcohol use and approximately one out of every 10 alcoholic drinks is consumed illegally.[25]

In the past, lobbyists for both the tobacco and alcohol industries worked to reduce excise taxes on beer and spirits, challenge bans or limits on advertising, nix requirements for nutrition labels on alcoholic beverages, promote ineffective voluntary regulation as a substitute for enforceable laws and even demanded a seat at the table when it came to the creation of regulations.

Now, marijuana lobbyists work tirelessly at the state level to reduce taxes, remove limits on the number of licenses available, remove bans on public consumption and the creation of "pot bars," lift advertising restrictions and reverse local bans on pot businesses or circumvent them by forcing the state to allow marijuana delivery services.

In a testament to its own size, the marijuana has spent $4 million on lobbyists in Colorado alone and has become one of the most influential forces in the state's capitol.[26]

Potential Links to Corruption

At the intersection of investment, lobbying clout, political power, and big business sits corruption. And the marijuana industry is not immune from it. There are many examples of this.

Take, for instance, the example of Green Renaissance Illinois, a marijuana company whose leadership includes a former Chicago police commander, a Republican Party operative, a former Transit Authority official, a marijuana industry insider related to a former state lawmaker, and a former director of the state agency that oversees marijuana dispensaries. Licenses for marijuana operations in Illinois are granted via a lottery system, but there has been serious concern that such a well-connected group will reap more success than the odds would dictate. In total, this company has submitted 25 license applications that could net it a maximum of 10 licenses worth more than $130 million.[27]

The company's listed address raised eyebrows even more: they're located in the same building as numerous influential lobbyists in the state. It's hard to imagine how this company, with all of its power players, warrants being included in a pool of social equity applicants, or applicants from traditionally underrepresented communities.

The social equity licensing process has been mocked by many in the state, including State Representative La Shawn Ford (D-Chicago) who said, ". . . the well-connected [are] having

their way in this cesspool of state government. Anybody that thought that they had a chance to get into cannabis with a fair shot, it seems as though they were wrong." Due to this example, and others, social justice organizations have filed lawsuits to stop the licensing lottery.

Unfortunately, these concerns aren't just confined to the Land of Lincoln.

In Missouri, the medical marijuana licensing process seemed rigged from the start. In fact, lawmakers are investigating Governor Mike Parson's questionable appointments to positions regulating the industry. Those include his appointment of former Republican state representative Lyndall Fraker to be the state's medical marijuana czar.

Of note: Fraker, a former Walmart manager, has no previous medical experience. The administration also hired Amy Moore to serve as Fraker's deputy after serving at the Missouri Public Service Commission. This hiring decision is notable, as Moore's husband is a lawyer who has numerous marijuana industry clients.

A further wrinkle with possible links to impropriety in Missouri's fledgling medical marijuana program is a concerning lack of transparency surrounding the state's licensing program. As it stands, the Missouri State Constitution prohibits the state granting more than five licenses to any single entity. However, an analysis by two newspapers in the state found numerous instances where this stipulation was completely ignored.[28]

Notably, all information regarding applications and licensing is kept in confidentiality by the state, so the general public is left to simply trust the regulators and the industry are acting in accordance with state law.

Conclusion

As a handful of states move to consider further expansion of the marijuana industry each major election cycle and the federal government discusses marijuana policy change, it is crucial that lawmakers and the general public are made aware of the realities of the impact marijuana commercialization has had.

Concerningly, many across the country fall victim to the rhetoric of the marijuana industry. The data is continually examined, but it cannot be clearer that marijuana legalization, commercialization, and normalization has led to negative outcomes to public health, safety, and has served as a breeding ground for corruption.

References

1. United States Department of Health and Human Services. (2018). U.S. Surgeon General's Advisory: Marijuana Use and the Developing Brain. https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-marijuana-use-and-developing-brain/index.html. Published August 29, 2019. Accessed July 9, 2021.
2. Chart: Marijuana store density surpasses Starbucks & McDonald's in many mature cannabis markets. Marijuana Business Daily. https://mjbizdaily.com/marijuana-store-density-surpasses-starbucks-and-mcdonalds-in-many-mature-cannabis-markets/. Accessed July 9. 2021.
3. Colorado Department of Revenue. (2019). MED licensed facilities. https://www.colorado.gov/pacific/enforcement/med-licenesed-facilities. Accessed July 9, 2021.
4. ElSohly M, Ross S, Mehmedic Z, Arafat R, Yi B, and Banahan B. Potency Trends of Δ9-THC and Other Cannabinoids in Confiscated Marijuana from 1980–1997. J Forensic Sci. 2000;45(1):14636J.
5. Chandra S, Radwan M, Majumdar C, Church J, Freeman T, and ElSohly M. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry ClinNeurosci. 2019;269(1):5-15.
6. Colorado Department of Public Health and Environment. (2019) Healthy Kids Colorado Survey. https://cdphe.colorado.gov/center-for-health-and-environmental-data/survey-research/healthy-kids-colorado-survey-data
7. *Ibid*
8. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-2227. doi:10.1056/NEJMra1402309
9. Gilman J, Kuster J, Lee S, Lee M, Kim B, Makris N, Blood A, Breiter H. Cannabis Use Is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users. J Neurosci. 2014;34(16). doi:10.1523/JNEUROSCI.4745-13.2014
10. Hasin D, Walsh C. Cannabis Use, Cannabis Use Disorder, and Comorbid Psychiatric Illness: A Narrative Review. J Clin Med. 2020;10(1):15. Published 2020 Dec 23. doi:10.3390/jcm10010015
11. National Institute on Drug Abuse. (2020) Is Marijuana Addictive? [online] Available at: <https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-addictive> [Accessed 9 July 2021]
12. Freels T, Baxter-Potter L, Lugo J, Glodosky N, Wrigh H, Baglot S, et al. (2020) Vaporized Cannabis Extracts Have Reinforcing Properties and Support Conditioned Drug-Seeking Behavior in Rats. J Neurosci. 2020;40(9). doi: https://doi.org/10.1523/JNEUROSCI.2416-19.2020
13. See: Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ. 2005;330(7481):11. doi:10.1136/bmj.38267.664086.63; Marconi A, Di Forti M, Lewis C, Murray R, Vassos E. (2016) Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull. 2016;42(5):1262–1269; Mustonen A, Niemelä S , Nordström T, Murray G, Mäki P, Jääskeläinen E. Adolescent Cannabis Use, Baseline Prodromal Symptoms and the Risk of Psychosis. Br J Psychiatry. 2018;212(4):227–233; and Niemi-Pynttäri J, Sund R, Putkonen H, Vorma H, Wahlbeck K and Pirkola S. Substance-induced Psychoses Converting into Schizophrenia: A Register-based Study of 18,478 Finnish Inpatient Cases. J Clin Psychiatry. 2018;74(1) (2013):94–99
14. See: Agrawal A, Nelson E, Bucholz K, Tillman R, Grucza R,

BOOK REVIEW

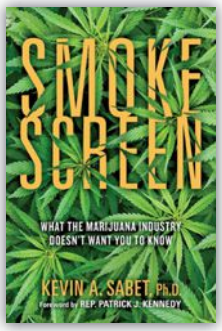
Smokescreen: What the Marijuana Industry Doesn't Want You to Know

Forefront Books
ISBN-10: 1948677873
ISBN-13: 978-1948677875

by Kevin Sabet, PhD

Reviewed by John C. Hagan, III, MD, FAAO, FACS, Ophthalmologist

Smokescreen: What the Marijuana Industry Doesn't Want You to Know examines the inside story behind the headlines, containing accounts from Dr. Sabet's time in the Obama administration to stunning revelations from whistleblowers speaking out for the first time. What it finds is how the marijuana industry is running rampant without proper oversight, leaving Americans' health seriously at risk.



Smokescreen features interviews with industry insiders who reveal the hidden dangers of a product they had once worshipped, insights from a major underground-market dealer who admits that legalization is hastening the growth of the illicit drug trade, and the tragic stories of those who have suffered and died as a result of marijuana use, and in many cases, as a result of its mischaracterization. Readers will learn how power brokers worked behind the scenes to market marijuana as a miracle plant in order to help it gain widespread acceptance and to set the stage for the lucrative expansion of recreational pot.

A book several years in the making, filled with vivid characters and informed by hundreds of interviews and scores of confidential documents, Dr. Sabet's *Smokescreen* lays bare the unvarnished truth about marijuana in America.

Statham and Madden P. Major Depressive Disorder, Suicidal Thoughts and Behaviors, and Cannabis Involvement in Discordant Twins: A Retrospective Cohort Study. Lancet Psychiatry 2017;4(9):706–714; Duperrouzel J, Hawes S, Lopez-Quintero C, Pacheco-Colón I, Comer J and Gonzalez R. The Association Between Adolescent Cannabis Use and Anxiety: A Parallel Process Analysis. Addict Behav 2018 March (78):107–113; and Gobbi G, Atkin T, Zytynski T, Wang S, Askari S, Boruff J, et al. Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2019;76(4): 426-434

15. Di Forti M, Quattraone D, Freeman T, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, et al. The Contribution of Cannabis Use to Variation in the Incidence of Psychotic Disorder Across Europe (EU-GEI): A Multicentre Case-control Study. Lancet Psychiatry. 2019;6(5): 427–436

16. See: Bidwell L, YorkWilliams S, Mueller R, Bryan A and Hutchinson K. Exploring Cannabis Concentrates on the Legal Market: User Profiles, Product Strength, and Health-related Outcomes. Addict Behav. 2018;8 102–106; Fischer B, Russell C, Sabioni P, van der Brink W, Le Foll B, Hall W, Rehm J, et al. Lower-risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. Am J Public Health. 2017;107(8): e1–e12; Pierre J, Gandal M and Son M. Cannabis-induced psychosis associated with high potency 'wax dabs. Schizophr Res. 2016;172(1–3): 211–212.

17. O'Connor S, and Méndez S. Concerning Cannabis-infused Edibles: Factors that Attract Children to Foods. https://lcb.wa.gov/publications/Marijuana/Concerning-MJ-Infused-Edibles-Factors-That-Attract-Children.pdf. Published June 2016. Accessed July 12, 2021.

18. Ayers J, Caputi T, Leas E. The Need for Federal Regulation of Marijuana Marketing. JAMA 2019;321(22): 2163–2164.

Lindsey, N (2018) The 12 Most Potent THC Concentrates. High Times. https://hightimes.com/dabs/most-potent-thc-concentrates/.

19. Stratton K, Bonnie R. Ending the Tobacco Problem: A Blueprint for the Nation. National Academies Press; 2007

20. Roberts C. (2021) How Tobacco Giant Altria is Becoming a Cannabis Company. Forbes https://www.forbes.com/sites/chrisroberts/2021/02/09/tobacco-giant-altria-is-pushing-marijuana-reform-on-congress-and-state-lawmakers/?sh=413909106041

21. Marijuana Business Daily (2019) British tobacco giant invests CA$123 million in Canadian cannabis firm Auxly. Marijuana Business Daily https://mjbizdaily.com/british-tobacco-giant-invests-ca123-milllion-in-canadian-cannabis-firm-auxly/

22. Kary T. (2021) With Lobbying Clout, Big Pot is Here. Bloomberg. https://www.bloomberg.com/news/articles/2021-02-14/with-new-lobbying-clout-big-pot-has-arrived-cannabis-weekly

23. *Ibid*

24. Raymond A. (2019) John Boehner Stands to Make Millions off Marijuana. Intelligencer. https://nymag.com/intelligencer/2019/06/john-boehner-stands-to-make-millions-off-marijuana.html

25. Editorial Staff. Underage Drinking Statistics Within the US. American Addiction Centers. https://www.alcohol.org/teens/underage-drinking-stats/

26. Fish S. (2019) Cannabis lobby gains new clout in Colorado as its spending tripled in the past five years. Colorado Sun. https://coloradosun.com/2019/03/13/colorado-cannabis-lobby-clout-legislature/

27. Schuba T. (2020) Clouted mix of insiders, others tied to state politics behind social equity pot bid. Chicago Sun Times. https://chicago.suntimes.com/cannabis/2020/9/15/21438371/illinois-marijuana-cannabis-pot-dispensary-social-equity-license-green-renaissance

28. Hancock J and Jain J. (2021) Secrecy around ownership records raises questions about Missouri marijuana networks. Missourian https://www.columbiamissourian.com/news/state_news/secrecy-around-ownership-records-raises-questions-about-missouri-marijuana-networks/article_3e1673f0-af46-11eb-821a-3f5a8796c5a0.html

MM

Correspondence

COVID Vaccine: What Concerns Our Patients

The COVID-19 vaccine guide in this issue of *Missouri Medicine* (pages 404-407) addresses the most common patient concerns and misconceptions about the COVID-19 pandemic. We are sharing this valuable guide available for patients. In our clinics, we encourage patients to discuss their vaccine status and, if not vaccinated, their reasons for not doing so. Because we were surprised to encounter so many patients who oppose COVID-19 vaccination, we emailed all clinic patients seen during 2020 and the first seven months of 2021, asking them to participate in a survey concerning COVID-19 vaccination. More than 1,500 patients responded to the 5,000 survey requests. We recorded age, gender, reasons for avoiding vaccination, preferred sources of information, and responses to various messages concerning vaccination.

One hundred ninety-five of the survey participants (13%) did not intend to receive COVID-19 vaccination. The most important variable associated with vaccination status was age. Thirty-eight percent of patients under 40 years of age were unvaccinated and did not intend to get vaccinated; while only 7% of patients over 70 were opposed to the COVID-19 vaccine. These percentages (rounded to the nearest integer) are higher than recent surveys of Missouri patients, including a July 2021 study of patients in St. Louis County,[1] which showed a similar decline in anti-vaccination status with increasing age, but differed in showing a lower vaccination status for all age groups. It is not surprising that patients in a dermatology specialty clinic do not represent the overall population. We must also consider the likelihood that vaccine-compliant patients might be more willing to participate in a vaccine survey. Preliminary analysis of survey responses showed patients' primary issue: 39% cited concern about adverse effects of the vaccine. Other responses from the unvaccinated cited overall lack of trust in the information available from the government about the vaccine (13%), lack of concern about COVID-19 severity (9%), and a prior COVID-19 infection (11%) as reasons to avoid vaccination.

The best role for physicians in vaccine decisions is no different from our role in all healthcare matters—to serve as a trusted guide. Our survey showed a high degree of mistrust of media sources. The most effective way physicians can encourage compliance is to listen to patients and determine the reason for vaccine avoidance. Complicating matters is vaccine misinformation, some of which physicians have generated. For those who cite Carrie Madej, DO, we explain how messenger RNA cannot change DNA which is protected in the nucleus and mitochondria. Patients who cite Dr. Robert W. Malone's claim that the spike protein generated by the vaccine is cytotoxic is debunk on the reuters.com factcheck website.[2]

Usually, unvaccinated patients will remain undecided after the discussion. Sometime after the vaccine discussion, clinic workers encountered about eight patients who had been against COVID-19 vaccine who surprised us by reporting they had been vaccinated. The effort we make in combatting vaccine misinformation can save lives.

William V. Stoecker, MD
Rolla Dermatology and Aesthetic Center
Rolla, Missouri

Anish S. Jagannathan
Rolla High School
Rolla, Missouri

1. St. Louis Post-Dispatch, July 29, 2021.
2. https://www.reuters.com/article/factcheck-vaccine-cytotoxic/fact-check-covid-19-vaccines-are-not-cytotoxic-idUSL2N2O01XP

More on Unhealthy Effects of Marijuana Use

We deeply appreciate the comments offered by Juan Corvalan, MD, (*Missouri Medicine* Correspondence, July/August 2021) particularly regarding the adverse psychiatric impact of marijuana use. For many years, those of us closely watching marijuana problems internationally, have recognized that the psychiatric impact of marijuana was worsening. Cannabis associated psychiatric problems are among the most serious

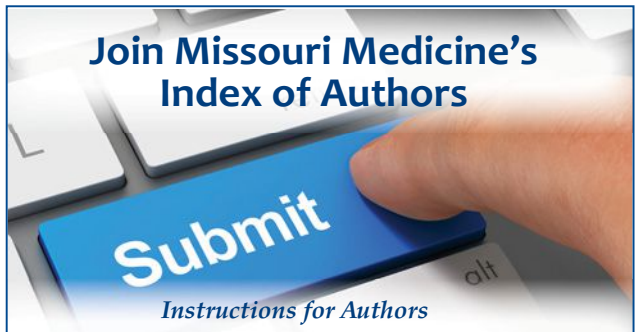


NEW MSMA MEMBERS!

Brandan Alleyne, MD – Plastic Surgery – St. Peters
Chris Chapman, DO – Unspecified – Kansas City
Ross Elliott, DO – Unspecified – N. Kansas City
Anna Gorman, DO – Obstetrics & Gynecology – Liberty
Paul Guidos, MD – Neurology – Kansas City
Samantha Herretes, MD – Ophthalmology – Leawood, Ks.
Farzana Hoque, MD – Internal Medicine – St. Louis
Vijaya Kumari, MD – Unspecified – St. Louis
Peter Lau, MD – Vascular Surgery – Kansas City
Becky Lynn, MD – Obstetrics & Gynecology – St. Louis
Adam Newman, MD – Obstetrics & Gynecology - Clinton
Dustin Smith, MD – Emergency Medicine – Chesterfield
Deepu Sudhakaran, MD – General Surgery – Chesterfield
Richard Thomas, DO – Unspecified – Hannibal
Rebecca Aft, MD – General Surgery – St. Louis
Tammie Benzinger, MD – Radiology – St. Louis
Daniel Bergmann, MD – General Sugery – St. Peters
John Billharz, MD – Pediatrics – Kansas City
John Bleazard, DO – Orthopedic Surgery – Lee's Summit
Suzanne Furesz, MD – Internal Medicine – St. Louis
Robert Hayashi, MD – Hematology/Oncology – St. Louis
Micah Hobbs, DO – Orthopedic Surgery – St. Louis
Carolyn Jachna, MD – Internal Medicine – St. Louis
Glen Johnson, MD – Orthopedic Surgery – Creve Coeur
Raffi Krikorian, MD – Internal Medicine – St. Louis
John McAtee, MD – Internal Medicine – Chesterfield
Noaman Siddiqi, MD – Radiology – St. Louis
Michael Tentori, DO – Family Practice – Canton
Kirk Wanless, MD – Otolaryngology – Moberly

and vexing problems associated with marijuana use. Several theories suggest that a central element of the untoward impact of marijuana upon psychiatric complications may have some or even strong connection to the THC concentrations that continue to increase. THC manufacturing and certain ingestion techniques such as dabbing and vaping may push THC contents well into the 90% range. This has been associated with more psychosis, violence, paranoia, depression, and mania. It is worth strong consideration for states to strongly limit the THC concentrations allowed with marijuana, or better yet, to reverse policies allowing street marijuana to be used as unproven medicine and avoid high THC recreational marijuana altogether.

Eric A. Voth, MD, FACP
Internal Medicine, Pain, Addiction Medicine
President and Chairman of the Board
International Academy on the Science Impact of Cannabis (IASIC)



Scientific & Clinical Manuscripts
Departments, Perspectives & Opinions

- Scientific/Clinical Manuscripts - Including First Literature Reports and Reviews
- Medical-Legal - Legal topics range from professional liability to ethics.
- Socio-Economic - Articles on legislation, policy, insurance, management, etc.
- Public Health - Reports that cover topical public health issues.
- Perspectives - Topics by health care professionals with different areas of expertise.
- As I See It - A forum of general interest.
- In the News - Summaries of MSMA business and highlights of members.
- Opinions - Praise, criticism, and comments about particular articles, events, or issues.

www.msma.org/missouri-medicine

Editor: John C. Hagan, III, MD, FACS | drjhagan3@gmail.com
Managing Editor: Lizabeth R. S. Fleenor, BJ, MA | lfleenor@msma.org

MSMA Members in the News

Did you make the news? Submit your success story and photo to lfleenor@msma.org.

New *Missouri Medicine* Editorial Board Member



Anne T. Christopher, MD, is the new Editorial Board member for Pain Medicine. Dr. Christopher is the Medical Director and CEO of St. Louis Pain Consultants in Chesterfield and has over 27 years of experience in that field. She graduated from Saint Louis University School of Medicine School of Medicine and is affiliated with Mercy Hospital St. Louis and Missouri Baptist Medical Center.

MSMA members **Briccio Cadiz III, MD**, **Shilpa Desai, MD**, and **Bhargav Kanani, MD**, are all celebrating 25 years of service at Ste. Genevieve County Memorial Hospital. Your dedication is commendable!



Lee Cummings, MD, (top), and **Jameson Forster, MD**, (bottom), have performed St. Luke's Health System's first-ever split liver transplant. With the addition of split-liver transplantation, these physicians hope to increase the organ donation pool and ease the liver demand-supply gap, thus helping more patients.





Jennifer DeLaney, MD, is part of a duo who received the Creve Coeur Economic Development Committee's Most Innovative Business Award 2021 for the design and development of a Powered Air-Purifying Respirator (PAPR). The device protects healthcare workers from exposure to infection via a comfortable, reusable fog-free face shield and air filter. Dr. DeLaney practices at Katzman & Delaney Personal Physicians in St. Louis.



The 2021 national meeting of the Association of Migraine Disorders featured **John C. Hagan III, MD**. Dr. Hagan spoke on the use of beta blocker eyedrops topical to eye, sublingual, or preferably nasal spray for the treatment of acute migraine. Dr. Hagan and Carl V. Migliazzo, MD, published the largest case history series on this novel treatment in *Missouri Medicine* in July/August 2014. Subsequently larger, placebo controlled studies published in *JAMA Neurology* and *JAMA Ophthalmology* have confirmed their favorable results. Scan the QR code above to read the overview, case study, and reviews.



David Keuhn, MD, has been named alternate Medical Director for the Fitzgibbon Mary Montgomery Hospice, the only locally-owned and not-for-profit hospice in Saline County. Dr. Keuhn is a Family Practice physician at Mid-Missouri Family Health in Marshall.



Deborah Krause, DO, has been chosen #1 Psychiatrist in the *Jefferson City News Tribune* Readers' Choice Awards. Dr. Krause is a psychiatrist at Capital Region Physicians – Center for Mental Wellness in Jefferson City.



David Kuhlmann, MD, Sleep Medicine specialist at Bothwell Regional Health Center in Sedalia, has been elected to the American Academy of Sleep Medicine (AASM) board. He also serves as MSMA's District 6 Councilor.



Congratulation to **Scott Kujath, MD**, who has been named medical staff president at North Kansas City Hospital. Dr. Kujath practices Vascular Surgery with the Midwest Aortic and Vascular Institute.



Jin-Moo Lee, MD, PhD, has been named head of the Department of Neurology and the Andrew B. and Gretchen P. Jones Professor of Neurology at Washington University School of Medicine in St. Louis. Dr. Lee is also a professor of radiology and biomedical engineering, co-director of the Stroke and Cerebrovascular Center at Barnes-Jewish Hospital and Washington University, and co-chair of BJC HealthCare's stroke care clinical program.



Pierre J. Moeser, MD, has joined the board of directors of Volunteers in Medicine-St. Charles, a nonprofit organization that provides health care services for the medically underserved in St. Charles and Lincoln Counties. Dr. Moeser currently works as a Rheumatologist in Springfield, Missouri, as well as Montana and North Dakota.







MSMA members **Amy Patel, MD**, (left), **Troy Voeltz, MD**, (middle), and **Allison Zupon, MD**, (right) have been named Leading Doctors of Kansas City by *HerLife* magazine. Dr. Patel is Medical Director of the Breast Care Center at Liberty Hospital, and serves as Vice Councilor of MSMA's Organized Medical Staff Section. Drs. Voeltz and Zupon are breast fellowship-trained and provide care at Imaging for Women in Kansas City.



Direct Primary Care Clinics, founded by **Jennifer Powell, MD**, has been named Best Family Practice in the 2021 Best of the Lake awards, hosted by *Lake Lifestyles* magazine. Dr. Powell offers membership-based healthcare in Osage Beach and also serves as MSMA's District 5 Vice Councilor.

Missouri Medicine Annual Statement of Ownership, Management & Circulation

1. Publication Title: Missouri Medicine
2. Publication No.: 0355-3800
3. Filing Date: 10/01/2021
4. Issue Frequency: Bi-Monthly
5. No. of Issues Published Annually: 6
6. Annual Subscription Price: $75
7. Complete Mailing Address of Known Office of Publication:
   113 Madison Street - Cole County
   Jefferson City, MO 65101
8. Complete Mailing Address of Headquarters or General Business Office of Publisher:
   113 Madison Street - Cole County
   Jefferson City, MO 65101
9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor:
   Publisher-Missouri State Medical Association
   113 Madison Street - Cole County
   Jefferson City, MO 65101
   Editor: John C. Hagan, III, MD
   113 Madison Street - Cole County
   Jefferson City, MO 65101
   Managing Editor: Lizabeth R. S. Fleenor
   113 Madison Street - Cole County
   Jefferson City, MO 65101
10. Owner: Missouri State Medical Association
    113 Madison Street - Cole County
    Jefferson City, MO 65101
11. Known Bondholders, Mortgagees & Other Security Holders: None
12. The purpose, function, and nonprofit exempt status for federal income tax purposes has not changed during the preceding 12 months.
13. Publication Name: Missouri Medicine
14. Issue Date for Circulation Data Below: July/August 2021
15. Extent and Average Actual number nature of number of copies of circulation copies each single issue during published preceding nearest to

	12 Months	Filing Date
15a. Total No. Copies (Net Press Run)	2259	2102
15b. Paid and/or Request Circulation		
(1) Paid/Requested Outside-County Mail Subscriptions	2259	2102
(2) Paid In-County Subscriptions	0	5
(3) Sales Through Dealers and Carriers, Street Vendors	0	0
(4) Other Classes Mailed Through the UPS	0	0
15c. Total Paid and/or Requested Circulation	2259	2107
15d. Free Distribution by Mail	0	0
15e. Free Distribution Outside the Mail	0	0
15f. Total Distribution	2259	2107
15g. Copies Not Distrib.	80	65
15h. Total	2339	2172
15i. Percent Paid	100%	100%
16. Electronic Copy Circulation		
16a. Paid Electronic Copies	2198	2198
16b. Total Paid Print Copies +Paid Electronic Copies	4457	2198
16c. Total Print Distribution + Paid Electronic Copies	4457	4305
16d. Percent Paid (Both Print and Electronic Copies)	100%	100%

This Statement of Ownership is printed in the September/October 2021 issue of this publication.

Kansas City University

Pandemic Brings Loss, Hardship, and Challenges; KCU Remains Committed and Dedicated

by *W. Joshua Cox, DO & Laura Rosch, DO*

The pandemic of COVID-19 required significant changes to medical education. With infection rates increasing in 2020, campuses closing, and shortage of PPE in clinical facilities, faculty were tasked with identifying innovative educational techniques to enable the students to continue learning remotely. This article provides a Dean's Update describing some of the actions Kansas City University College of Osteopathic Medicine took to enable students to continue progressing in their medical education during this global pandemic.

After briefly transitioning to all distance/remote learning mid-spring semester of 2020 due to the pandemic, KCU students have safely returned to both the Kansas City and Joplin campuses with modified operations and structure.

Kansas City University College of Osteopathic Medicine was founded in 1916 and in operation when the 1918 pandemic occurred. Few records exist detailing the actions of the university in 1918 but KCU's history and heritage played a key role in continuing to educate students during the pandemic of 2020. This was not the first pandemic the College of Osteopathic Medicine had faced. If KCU could successfully navigate through the pandemic of 1918, it could successfully navigate the pandemic of 2020.



W. Joshua Cox, DO, FACOFP, (left), is the Interim Executive Dean and Vice Provost for Health Affairs, Kansas City University, Kansas City Campus, Kansas City, Missouri, and **Laura Rosch, DO, FACOI**, is Dean, Kansas City University, Joplin Campus, Joplin, Missouri.

Initial Actions Taken

The pandemic triggered the need to operationalize KCU's crisis management, campus reawakening, and academic response teams. These teams met regularly (weekly or several times a week at the onset of the pandemic) to evaluate the status of the pandemic nationally, in the state and locally, and identify changes required in the curriculum to move the students forward as seamlessly as possible.

The campus reopening required the implementation of strict safety guidelines and protocols, screening apps, physical distancing measures, and personal protective equipment requirements in order to promote health, safety, and well-being. Baseline and surveillance COVID-19 PCR testing of employees and students from both campuses consistently show a much lower incidence of infection than the surrounding communities.

Engaging Student Learners

The events of the last year have certainly created an opportunity to pursue new ways to engage our medical school learners. Our KCU students have been able to participate safely in a number of on-campus, in-person activities as our pursuit of excellence in education continues. Additionally, the pandemic created the necessity to develop and implement a hybrid delivery that included synchronous and asynchronous learning, remote live opportunities, telemedicine experiences, and virtual reality experiences.

KCU learned that students, faculty, and staff required increased support services while they were learning and working remotely. Medical school leaders (Executive Dean and Campus Deans) met regularly with student government leaders during this time to identify and address the needs of the medical students. Regular faculty meetings were held to provide the support faculty needed to transition their

> This was not the first pandemic the College of Osteopathic Medicine had faced. If KCU could successfully navigate through the pandemic of 1918, it could successfully navigate the pandemic of 2020.

classes from an in-person to virtual learning format. We enhanced our initiatives in counseling services, learning enhancement, tutoring services, study groups, and administrative town halls. We created a "Student Hardship Fund" from donations from faculty, staff, and alumni as we realized that many students required additional support when education transitioned to remote learning. Criteria for awards were developed and this fund was launched providing financial support to a number of students who incurred unexpected expenses during the pandemic.

Addressing Health Equity, Diversity, and Inclusion

Diversity and inclusion have continued to be a priority for KCU. Healthcare disparities across communities in Missouri have made it critical to support an ever-growing diverse population of students and faculty. KCU recognizes the importance of working together with healthcare stakeholders across the state to identify and implement initiatives that will promote healthy and safe communities for our future.

Clinical Education

The highly contagious nature of COVID-19 virus placed several of our clinical partners in a situation where resources for providers were stressed. In response, KCU made a commitment to assist our clinical partners and provided students on rotations with appropriate personal protective equipment, such as masks and eye protection. Additionally, our clinical education department developed multiple pathways and scenarios to continue the education process, including online and virtual experiences, telemedicine opportunities, in-person clinical opportunities, as well as a hybrid approach that would combine these platforms. Even though residency interviews for fourth year students took place virtually this year, KCU students experienced a very successful placement rate.

Medical Students as Vaccinators

When the vaccine became available, KCU worked through scheduling conflicts with the curriculum for the first- and second-year students to enable them to administer vaccines. Medical students were required to participate in several CDC courses on vaccines and learn to administer IM injections prior to the students be allowed to participate in the vaccine clinics.

KCU collaborated with local health departments, health systems, the Missouri National Guard, and local, federally qualified health centers to train and deploy a large student and faculty vaccinator workforce that participates in several COVID-19 vaccine clinics each week. This has been an outstanding opportunity to link directly with the KCU mission of "improving the well-being of the communities we serve" by actively contributing and being a part of the solution. Feedback from the medical students about participating in the vaccine clinics has been very favorable. As of May 31, 2021, KCU students helped administer over 50,000 vaccinations in Missouri.

Admissions

Events during the past 15 months have accelerated the need to educate future healthcare providers, and KCU is well-positioned to train new professionals to serve the community moving forward. KCU conducted admissions recruiting virtually during 2020 for the 2021-22 academic year, and KCU has experienced record numbers of applications for admissions for all the programs KCU offers, including the College of Osteopathic Medicine.

Conclusion

While 2020 certainly brought loss, hardship, and consistently presented challenges, KCU students, faculty, staff and administration remained committed and dedicated. Many of the educational innovations will remain part of the curriculum. We have entered a new era of higher education. KCU has successfully navigated through the pandemic of 2020 thanks to the creativity and resilience of faculty, staff and students. And our students, with their steadfast dedication and focus, remain an inspiration to us all. **MM**

Innovations Through Virtual Reality Simulation

by Robert Tyler, DO, Galina Danilova, MBA, Schoen Kruse, PhD & Angela Pierce, PhD

Kansas City University

Our goal in this project was to identify activities that would engage pre-clinical simulation through asynchronous virtual reality case scenarios.



Robert Tyler, DO, MMEL, FACP, (above), is Assistant Professor of Internal Medicine, and Clinical Medicine Course Director, Kansas City University, College of Osteopathic Medicine (KCU-COM), Kansas City Campus, Kansas City, Missouri. Galina Danilova, MBA, is Senior Data Analyst, COM Effectiveness, KCU-COM. Schoen Kruse, PhD, FNAOME, is Associate Dean for Curriculum Integration and Learning, Professor of Pharmacology, KCU-COM; and Angela Pierce, DC, PhD, is Phase II Director – Joplin Campus, Joplin, Missouri, and Assistant Professor of Physiology, KCU-COM.

Abstract

The need to augment standardized learner outcomes related to performance and clinical competency led to creating curricular elements that would provide instruction and assessment from multiple perspectives. The COVID-19 pandemic brought about needs for re-imagination of standardized simulated clinical experiences given the need for increased distance-learning and asynchronous formats. Our goal was to identify activities that would engage pre-clinical simulation through asynchronous virtual reality (VR) case scenarios. The intent was to provide additional resources whereby competencies could be more defined through performance metrics and standardized assessments additive to our established simulation-based curriculum throughout all curricular phases. Student reflection and metacognition identified gaps to guide future performance improvement through the VR activities. Learner outcomes encompassing history-taking, physical assessment, evidence-based clinical reasoning, and medical decision-making guided the instructional objectives. The composite data showed progressive improvements over five scenarios delivered in our second-year clinical medicine curriculum.

Challenges

Take a moment to reflect on the following question: "How can we teach medical students to become physicians without them having the opportunity to touch a patient?" It is felt that in our collective experience this notion is unrealistic. Yet, given the COVID-19 pandemic, with its ongoing tumultuous associations, we have stepped into challenges surrounding such questions that were otherwise beyond our comprehension.

Many medical school curriculums across the globe were faced with similar challenges in looking at facilitating transitions to distance-education where curriculum delivery took on the form of remote, virtual, synchronous, and asynchronous deliveries. Innovations and re-imaginative processes were suddenly thrust into our planning and strategy. The rapidity with which these aspects needed to reach a form of implementation was something many have not experienced. The Kansas City University College of Osteopathic Medicine (COM) was faced with the task of realigning our curriculum to maintain the goal of optimal medical education delivery during the pandemic while addressing needs across all programmatic phases of our institution.

Beyond our concerns in augmenting our didactic activities to distance-learning formats, we realized the enormous need to align our simulation-based activities given the importance of "in-person"

and "hands-on" modalities that defined our norms at the time. Faculty derived questions such as, "How do we move our present activities to provide meaningful remote activities that propagate learning within clinical skills development?" We likewise sought to construct appropriate assessments in determining clinical skills performance within remote environments. How would our assessments need to be developed as we transitioned to remote, or virtual, environments?

The purpose of this project was to consider ways the current simulation-based activities could be augmented through VR simulation. The intent was to consider developing VR with implementation not only in the pre-clinical years, but for those in clinical clerkship rotations as well. With the pandemic, we saw students pulled out of their clerkships putting them in a position whereby they were unable to continue their journey with real patient experiences. Our pre-clinical students were placed in a distance format where the usual clinical skills development involving direct contact with standardized patients became a Zoom room of activities promoting their development- without ever touching a patient.

Additional challenges surrounded our ability to establish standardized assessments which would appropriately identify performance outcomes and competencies throughout our entire program. These assessments are integral to the functionality of the virtual reality simulation as we worked to integrate all our simulation-based activities.

Approach

Our move to develop the VR project was based on a needs assessment where we partnered with Oxford Medical Simulation (OMS) in providing a virtual reality simulation platform. This commercial entity allowed for integration of VR scenarios with options allowing for VR headsets as a potential immersion experience. Once constructing a plan of deliverable elements, it was decided to pilot the OMS platform to objectively establish student responses as we felt integrating an activity that propagated student engagement would be paramount in continuing skills development.

The Scenario

It is useful to understand how these VR experiences are conducted as we compare its utility with real-world patient experiences. Remember, the students need to have a clinical experience that will simulate a live patient encounter since they are not able to be in front of an actual patient. Playing the role of a medical student takes us to our computer or laptop. We log in to the system and once loaded, we choose our assigned scenario. The screen changes to a clinical setting, commonly based in an Emergency Room bay. A nurse approaches you and explains they have triaged a patient who is febrile and does not look well. You move to the bedside and click on the patient's head which opens a communication pick list giving options for questions that can be asked of the patient. You choose to ask them "How are you feeling?" The patient responds with some mumbled words where they basically ask where they are. You then turn to the nurse and click to bring up a menu for nursing tasks such as placing the patient on a monitor to obtain vital signs while choosing the task to start a peripheral IV and start a normal saline bolus at 500 ml/hr. You ask for an electrocardiogram and basic laboratory samples for complete blood count, comprehensive metabolic panel, lactate level, and a urinalysis. Additionally, you ask for a point-of-care glucose since you recognize the patient has altered mentation.

Having set up these tasks, you move to the computer in the room and click to pull up the patient's electronic medical record where you find they have a diagnosis of testicular cancer and type I diabetes mellitus. The home medications are reviewed, and you find the patient has just finished a round of chemotherapy one week prior.

As you turn back to the monitor, you realize the patient has a temperature of 101.3 °F (38.5° C) and displays tachycardia and tachypnea. It is decided you want to perform an initial physical exam by clicking on the patient's chest where a menu comes up allowing you to choose the system you wish to examine. The platform will then give you heart and lung sounds as you listen. As you palpate and inspect, the platform verbalizes those findings as they are examined.

By this time, you can go back to the computer and pull up the laboratory results ordered. The patient has leukopenia, acute kidney injury, and an elevated lactate level of 4.0 mEq/L. You are concerned for sepsis; thus, in going back to the computer you navigate to guidelines in treating sepsis and find a list of appropriate antibiotics. You choose the antibiotics you want given and the nurse responds, "Those medications have been given."

At this point, available options are to order diagnostic imaging such as a chest x-ray while you can update the nurse on your plan as well as choosing to discuss things with the family. There is an option to call the attending and report on the patient's presentation and receive further guidance as necessary.

As you come to a point where you exit the room, the platform takes you to a reflection phase where you, as the medical student, can evaluate the experience. Once that is complete, the scenario goes into a debriefing mode where



Learning Objectives

Diagnosis

Neutropenic sepsis and penicillin allergy

Case Summary

Acutely septic patient, immunocompromised due to chemotherapy. Penicillin allergic.

Clinical Findings

- Tachycardic, tachypneic, hypotensive, hypoxic
- Neutropenic, lactate > 4
- No clear source of sepsis identifiable

Technical Skills

Assessment
- Perform ABCDE assessment
- Take a focused patient history

Initial Investigations
- Take blood tests
- Take blood gas (for lactate)
- Order and review a urine dip
- Request and review chest X-ray
- Take blood cultures

Management
- Deliver oxygen to maintain saturations over 94%
- Start appropriate IV fluid resuscitation
- Administer appropriate IV antibiotics
- Commence appropriate urine output monitoring

Non-technical Skills
- Make rational, timely clinical decisions
- Effectively communicate with patient and team
- Appropriately utilize other team members
- Maintain patient safety and comfort

Figure 1. Technical and Non-Technical Tasks

you can see the objectives for the scenario giving the clinical summary involving neutropenic fever and sepsis. Figure 1 illustrates the important technical and non-technical tasks that you should have performed during the experience (Figure 1).

After reviewing the scenario, you move down the page to your performance scores. The platform gives you a green checkmark for those things you addressed appropriately while adding a red checkmark for the tasks you missed. There is an option to click on each performance task where you can review rationales and references as to why these items are important.

Phased Implementation

To provide a structured environment in which to implement this activity, we developed three phases to move toward effective curriculum integration with our simulation-based activities. Phase I consisted of introducing the scenarios to our second-year clinical medicine curriculum by choosing three scenarios per semester. The initial scenarios were implemented using student reflective responses while monitoring performance metrics. We experienced some degree of hesitation in that many of the scenarios were developed for residency-level training. With that in mind, we developed pre-session fact sheets for the students to review along with a platform orientation given its technical elements in navigating the scenario environment. The VR scenarios were made available through asynchronous learning via the web-based OMS platform.

Phase II added formal synchronous faculty-facilitated simulation debriefing sessions in small group remote environments to explore student recognition of learning gaps through metacognitive aspects while continuing individual reflective processes associated with each scenario experience.

Phase III will serve to define how the VR platform can be utilized outside of the second year, which is especially important to our third- and fourth-year programming with students in clinical rotations. Delivering clinical education in a distributive model, where our students are positioned all over the nation, serves as a driving force in providing those standardized processes in assessments, outcome designations, and performance levels in formulating objective evaluation of clinical skills throughout our curriculum.

Results

The focus of Phase I included student reflective responses about their experiences as they worked through the assigned scenarios. We were able to collate performance data from the OMS platform which served to identify overall student progress based on algorithmic results tied to various tasks required for completion within each scenario as described above. The thematic representations brought out student responses such as “stress,” “think,” “learn,” and “good.”

We stated previously that our intent was to create a simulation-based activity that would meet expectations of learners and establish appropriate learning environments with elements that would propagate student motivation. In comparing the overall student satisfaction, we realized a progressively positive approval rating between our first and last scenario experience within the first semester (Figure 2).

Performance metrics were evaluated in stages of first and second attempts. It was felt there were issues with navigating the virtual platform whereby students had to learn where various resources were located within the environment. To determine issues with performance results, we elected to appraise the various attempts for purposes of evaluating the activity regarding further development, delivery, and assessment.

The means of the performance metrics were established through the OMS platform in our overall data retrieval. The scenario outcomes were graded through scenario specific items required in each case related to history-taking, treatment, and diagnosis. These tasks required transfer of biomedical knowledge, processes in critical-thinking and problem-solving, and medical decision-making for successful completion. Students could work through the scenario as often as they desired which we felt would take

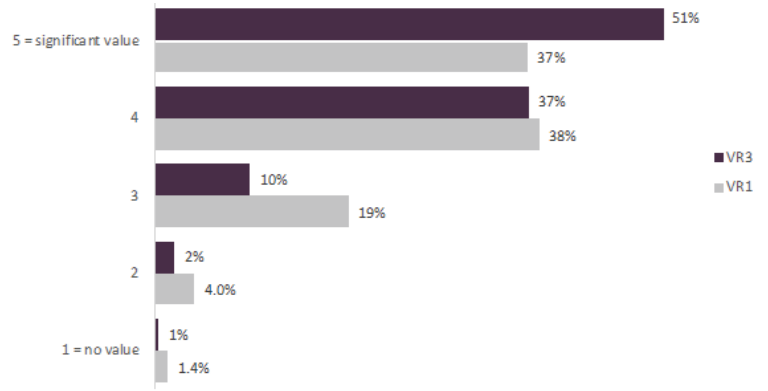


Figure 2. A progressively positive approval rating is illustrated between our first and last scenario experience within the first semester.

the form of deliberate practice and cognitive assimilation. The overall scores in the first, second, and third VR scenarios were 61%, 74%, and 77% respectively. In review of these scores, we were able to assess areas of performance within the second year with plans to extrapolate these outcomes for our third- and fourth-year experiences. Future development will likely involve constructing our own scenarios whereby appropriate competency-level learning can be highlighted.

Phase II of our project is not yet completed at the time of this paper; however, preliminary comparisons have been noted between the overall mean scores for those scenarios completed in the first and second semesters showing an average of successful performance of 66% in the first semester with 79% in the second semester.

In performing a two-tailed t-test of the means comparing our first semester performance scores with those from the second semester, there was significance with a t value equal to 1.96 ($p = 0.004$). While this shows positive progression, the significance related to improvement in competencies has yet to be determined. Our intent is to further define the data points related to individual tasks to make determinations of specific competencies and their performance levels.

Conclusions

Our goal in this project was to identify activities that would engage pre-clinical simulation through asynchronous virtual reality (VR) case scenarios. The intent was to provide additional resources whereby competencies could be more defined through performance metrics and standardized assessments additive to our established simulation-based curriculum throughout all curricular phases. We chose to integrate the virtual reality simulation through a pilot study into the curricular programming and obtain student responses. Given our student-centered approach, it was felt the VR activity would be a positive addition for student learning during transitioning to distance-learning formats due to the COVID-19 pandemic. To evaluate the VR simulation piece within our current simulation-based activities, we integrated the VR simulation platform into our existing second-year clinical medicine course to further assess and evaluate potential learning enhancements in a controlled environment. The impetus relates to how this activity could then be used in other phases of our curriculum, specifically as it relates to students rotating through clinical clerkships.

The pandemic experience has required creative thinking and innovations in how we deliver medical education. Faculty felt that more robust simulation activities using VR simulation would allow for greater opportunities in clinical skills development, and additional meaningful and effective assessment tools for outcome measures throughout the COM.

Our initial data shows preliminary favorable outcomes. Outcomes will need to be assessed through data mining related to individual competencies. Further development of the virtual reality simulation will require development of specific tools that allow for accurate assessment and evaluation of performance levels and their associated learning dynamics.

Bibliography

- Andersen, S. A. W., Mikkelsen, P. T., & Sorensen, M. S. (2020). The Effect of Simulator-Integrated Tutoring for Guidance in Virtual Reality Simulation Training. Simul Healthc, 15(3), 147-153. https://doi.org/10.1097/SIH.0000000000000414
- Boursicot, K., Kemp, S., Wilkinson, T., Findyartini, A., Canning, C., Cilliers, F., & Fuller, R. (2020). Performance assessment: Consensus statement and recommendations from the 2020 Ottawa Conference. Med Teach, 1-10. https://doi.org/10.1080/0142159X.2020.1830052
- Bracq, M. S., Michinov, E., & Jannin, P. (2019). Virtual Reality Simulation in Nontechnical Skills Training for Healthcare Professionals: A Systematic Review. Simul Healthc, 14(3), 188-194. https://doi.org/10.1097/SIH.0000000000000347
- Mateen, M., & Kan, C. Y. P. (2020). Education during COVID-19: Ready, headset, go! Clin Teach. https://doi.org/10.1111/tct.13266
- Pottle, J. (2019). Virtual reality and the transformation of medical education [Journal]. Future Health Care Journal, 6(3), 181-185.
- Schuwirth, L. W., & Van der Vleuten, C. P. (2011). Programmatic assessment: From assessment of learning to assessment for learning. Med Teach, 33(6), 478-485. https://doi.org/10.3109/0142159X.2011.565828
- Tabatabai, S. (2020). COVID-19 impact and virtual medical education. J Adv Med Educ Prof, 8(3), 140-143. https://doi.org/10.30476/jamp.2020.86070.1213

Disclosure

None reported. **MM**

It Is Time for an Oil Change: Polyunsaturated Fatty Acids and Human Health

by Natalie Powell, Suman Chaudhary, MS & Asma Zaidi, PhD

Long chain PUFAs such as EPA and DHA are worth mentioning because of their direct influence in the immunological response to viral infections such as COVID-19.



Natalie Powell is a medical student at Kansas City University College of Osteopathic Medicine (KCU-COM). Suman Chaudhary, MS, is a Research Associate at KCU-COM, and Asma Zaidi, PhD, (above), is Vice Chair of Basic Sciences and Professor of Biochemistry at KCU-COM, Kansas City Campus, Kansas City, Missouri.

Abstract

Polyunsaturated fatty acids (PUFAs) such as docosahexaneoic acid (DHA) and eicosapentaneoic acid (EPA), play a critical role in a variety of neuronal functions, including facilitating neuronal growth and differentiation, increasing the density of the neuritic network, modulating cell membrane fluidity, regulating intracellular signaling and gene expression, and exhibiting antioxidant characteristics. Dietary DHA is selectively enriched and actively retained in the central nervous system, mainly in synaptic membranes, dendrites, and photoreceptors. In this review, we highlight the myriad roles of PUFAs in brain function and human health. Diets rich in DHA are inversely proportional to cognitive decline and incidence of neurodegenerative disorders. Conversely, diets deficient in DHA impair the proper development of brain and the visual system in children and increase risk of brain disorders in the elderly. Finally, DHA and EPA have been shown to reduce inflammation and may prove to be beneficial in reducing the severity of the SARS-COVID infection.

Introduction: Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are required for optimal human health and wellbeing. PUFAs are classified by the position of the first double bond in a fatty acid counting from the methyl end. There are two major classes of PUFAs: omega-6 fatty acids (first double bond is at the sixth carbon from methyl end) and omega-3 fatty acids (first double bond is at the third carbon from methyl end). PUFAs are derived from essential fatty acids (EFA) such as linoleic acid (LA) and alpha-linolenic acid (ALA), fatty acids that cannot be synthesized in the body and need to be ingested through diet. The parent omega-6 fatty acid, LA is desaturated in the body to form arachidonic acid while parent omega-3 fatty acid ALA is desaturated by a microsomal enzyme system to form DHA and EPA. However, there is a limited metabolic capability in humans for this conversion underscoring the need for their inclusion in diet.

PUFAs and Brain Health

EFAs and PUFAs and their metabolic products play a critical role in the maintenance of

structural and functional integrity of the central nervous system and retina.[1] Extensive research has shown their crucial role in maintaining neuronal homeostasis. PUFA's exert their effects through modulating the fluidity of the neuronal membrane, regulating signal transduction, promoting neurite outgrowth, and impacting the function of key ion channels and receptors.[2] DHA has also been shown to influence cell membrane fluidity by promoting signaling interactions between macromolecules to form lipid rafts: cholesterol and sphingolipid-enriched microdomains in the plasma membrane, known to serve as local sites for housing signaling proteins, and orchestrating key signaling processes.[3] The most extensively studied PUFA is the omega-3 fatty acid called DHA.[2] This is the most abundant fatty acid in the brain and is a structural component of the neuronal membrane. DHA plays a critical role in neuronal growth and differentiation, neuronal signaling, synthesis of bioactive mediators, synaptic plasticity, and remodeling of the neuritic network.[4] Diets high in DHA are inversely proportional to cognitive decline and the onset of neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.

As mentioned above, DHA (22:6 n-3) is a product of ALA, an essential fatty acid that must be obtained from the diet. There is a significant body of evidence showing that a high (n-3):(n-6) dietary intake ratio, such as in the Mediterranean diet, has widespread positive health effects.[5] Mediterranean diets have lower intakes of added sugar, saturated fat, trans-fat, lower glycemic index, and a lower ratio of (n-6):(n-3) fatty acids. This type of diet appears to reduce risk for Alzheimer's disease and other forms of dementia. Additionally, a Mediterranean diet includes most of the nutritional components important for lowering risk for cardiovascular disease, hypertension, and type II diabetes.[6]

Western diets are low in omega-3 fatty acids, including ALA found mainly in plant oils, and DHA, which is found in fish. Epidemiological studies have linked low maternal DHA to increased risk of poor neural development in infants.[7] Dietary deficiency of n-3 fatty acids during fetal development *in utero* and postnatal state has shown negative effects on cognitive abilities and a loss of discriminative learning ability.[8] Intervention studies have shown that improving maternal DHA intake decreases the risk of poor visual and neural development in children. Sufficient evidence has concluded the occurrence of efficient transfer of DHA from mother to fetus before birth and during lactation after birth, with short and long-term implications for neural function. Most of the brain growth is completed by five to six years of age. It is recommended for pregnant and nursing women to take at least 2.6 g of omega-3 fatty acids and 100-300 mg of DHA daily to meet the needs of the fetus and suckling infant.[1] Follow-up studies have shown that infants of mothers who took supplements of EFAs and DHA have higher mental processing scores, eye-hand coordination, psychomotor scores, and stereo acuity at four years of age. Intake of EFAs and DHA during preschool years may have a beneficial role in prevention of attention deficit hyperactivity disorder and enhancing capability and academic performance.[1]

Although a good natural source of PUFAs is seafood, especially oily fish, one can obtain them via consuming fish oil capsules. Very long chain omega-3 fatty acids are readily incorporated from capsules into transport (blood lipids), functional (cell and tissue), and storage (adipose) pools.[9] At sufficient levels of incorporation, EPA and DHA influence the physical nature of cell membranes and membrane protein-mediated responses, increase the generation of bioactive lipids, and promote cell signaling and gene expression in many different cell types.[9] Through these mechanisms, they impact overall cellular homeostasis and modulate the cellular response to external signals. In most cases the effects seen are associated with improvements in disease biomarker profiles and health-related outcomes.[9] Given that the capacity

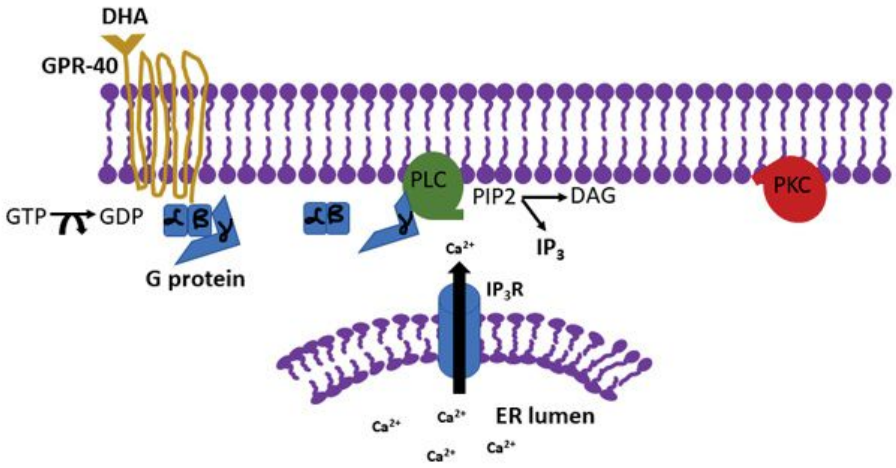


Figure 1. Mechanism of action of docosahexaenoic acid. Docosahexaenoic acid (DHA) binds to the G protein coupled receptor GPR-40 which leads to the activation of phospholipiase C (PLC), conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to form diacylglycerol (DAG) and inositol tris phosphate (IP3), which activates the IP3 receptor leading to the release of calcium from ER stores. The increase of intracellular Ca2+ activates protein kinase C (PKC) which leads to synaptogenesis
Adapted from Ma et al., 2010, DHA promotes the neuronal differentiation of rat neural stem cells transfected with GPR40 gene, Brain Research, 2010, 1330, 1 – 8.

of the human brain to synthesize DHA locally is appreciably low, the uptake of DHA from circulating lipid pools is essential to maintaining its homeostatic levels. Although, several plasma pools have been proposed to supply the brain with DHA, recent evidence suggests non-esterified-DHA and lysophosphatidycholine-DHA are the primary sources.[10] The uptake of DHA and its enrichment in the brain appears to be regulated by several complementary pathways associated with its metabolism. Following entry into the brain, DHA is esterified into and recycled amongst membrane phospholipids and converted to bioactive mediators which regulate signaling pathway important to synaptogenesis, cell survival, and neuroinflammation, and may be relevant to treating neurological diseases.[10]

Role of DHA in Neurite Formation in Brain

DHA is a critical component in the development of neurons and neurites in young mammals, since its peak concentration has been observed to be in the late gestational period.[11] However, it has been shown that DHA plays a critical role in the adult brain as well. DHA accounts for roughly 15% of the fatty acid content in the mature human brain, and it is believed that decreased levels can lead to cognitive decline and the onset of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.[4] Various studies have been done to unravel the precise mechanisms underlying the protective and proliferative properties of DHA in the brain. One study found the DHA to be an endogenous ligand for the G protein coupled receptor called GPR40, which is expressed in the hippocampus of adult monkeys, and was shown to be associated with neurogenesis after ischemia.[12] It is important to note that the hippocampus, an area of the brain critical for memory, is especially sensitive to changes in membrane fluidity, hence DHA levels are likely to have a more substantial impact in this region. Interaction of DHA with the GPR40 was found to be responsible for promoting neurogenesis and neuritogenesis. This effect was mediated through increase in intracellular Ca^{2+} which was released via activation of inositol tris phosphate receptor (IP3-R) (Figure 1). This finding implies that DHA, at least partially, acts through the IP3 receptor-mediated signaling.[12]

Role of DHA in Cognitive Decline

A significant body of literature supports the role of DHA in overall brain function, including neuronal growth and differentiation as well as optimizing neuronal signaling. Most data from human studies show its contribution

to optimal visual acuity development, an assertion supported by the presence of high amounts of DHA in rod outer segment membranes.[13] While DHA levels affect early brain development in infants, potential effects are also increasingly observed during adult life. Epidemiological studies support a link between low dietary intake of DHA and a higher risk of cognitive decline and onset of neurodegenerative and psychiatric disorders.[14] The primary insult from loss of DHA from membrane glycerophospholipids, is on the flexibility and fluidity of membrane lipids which in turn affects the optimal function of critical integral membrane proteins (receptors, voltage-gated ion channels and enzymes).[15] This leads to effects on second messenger systems, neurotransmitter release, and subsequent downstream cascade likely to have deleterious changes in brain and visual function. Many studies have also reported that dietary omega-3 deficiency results in changes in learning, coping with stress, behavioral changes, and responses in visual function.[13] Circulating plasma DHA is significantly related to cognitive abilities during aging, and is inversely associated with cognitive decline. A diet characterized by higher intakes of foods containing high levels of n-3 fatty acids, and/or lower intake of n-6 fatty acids is strongly associated with a lower incidence of Alzheimer's disease and other brain disorders. Supplementation of DHA improves some behaviors associated with attention deficit hyperactivity, bipolar disorder, schizophrenia, and impulsive behavior, as well as cognition.[8]

DHA, Inflammation, and COVID

Inflammation is a normal process that is a critical part of host defense and tissue healing. However, excessive and/or unresolved inflammation can lead to progressive tissue damage, disease, and pathology. Omega-3 fatty acids are generally considered anti-inflammatory, and different mechanisms that promote these effects have been elucidated. DHA exhibits antioxidant properties by decreasing the accumulation of reactive oxygen species (ROS) such as lipid peroxide *in vivo*, which may protect neurons from oxidative damage and hence prevent neuron loss. The omega-6 polyunsaturated fatty acid arachidonic acid (ARA) makes a significant contribution to the fatty acids present in the membrane phospholipids of cells involved in inflammation. ARA is a precursor to potent pro-inflammatory mediators including prostaglandins and leukotrienes. For this reason, many anti-inflammatory pharmaceuticals have been developed that target the ARA pathway to successfully control inflammation. There is also evidence that a high omega-6 fatty acid diet inhibits the anti-inflammatory and inflammation-resolving effect of omega-3 fatty acids.[16]

In the recent COVID-19 pandemic, a section of infected patients experienced a condition referred to as a "cytokine storm."[17] A full understanding of the cellular and molecular mechanisms underlying the "cytokine storm" has not yet been unraveled.[18] Recent articles suggest that specific nutrients such as vitamin B6, B12, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper may play a key role in the management of the cytokine storm.[19,20] Among these micronutrients, long chain PUFAs such as EPA and DHA are worth mentioning because of their direct influence in the immunological response to viral infections.[21,22] The possible beneficial effects of EPA and DHA supplementation in the modulation of immune response in SARS-CoV-2 infection is under investigation.[23,24,25,26,27,28] Among these complex immunomodulatory effects, interleukin-6 (IL-6) and interleukin-1β (IL-1β) have been shown to be affected by dietary EPA and DHA intake. In addition, poly (ADP-ribose) polymerase enzymes with anti-inflammatory properties translatable to human COVID-19 infection were shown to improve tissue levels of DHA and EPA and their downstream anti-inflammatory

metabolites,[29,30] further underscoring the applicability of DHA and EPA in the management of COVID-19. Neutralization of IL-6 via a monoclonal antibody (Tocilizumab) has been identified as a feasible therapeutic target in SARS-CoV-infections,[31] nevertheless, reducing the expression of additional proinflammatory cytokines (e.g., IL-1β, IL-38) may have additional therapeutic and protective effects.[32]

References

1. Singh, M., Essential fatty acids, DHA and human brain. Indian J Pediatr, 2005. 72(3): p. 239-42.
2. Yehuda, S., et al., The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. Neurobiol Aging, 2002. 23(5): p. 843-53.
3. Marin, R. and M. Diaz, Estrogen Interactions With Lipid Rafts Related to Neuroprotection. Impact of Brain Ageing and Menopause. Front Neurosci, 2018. 12: p. 128.
4. Ma, D., et al., DHA promotes the neuronal differentiation of rat neural stem cells transfected with GPR40 gene. Brain Res, 2010. 1330: p. 1-8.
5. Kan, I., et al., Docosahexaenoic acid and arachidonic acid are fundamental supplements for the induction of neuronal differentiation. J Lipid Res, 2007. 48(3): p. 513-7.
6. Cole, G.M., Q.L. Ma, and S.A. Frautschy, Dietary fatty acids and the aging brain. Nutr Rev, 2010. 68 Suppl 2: p. S102-11.
7. Innis, S.M., Dietary omega 3 fatty acids and the developing brain. Brain Res, 2008. 1237: p. 35-43.
8. Mallick, R., S. Basak, and A.K. Duttaroy, Docosahexaenoic acid,22:6n-3: Its roles in the structure and function of the brain. Int J Dev Neurosci, 2019. 79: p. 21-31.
9. Calder, P.C. and P. Yaqoob, Understanding omega-3 polyunsaturated fatty acids. Postgrad Med, 2009. 121(6): p. 148-57.
10. Lacombe, R.J.S., R. Chouinard-Watkins, and R.P. Bazinet, Brain docosahexaenoic acid uptake and metabolism. Mol Aspects Med, 2018. 64: p. 109-134.
11. Uauy, R., et al., Essential fatty acids in visual and brain development. Lipids, 2001. 36(9): p. 885-95.
12. Ma, D., et al., Expression of free fatty acid receptor GPR40 in the neurogenic niche of adult monkey hippocampus. Hippocampus, 2008. 18(3): p. 326-33.
13. Sinclair, A.J., Docosahexaenoic acid and the brain- what is its role? Asia Pac J Clin Nutr, 2019. 28(4): p. 675-688.
14. Lauritzen, L., et al., DHA Effects in Brain Development and Function. Nutrients, 2016. 8(1).
15. Bazan, N.G., Docosanoids and elovanoids from omega-3 fatty acids are pro-homeostatic modulators of inflammatory responses, cell damage and neuroprotection. Mol Aspects Med, 2018. 64: p. 18-33.
16. Innes, J.K. and P.C. Calder, Omega-6 fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids, 2018. 132: p. 41-48.
17. Mehta, P., et al., COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet, 2020. 395(10229): p. 1033-1034.
18. Tisoncik, J.R., et al., Into the eye of the cytokine storm. Microbiol Mol Biol Rev, 2012. 76(1): p. 16-32.
19. Muscogiuri, G., et al., Nutritional recommendations for CoVID-19 quarantine. Eur J Clin Nutr, 2020. 74(6): p. 850-851.
20. Grant, W.B., et al., Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients, 2020. 12(4).
21. Calder, P.C., et al., Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. Nutrients, 2020. 12(4).
22. Messina, G., et al., Functional Role of Dietary Intervention to Improve the Outcome of COVID-19: A Hypothesis of Work. Int J Mol Sci, 2020. 21(9).
23. Tao, L., Oxidation of Polyunsaturated Fatty Acids and its Impact on Food Quality and Human Health. Advances in Food Technology and Nutritional Sciences - Open Journal, 2015. 1(6): p. 135-142.
24. Calder, P.C., n-3 fatty acids, inflammation and immunity: new mechanisms to explain old actions. Proc Nutr Soc, 2013. 72(3): p. 326-36.
25. Calder, P.C., Immunomodulation by omega-3 fatty acids. Prostaglandins Leukot Essent Fatty Acids, 2007. 77(5-6): p. 327-35.
26. Allam-Ndoul, B., et al., A Study of the Differential Effects of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) on Gene Expression Profiles of Stimulated Thp-1 Macrophages. Nutrients, 2017. 9(5).
27. Maskrey, B.H., et al., Emerging importance of omega-3 fatty acids in the innate immune response: molecular mechanisms and lipidomic strategies for their analysis. Mol Nutr Food Res, 2013. 57(8): p. 1390-400.
28. Zivkovic, A.M., et al., Dietary omega-3 fatty acids aid in the modulation of inflammation and metabolic health. Calif Agric (Berkeley), 2011. 65(3): p. 106-111.
29. Curtin, N., et al., Repositioning PARP inhibitors for SARS-CoV-2 infection(COVID-19); a new multi-pronged therapy for acute respiratory distress syndrome? Br J Pharmacol, 2020. 177(16): p. 3635-3645.
30. Kiss, B., et al., Poly(ADP) ribose polymerase-1 ablation alters eicosanoid and docosanoid signaling and metabolism in a murine model of contact hypersensitivity. Mol Med Rep, 2015. 11(4): p. 2861-7.
31. Liu, B., et al., Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun, 2020. 111: p. 102452.
32. Conti, P., et al., Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents, 2020. 34(2): p. 327-331.

Acknowledgment

This project was funded by KCU's Summer Student Research Fellowship. The author would like to thank all the contributors to the original work described in this review.

Disclosure

None reported.

MM

Exploring the Influence of a Pandemic on Medical Education

by Mariam Akhtar, MD

In the event of another critical wave of the COVID or other new respiratory transmitted virus, many of the recently adapted methods can be used to bridge the gap for clinical education if students are once again quarantined.



Mariam Akhtar, MD, is Assistant Professor, Primary Care-Joplin Campus, Kansas City University College of Osteopathic Medicine, Joplin, Missouri.

Abstract

A shift occurred in medical school education due to the novel coronavirus disease-19 (COVID-19) pandemic. It has been more than a year since the start of the pandemic, and many medical schools have had to adapt quickly. The medical school curriculum had to be changed in order to accommodate the risk of the virus, which has caused an interruption in clinical education for both preclinical and clinical medical students. Limited hands-on labs, remote standardized patient encounters, telemedicine education and other substitutes have been used to bridge this gap within in-person learning. This review discusses the changes in curricula that some schools have taken, and the benefits and disadvantages of these selected methods.

Introduction

The novel coronavirus disease-19 (COVID-19) has changed life in many ways all over the world. It has especially provided a challenge for the healthcare industry, and demonstrated how quickly this system can become overwhelmed by a pandemic. The future of healthcare rests with medical students as they are future medical workforce. However, the COVID-19 pandemic has had a significant impact on the usual path medical students obtain technical and clinical skill levels, and forced medicals schools to re-imagine how training should appear. While this has propelled innovations, such as, remote/virtual learning and telemedicine, it also has had detrimental effects on hands-on medical training with possible long-term consequences.

This article will present examples of the innovations and adaptations that have occurred as a result of COVID-19 for both preclinical and clinical students and discuss the benefits and pitfalls of these decisions. It will also discuss how medical school preclinical faculty and clinical faculty have changed their methods of teaching through this pandemic. For the purposes of this article, virtual and remote will be used interchangeably.

Preclinical Students

When the pandemic first began, preclinical students were plunged into complete-remote learning systems. In the early months of the pandemic, on-campus and live lectures were immediately turned into



During the pandemic, some medical schools changed their curriculum to implement remote/virtual standardized patient encounter to simulate patient encounters as telemedicine or telehealth.

remote lectures, prerecorded lectures, voiced over powerpoint presentations, and small group interactive sessions.[1,2,3] Gross anatomy turned into video dissections performed by faculty and observed by students remotely.[4] With the shock of this sudden transition, faculty and staff scrambled to make this new learning environment work. Faculty and staff were forced to become familiar with web-based platforms (i.e. Zoom, Microsoft Teams, etc.) in order to interact for day to day operations between teaching staff and to deliver education to the students. For some, this was an easy shift, but for others it was a steeper learning curve.[5] There was also an increased need for equipment for both students and faculty such as headsets, laptops, and other equipment, which may have been an extra financial burden.[4]

Although lectures were easily able to shift into remote delivery, clinical courses and skills did not have as smooth of a transition. It was observed that some clinical knowledge could be taught using these remote methods, but students were lacking hands-on training, such as physical exam and other clinical skills. As the pandemic wore on, many schools attempted to rectify this deficiency in hands-on education by implementing in-person physical exam labs. These activities came at a steep monetary and time cost. To mitigate risk and to keep students safe, these in-person activities required smaller groups of students, COVID-19 testing for students and faculty, N95/KN95 masks, goggles, social distancing and faculty monitoring the interaction within that setting. These activities also required more faculty time due to the size limitation of the cohorts who could interact at any given time. This also limited the practice of certain physical exams to reduce risk of virus transmission, such as, deferring oral or nasal exams on standardized patients, and instead using task trainer-based practice for those types of exams.

Some medical schools also changed their curriculum to implement remote/virtual

standardized patient (SP) encounter to simulate patient encounters as telemedicine or telehealth.[5,6] Standardized patients were trained to interact with students remotely. This required these SP to have good internet access, have a good working knowledge of web-based platforms, and have a high comfort level using this form of technology. Students were required to obtain a history and verbalize the physical exam or instruct SPs to perform certain physical exam maneuvers, if possible. By using these remote encounters, student continued to develop their humanism skills, history-taking skills, and also allowed early exposure to telemedicine/telehealth. Other methods such as virtual reality case based simulation were also implemented by some (See article, Tyler, et al., "Innovations through Virtual Reality Simulation" in this issue). Although these methods were not ideal student and patient encounters, this did fill some of the gaps in the students' skills development. They allowed students to continue to learn how to develop differential diagnosis and practice clinical and technical skills in preparation for their clinical years.

Adapting clinical skills training were not the only obstacles medical students faced during this rapid shift to remote learning during the pandemic. During the early adaptation to the remote curriculum, many students went back home (with family) whereas others stayed where they were to continue their education. For some, this created a comfortable and familiar environment to study, but for others it created some disadvantages. Learning from home created a distraction if there were other family members or children present due to lack of child care. Some had stressors such as feeling of isolation, stress over finances, unreliable internet access, or inadequate access to digital devices.[7]

As the pandemic continued, freshly accepted first-year medical students started their introduction into medicine and second-year students returned back to remote lectures. First-year students were interviewed virtually before acceptance to medical school. Orientation was also virtual with attempts to do virtual ice breakers and student bonding with help of faculty and staff. Due to the very restricted student interaction through remote learning and some possible limited onsite labs, students may have had the same feeling of isolation as earlier in the pandemic. For some students, this isolation translated into anxiety and depression.[4,7] For others with preexisting mental health issues, this was an added stressor to already stressful environment of a pandemic and medical school. This caused decreased morale as they did not have the feeling of camaraderie that usually comes with being familiar with your classmates. To remedy this, some students formed remote groups and found ways to message each other to provide support. Some schools provided remote access to school psychologists and other mental health providers. In other instances, students individually sought out help via telemedicine mental health providers or remote cognitive behavior therapy.[4]

Clinical Students

Third- and fourth-year students in their clinical years were taken out of clinics and hospitals early during the pandemic to reduce risk of infection, decrease risk of transmission of the virus, and due to shortages of personal protective equipment (PPE).[5] Some clinical faculty and other teaching clinicians were also required to focus on the influx of sick patients and devote more time to patient care in general during the pandemic, and therefore were unable to dedicate time for strictly educating medical students or other learners. This raised concerns from both students, medical school faculty and accrediting bodies. There were many worries that this group of students would not be able to develop and practice the skills they learned during their preclinical years.[4] Due to this removal from the clinical setting, it appeared as though students may not have had sufficient exposure to clinical practice, and they now lacked face to face patient interaction.[4,6] Initially, like their preclinical counterparts, these third- and fourth-year medical students were given a remote education. This entailed completing online modules, virtual reality simulations, review assigned cases in web-based case banks, following patients in remote electronic medical records (EMR) and attending remote lectures.[6] The online modules and case banks helped students develop their differential diagnosis skills. Remote lectures were in the form of remote grand rounds, remote morning reports, or remotely

listening to faculty discuss patient presentation.[6] Students were also able to participate in the remote standardized patient encounter to simulate telemedicine/telehealth.

During the pandemic, telemedicine or telehealth became a necessity for most clinic-based practice. United States Department of Health and Human Services (HHS) delineates telehealth or telemedicine as healthcare delivered with the use of electronic information and telecommunications technologies for communication between patient and provider when face to face encounter cannot take place.[6] This is broad definition for interaction with patient using various forms of this type of technology.[6] For some patients, especially those without internet access or smart phone, this can be a phone call interaction with the clinician. For other patients this can mean using a web-based platform via computer, laptop, smart phone or other digital device (i.e. ipad, tablet, etc.) to do a video based telemedicine interaction with clinician.[5,6] Some clerkship faculty helped bridge the clinical gap by allowing students to also participate in telemedicine to a limited extent.[1, 5, 6]

In some settings, telemedicine was a learning opportunity for both the clinical faculty and the student. Although this was a good alternative to a face to face visit, there are some cons including patient privacy concerns, limited physical exam, no way to obtain vital signs, and risks of poor outcome if the reason for the visit was an urgent or emergent issue.

As the pandemic became controlled in the United States, and PPE became more readily available, students in their clinical years have cautiously entered back into clinics and hospitals. With development and release of the vaccine to healthcare workers and adults, students have now started to see patients again and fully interact with clinicians. For preclinical students, medical schools are cautiously allowing students to return to campus and have established a new normal of mask wearing and taking other necessary precautions. The larger educational events such as lectures, grand rounds, and journal clubs continue to remain remote to mitigate exposure for events with larger attendance.

Conclusion

There were many things learned from the quick adaptation of medical schools to a remote/virtual curricula. Medical schools anticipate continuing some of these learning modifications in the curriculum after the pandemic. In the event of another critical wave of the COVID or other new respiratory transmitted virus, many of the recently adapted methods can be used to bridge the gap for clinical education if students are once again quarantined. Virtual reality case simulations may continue to supplement the development of clinical and technical skills with standardized patients. Telemedicine with standardized patients for preclinical students and telemedicine with clinical students may continue in clinical education. The long-term outcome of these change in medical education on student's abilities to practice medicine and care for patients is currently unknown. Residency program directors will most likely be the first to observe these graduates clinical knowledge and skills as these medical students move on to residency and practice.

References

1. Cairney-Hill J, Edwards AE, Jaafar N, Gunganah K, Macavei VM, Khanji MY. Challenges and opportunities for undergraduate clinical teaching during and beyond the COVID-19 pandemic. Journal of the Royal Society of Medicine. 2021;114(3):113-116.
2. Vollbrecht PJ, Kirsten A. Porter-Stransky, and Wendy L. Lackey-Cornelison Lessons learned while creating an effective emergency remote learning environment for students during the COVID-19 pandemic Advances in Physiology Education 2020 44:4, 722-725.
3. Hilburg R, Niralee Patel, Sophia Ambruso, Mollie A. Biewald, Samira S. Farouk, Medical Education During the Coronavirus Disease-2019 Pandemic: Learning From a Distance, Advances in Chronic Kidney Disease, Volume 27, Issue 5,2020, Pages 412-417.
4. Sharma D and Bhaskar S (2020) Addressing the Covid-19 Burden on Medical Education and Training: The Role of Telemedicine and Tele-Education During and Beyond the Pandemic. Front. Public Health 8:589669. doi: 10.3389/fpubh.2020.589669.
5. Jumreornvong O, Yang E, Race J, Appel J. Telemedicine and Medical Education in the Age of COVID-19. Acad Med. 2020 Dec;95(12):1838-1843.
6. Franklin, G.; Martin, C.; Ruszaj, M.; Matin, M.; Kataria, A.; Hu, J.; Brickman, A.; Elkin, P.L. How the COVID-19 Pandemic Impacted Medical Education during the Last Year of Medical School: A Class Survey. Life, 2021, 11, 294.
7. Stoller JK, A Perspective on the Educational "SWOT" of the Coronavirus Pandemic, Chest, Volume 159, Issue 2, 2021, Pages 743-748.

Disclosure

None reported. **MM**

Osteopathic Manipulative Treatment as an Intervention to Reduce Stress, Anxiety, and Depression in First Responders: A Pilot Study

by Christena Abraham, BS, Shelly N.B. Sloan, MS, Charles Coker, BS, Blair Freed, BS, Matthew McAuliffe, BS, Halden Nielsen, BA, Tanner Riscoe, BS, Robert Steele, MS, Andrew Dettwiler, BS, Gia Oberley, BS, Kenneth Zaremski, DO, Kelley Joy, DO, Andi Selby, DO, Ree Wells-Lewis, PhD & Bradley A. Creamer, PhD



Christena Abraham, BS, Charles Coker, BS, Blair Freed, BS, Matthew McAuliffe, BS, Halden Nielsen, BA, **Tanner Riscoe, BS**, Robert Steele, MS, and Andrew Dettwiler, BS, are medical students at Kansas City University College of Osteopathic Medicine (KCU-COM). Shelly N.B. Sloan, MS, is a Research Associate at KCU-COM. Gia Oberley, BS, is an undergraduate student at Missouri Southern State University in Joplin. Kenneth Zaremski, DO, is an Assistant Professor in the Department of Osteopathic Manipulative Medicine, Kansas City Campus of KCU-COM. Kelley Joy, DO, is Vice Chair of Osteopathic Manipulative Medicine, Joplin Campus of KCU-COM. Andi Selby, DO, is an Assistant Professor in the Department of Osteopathic Manipulative Medicine, Joplin Campus of KCU-COM. Ree Wells-Lewis, PhD, is a Professor in the Department of Social Sciences, Missouri Southern State University in Joplin. Bradley Creamer, PhD, (above), is an Associate Professor in the Department of Basic Sciences, Joplin Campus of KCU-COM.

Abstract

In this pilot study, we examined the efficacy of Osteopathic Manipulative Treatment (OMT) for improving symptoms of stress, anxiety, and depression (SAD) to determine a correlation between overall improvement in health and quality of life for first responders. Participants received weekly OMT or sham OMT targeting autonomic imbalance. Indicators of SAD were examined pre- and post-study. Overall, this pilot study suggests improvement in both the social-psychological (mental) self-assessments, and alterations in SAD-associated biomarkers from OMT.

Introduction

Recent data has shown that at least 30% of first responders in the United States will develop behavioral health conditions such as SAD.[1] Traumatic events such as death, serious injury, and violence are at higher prevalence in these fields when compared to other civilian professions and put personnel at an increased risk for experiencing poor physical and mental health. Of the most notable psychological consequences from repeated exposure to traumatic events is the development of serious stress, anxiety, and/or depression that can sometimes lead to Post-traumatic Stress Disorder (PTSD).[2] In fact studies have shown law enforcement officers to develop PTSD at rates ranging from 6-32%, EMT/paramedics ranging from 9-22% and firefighters with rates of 17-32%, whereas adults in the United States typically range from 7-12%.[3] Such large ranges in rates would suggest other third-variable risk factors are at play such as, within groups — at the individual level and between groups — at the level of occupation type. Regardless of these other variables, first responders should be considered a special population at an increased risk for developing even mild to moderate mental health disorders, including stress and anxiety. In addition to PTSD, first responders are also at greater risk for developing depression, substance abuse, and suicide ideation and attempts.[4] A 2017 survey of more than 4,000 first responders found that 6.6% had attempted suicide, which is more than 10 times the rate in the general population.[5] Additionally, a 2016 study has shown that amongst

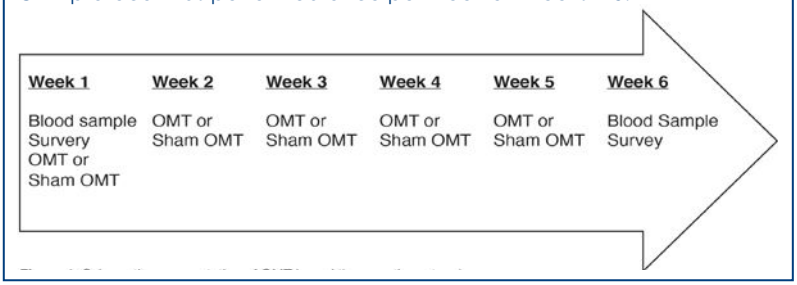
34 first responders who completed biological and psychological evaluations, 18% (n=6) met criteria for anxiety, 47% (n=16) met criteria for depression and 33% (n=12) met criteria for PTSD.[6] While there is some success for treatment with efficacious, evidence-based therapies, current treatments are associated with either nonresponse, or high rates of dropout.[7-9] As such, there is a tremendous need for the development of comprehensive interventions which aim to relieve the allostatic load in first responders.[10]

Since mental stress can cause measurable musculoskeletal tension, the concept of using OMT as a therapy to alleviate such symptoms has been examined.[11, 12] Osteopathic manipulative treatment is targeted to treat somatic dysfunction—the impaired or altered function of related components of the body framework system: skeletal, arthrodial, and myofascial structures, and their related vascular, lymphatic, and neural elements (*Glossary of Osteopathic Terminology*). Stress may result in segment facilitation demonstrated as exaggerated muscle tension. The reduction in muscular tension through the use of OMT may reciprocally reduce emotional stress by shifting the balance of sympathetic and parasympathetic systems to a more parasympathetic/relaxed state and could therefore benefit the mental health of those who are dealing with stress, anxiety, and depression resulting from their profession. To date, there have been only a few studies investigating the effectiveness of OMT in patients experiencing stress, anxiety, and/or depression. Nevertheless, it seems logical that OMT could benefit these patients.

It is known that emotional and physical stress can induce a physiological response in the human body that allows us to adapt and respond to that stress. Chronic exposure to stress can lead to maladaptive alterations in stress response, hormone levels, and many other physiological processes in response to the increased allostatic load. Recent data suggests that stress, anxiety, and depression can alter the levels of serum inflammatory biomarkers such as interleukins, in addition to a number of hormones.[13, 14] In a state of stress, the body shifts to a sympathetic dominant state with relative increased sympathetic activity and decreased parasympathetic activity. When a person experiences chronic stress, there will be elevated levels of catecholamines (epinephrine and norepinephrine) and decreased levels of acetylcholine. A major physiological response to stress is to induce the hypothalamic-pituitary-adrenal (HPA) axis to cause the release of cortisol, a glucocorticoid which triggers gene-expression changes in target tissues.[15-19] Proposed mechanisms include altered circulating cortisol levels, dysregulated sensitivity to glucocorticoids, or alterations in feedback mechanisms, all which facilitate an extended or possibly intensified sympathetic nervous system activation.[11] This inability to regulate the HPA axis has been reported following chronic or severe stress and can lead to an allostatic load which transitions into an overexposure to stress molecules.[20] Increased allostatic load has also been linked to increased vulnerability to many psychiatric and physical disorders.[21, 22] One might hypothesize that patients with increased stress are likely to have sympathetic nervous system associated somatic dysfunction. Addressing these dysfunctions with appropriate osteopathic manipulative techniques could aid in as above.[23] It is important to note that serious adverse effects of OMT are extremely rare and thus are considered to be a safe method of treatment.[24]

Examples of stress-related treatments include a specific focus on the suboccipital and thoracic regions which are associated with increased heart rate variability, improved autonomic homeostasis, decreased muscular tension, and reduced perception of stress.[20] Rib raising treatment has been shown to reduce sympathetic output which results in parasympathetic predominant state-otherwise understood as a relaxed state.[25] Compression of the fourth ventricle (CV4) influences ANS function, and has been shown to alter the physiological parameters of blood flow velocity, heart rate, blood pressure, and cerebral tissue oxygenation.[21] In a study done by Cutler et al. in 2005,[26] patients who received CV4 when compared to those who received the sham treatment were found to have more rapid sleep onset and decreased muscle sympathetic nerve activity. Other studies determined that CV4 promotes muscle relaxation and a general state of relaxation when measuring alpha band activity (related to relaxation, awake and idle state) on EEG.[27] Stimulation of the parasympathetic nervous system is achieved as a result of the effect on the brainstem. Similar to rib raising, CV4 shifts autonomic balance to a parasympathetic predominant state by increasing parasympathetic activity and decreasing sympathetic activity resulting in an overall relaxed state.[28] Sacral rocking is an OMT technique that exaggerates sacral movement.[29] Sacral rocking can relieve patients of lower back pain and balance autonomic dysfunctions influencing the gastrointestinal and genitourinary systems. Treatment increases parasympathetic outflow from the sacral

Figure 1. Schematic representation of OMT-based therapeutic protocol. Blood sampling and self-reported social-psychological (mental) assessment surveys were collected on weeks 1 and 6. The OMT or Sham OMT protocol was performed once per week on weeks 1-5.



nerves.[30] Inhibitory techniques use mechanical pressure to reduce regional autonomic output (habituation). Suboccipital inhibition (SI) reduces the muscle tension reducing parasympathetic inhibition.[31] Tension headaches are often associated with myofascial trigger points or muscle tenderness,[32] which can lead to autonomic imbalance and motor disturbances in that region. Treatment using SI led to hypoalgesic effects-decreased sensitivity to painful stimuli and relieving pain.[33] Treatment with SI improved the emotional and mental well-being, and better quality of life.[32]

The benefit of human touch has also been shown to have therapeutic effects, which OMT is expected to provide as well. For example a review of research by Tiffany Field, a leader in the field of touch, found that benefits from touch start at birth, showing newborns that received just three 15-minute sessions of touch therapy each day for 5-10 days gained 47% more weight than premature infants who had received standard medical treatment.[34] She also found that massage therapy reduces pain in pregnant women and alleviates prenatal depression in both them and their spouse.[35] Another study from UC Berkeley's School of Public Health found that receiving eye contact and a pat on the back from a doctor may help survival rates for those suffering with complex diseases.[22] While OMT is a focused therapy option conducted only by a trained licensed doctor of osteopathy, touch therapy and its benefits were also taken into account for this research by including a sham OMT group. Sham therapy is defined as false treatment. It is typically used as the control group in OMT studies in order to compare the effects of the treatment or therapy in question.[36] In a study done by Licciardone et al. 2013, sham OMT involved light touch, active and passive ranges of motion, improper patient positioning, decreased physician force, and purposeful misdirected movements.[37]

In this pilot study we examined the efficacy of OMT for improving symptoms of SAD and sought to determine a correlation between overall improvement in health and quality of life for first responders who received OMT.

Methods

Research Study Design

We designed a single blind study to investigate OMT as a therapy for reducing stress, anxiety, and depression in the first responder population of a rural area in Joplin, Missouri. Approval was obtained from the Missouri Southern State University Institutional Review Board (IRB# 1512565-1). Participants were assigned randomly to either: 1) an OMT group, or 2) a sham OMT group. Names and any identifying information were not used, and all participants were assigned a random identifier on all documents throughout the study. Each participant signed a consent form authorizing participation in the pilot study. The duration of the pilot study was six weeks. Intravenous blood samples and surveys were collected on week one and week six. OMT was performed week one through week five, for a total of five treatments (Figure 1).

Baseline Demographics

Socio-demographic data were collected for each first responder: age, gender, marital status, racial/ethnic identity, highest education, and household income at the initial timepoint (Table 1).

Osteopathic Manipulative Therapy Protocol

The OMT protocol for this study was developed by Andi Selby, DO, and Kelley Joy, DO, consisting of four standard OMT methods: Rib Raising, Sacral Rock, Suboccipital Inhibition, and CV4 treatments (Table 2). Participants were instructed by the operator when to inhale and exhale as to receive better extension and flexion of the treated area and ultimately the desired outcome of treatment.

Sham Protocol

The sham protocol, also created by Dr. Selby, was adapted from the OMT protocol described above. Sham OMT was performed by individuals who received sham training but had no additional experience in performing OMT prior to this study. Participants were

Total Participants	N=9
Gender	
Male	9 (100%)
Age (years/mean)	
	40 (range: 34-47 years old)
Education	
Some college/Associate's	5 (55%)
Bachelor's	3 (33%)
Professional Degree	1 (11%)
Race/Ethnicity	
White	8 (89%)
Hispanic	1 (11%)
Household Income	
<$49,000	2 (22%)
$50,000-$99,999	5 (53%)
>$100,000	2 (22%)
Marital Status	
Never Married	1 (11%)
Married	7 (78%)
Separated/divorced	1 (11%)

Table 1. Participant socio-demographic profile variables.

OMT Technique	Key Steps in Treatment	Desired Outcome
Rib raising	4 second cycles of rhythmic pressure on rib angle	Reduced sympathetic output
Sacral Rock	Augmentation of sacral flexion and extension	Increased parasympathetic outpiut
Suboccipital Inhibition	Continuous unaltered pressure	Increased parasympathetic output
CV4 (stillpoint induction)	Progressive encouragement of occipital extension until a still point is reached	Global shift towards parasympathetic balance

Table 2. OMT study protocol procedures, key steps, and desired outcomes

not instructed when to inhale or exhale and any touch used did not consist of extension or flexion, but rather only enough pressure to make the participants were aware they were being touched.

Scales

Various assessments of stress and anxiety were collected at week one and at week six. The Perceived Stress Scale was completed by participants to self-report their perception of stress.[38] For first responders' self-reported measurement of anxiety, we used the State Trait Anxiety Inventory.[39] We incorporated three scales previously used in trauma studies,[40] including a seven-point Likert scale (strongly agree to strongly disagree) that measured indicators of Satisfaction with Work and a Vicarious Trauma Scale with measures of distress from exposure to work experiences, such as interactions with traumatized or distressed people and difficult situations, as well as feelings of helplessness, and being overwhelmed by their workloads. Finally, a Coping Mechanisms Scale with nearly a dozen possible items (including both positivity and negatively perceived coping mechanisms) was administered.

Vital Signs Collection

Participant vital signs, including height, weight, pulse oximetry, blood pressure, pulse, and respiration rate were recorded prior to each OMT or sham session.

Biomarker Sample Collection

The amount of 5mL of whole blood was collected via venipuncture from each participant using sterile techniques at week one and week six timepoints. Samples were stored and processed according to ELISA manufacturer directions.

ELISA

Biological indicators of stress and anxiety were assessed using enzyme-linked immunosorbent assays. Measures of human IL-6 (KHC0061), IL-1beta (BMS224-2), TNF-alpha (BMS223HS), cortisol (EIAHCOR), IL-2 (EH2IL2), C reactive protein (KHA0031), and IL-17alpha (BMS2017) were purchased from Thermo Fisher Scientific (http://www.thermofisher.com). Human BDNF (ab99978) was purchased from Abcam (http://www.abcam.com). Manufacturer protocols were followed, and assays were carried out using Synergy HTX Multimode Reader, software Gen5 3.05.

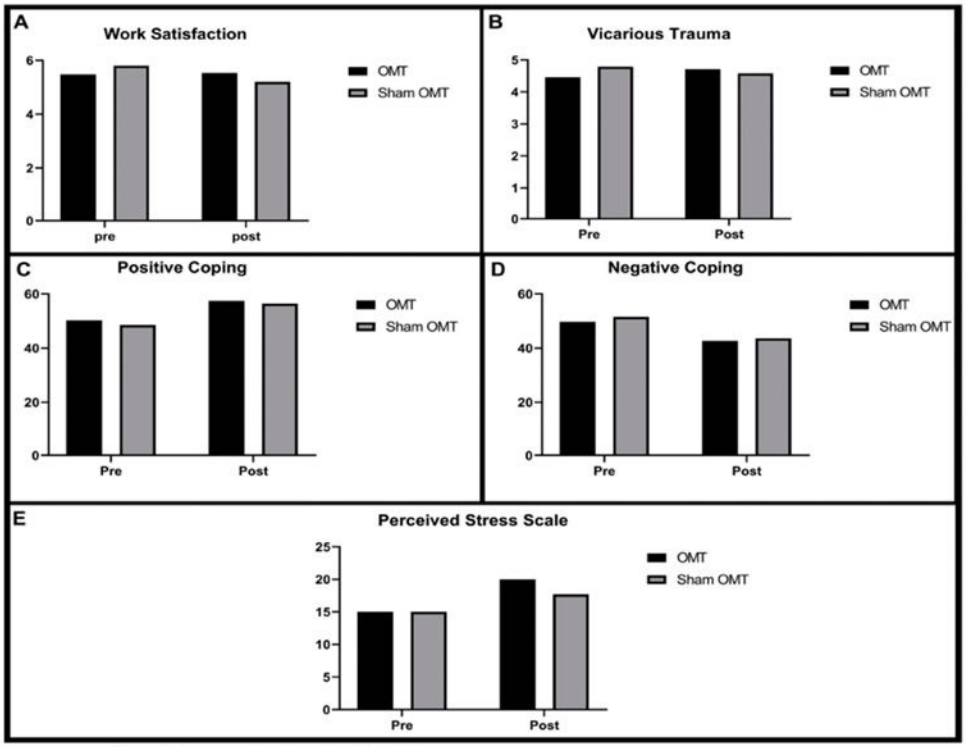


Figure 2. Mean values of self-reported social-psychological (mental assessments of stress and anxiety were performed using the following scales and surveys collected on week 1 (Pre) and week 6 (Post). A. Work Satisfaction (scale of 1-7) B. Vicarious Trauma (scale of 1-10), C. Positive Coping Mechanisms (mean total), D. Negative Coping Mechanisms (Mean total), E. Perceived Stress Scale.

Statistics

All statistical analysis was carried out using GraphPad Prism version 8.2.1 for Windows, GraphPad Software, San Diego, California USA. All statistical significance was measured at p=.05.

Results

A total of nine participants were recruited into the pilot study (six OMT and three sham OMT). Six total participants completed the study (three OMT and three sham OMT). Socio-demographic data for the nine total participants are presented in Table 1.

When evaluating the social-psychological (mental) survey data, we observed that the average work satisfaction (Figure 2A) for both groups was on the higher side (5.2 – 5.8 out of 7), with the OMT (experimental) group reporting a slight increase in job satisfaction from week one to week six, and the sham OMT (control) group reporting a slight decrease in their job satisfaction. These data also indicate that the sham OMT group experienced a slight decrease in vicarious trauma indicators (Figure 2B) across the course of the study, while the OMT group's indicators of vicarious trauma increased slightly over the six-week period. Both the sham OMT group and the OMT group increased their positive coping mechanisms (Figure 2C) over the study, and both groups also reported a decrease in negative coping strategies (Figure 2D). Finally, both the sham OMT and OMT groups reported increases in their perceived stress scores at the end of the six-week study (Figure 2E).

Analysis of serum biomarkers for stress, anxiety and depression were carried out via ELISA assay on week one and week six of the study. No statistically significant change in biomarker levels were observed, however, there were trends that indicate a slight decrease (Figure 3). Levels of IL-6, BDNF, IL-2, IL-17α, and cortisol trended lower at week six than week 1 in the OMT group. In addition, IL-17α levels were also decreased in the sham OMT group at week six when compared to week one. Only levels of human C reactive protein trended higher at week six in the OMT group (Figure 3D). In the sham OMT group, IL-6, IL-2, hCRP, and cortisol all trended higher, but did not reach statistical significance. It is important to note that there was a high degree of variance across each group, and due to the relatively small number of participants, this likely is associated with a lack of statistical significance over time.

Discussion

In this pilot study we were able to identify numerical increases in positive coping mechanisms and decreases in negative coping mechanisms for all participants over the course of the study. The pre- to post-study increases in satisfaction with work satisfaction for the OMT treatment group was in the expected direction. On the other hand, data on first responders' impressions of vicarious trauma associated

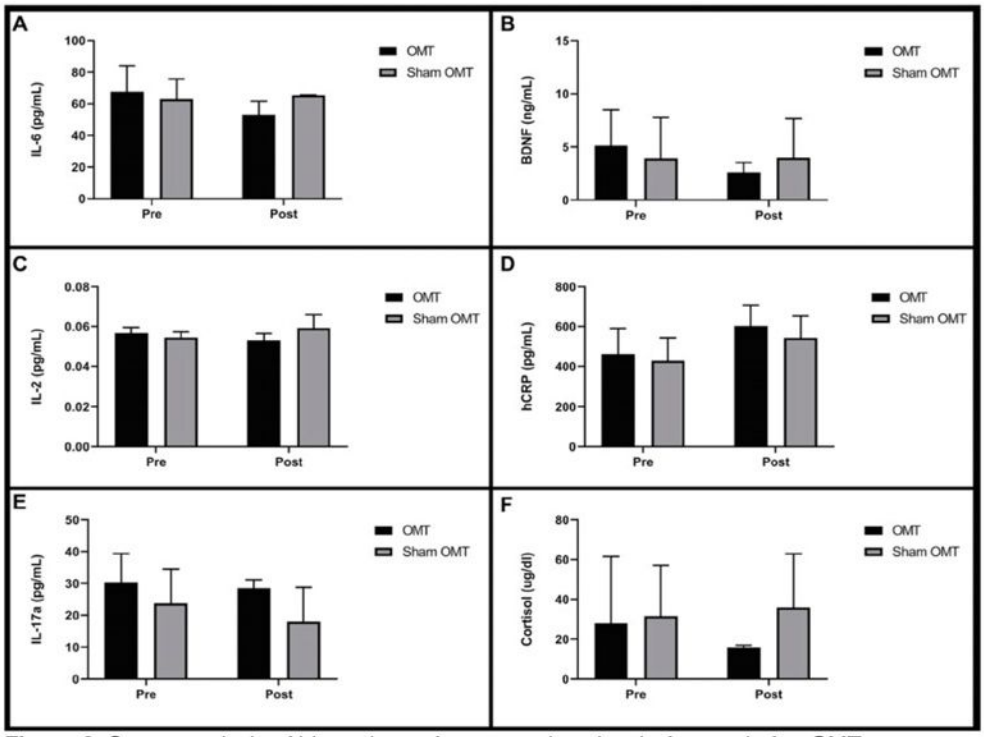


Figure 3. Serum analysis of biomarkers of stress and anxiety before and after OMT. 5mL of whole blood was collected on week 1 (Pre) and week 6 (Post) from each participant. Biological indicators of stress and anxiety were assessed using enzyme-linked immunosorbent assays (ELISA) for measures of: A. IL-6, B. BDNF, C. IL-2, D. hCRP, E. IL-17a, F. Cortisol. Samples were analyzed in triplicate and group means are reported along with +/- SE of the mean.

with work were not expected: control group members felt less and treatment group members felt more vicarious trauma by the end of the study.

Further, perceived stressors increased for both groups. These findings could be influenced by variations in individuals' exposure to stressful or anxious situations, such as differing responsibilities held across work positions, having different shifts or working in different stations that influence the calls to which each first responder was dispatched. However, a larger social factor may have been the emergence of the Covid-19 pandemic, increasing national, state and community-level fears and requiring the quick implementation of social distancing protocols. Somewhat contradictory, both groups also reported increased calmness, security, and feelings of ease and relaxation by the end of the study. The extra attention, human touch, and social interactions experienced by our participants were likely felt by those who received both authentic or sham OMT.

The authors note a likely confounding effect of having both prescription and non-prescription drugs labeled as a "negative" coping strategy to work-related stressors. Future studies may deconstruct this item, since compliance with physician's orders to take prescription medication may be perceived as a "positive."

This pilot study detected trends toward a decrease in serum biomarkers associated with stress, anxiety, and depression. Inflammatory cytokines are currently being further investigated as primary biomarkers for a number of neurological conditions, including anxiety and major depressive disorder. Our data indicate that several of the interleukins and other hormones potentially associated with these conditions were influenced by this protocol. Increasing the frequency of treatment and/or the duration of the study may show a continuation of this trend to statistical significance. In addition, the addition of educational materials designed for the reduction of stress, anxiety and feelings of depression may work in conjunction with OMT to improve these conditions in first responders.

Conclusion

First responders are commonly exposed to traumatizing incidents or disasters in the course of their duties. Police, firefighters, EMTs, and paramedics who respond to these emergencies and tragedies are likely to experience psychological and physical stress, and this constitutes a great risk for their physical and behavioral health. This pilot study highlights the therapeutic potential of OMT for SAD reduction in this population. Further research is needed on this topic, expanding the sample size and modifying the methods based on the findings of this study to develop more evidence-based conclusions.

References

1. Abbot C, Barber E, Burke B, et al. What's killing our medics? http://www.revivingresponders.com/originalpaper
2. McKeon G, Steel Z, Wells R, et al. Mental health informed physical activity for first responders and their support partner: a protocol for a stepped-wedge evaluation of an online, codesigned intervention. BMJ Open. Sep 11 2019;9(9):e030668. doi:10.1136/bmjopen-2019-030668
3. Lewis-Schroeder NF, Kieran K, Murphy BL, Wolff JD, Robinson MA, Kaufman ML. Conceptualization, Assessment, and Treatment of Traumatic Stress in First Responders: A Review of Critical Issues. Harv Rev Psychiatry. Jul/Aug 2018;26(4):216-227. doi:10.1097/hrp.0000000000000176
4. Administration SAaMHS. First Responders: Behavioral Health Concerns, Emergecy Response, and Trauma. 2018.
5. Venteicher W. Increasing suicide rates among first responders spark concern, in The Pittsburgh Tirbune-Review. Philadelpha. 2017;
6. Bergen-Cico D, Lane S, Thompson M, et al. The impact of post-traumatic stress on first responders: analysis of cortisol, anxiety, depression, sleep impairment and pain. International Paramedic Practice. 2015;5(3):78-87.
7. Hembree EA, Foa EB, Dorfan NM, Street GP, Kowalski J, Tu X. Do patients drop out prematurely from exposure therapy for PTSD? J Trauma Stress. Dec 2003;16(6):555-62. doi:10.1023/B:JOTS.0000004078.93012.7d
8. Libby DJ, Pilver CE, Desai R. Complementary and alternative medicine use among individuals with posttraumatic stress disorder. Psychological Trauma: Theory, Research, Practice, and Policy. 2013;5(3):277-285. doi:https://psycnet.apa.org/doi/10.1037/a0027082
9. Schottenbauer MA, Glass CR, Arnkoff DB, Tendick V, Gray SH. Nonresponse and dropout rates in outcome studies on PTSD: review and methodological considerations. Psychiatry. Summer 2008;71(2):134-68. doi:10.1521/psyc.2008.71.2.134
10. Reynolds CW, Wagner SL. Stress and First Responders: The need for a Multidimensional Approcah to Stress Management. Int J Disability Management. 2012;2(2):27-36. doi:10.1375/jdmr.2.2.27
11. Fornari M, Carnevali L, Sgoifo A. Single Osteopathic Manipulative Therapy Session Dampens Acute Autonomic and Neuroendocrine Responses to Mental Stress in Healthy Male Participants. J Am Osteopath Assoc. Sep 1 2017;117(9):559-567. doi:10.7556/jaoa.2017.110
12. Plotkin BJ, Rodos JJ, Kappler R, et al. Adjunctive osteopathic manipulative treatment in women with depression: a pilot study. J Am Osteopath Assoc. Sep 2001;101(9):517-23.
13. Kopschina Feltes P, Doorduin J, Klein HC, et al. Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. J Psychopharmacol. Sep 2017;31(9):1149-1165. doi:10.1177/0269881117711708
14. Bandelow B, Baldwin D, Abelli M, et al. Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. World J Biol Psychiatry. Apr 2017;18(3):162-214. doi:10.1080/15622975.2016.1190867
15. Antonijevic I. HPA axis and sleep: identifying subtypes of major depression. Stress. Jan 2008;11(1):15-27. doi:10.1080/10253890701378967
16. Tsigos C, Kyrou I, Kassi E, Chrousos GP. Stress: Endocrine Physiology and Pathophysiology. In: Feingold KR, Anawalt B, Boyce A, et al, eds. Endotext. MDText.com, Inc.
Copyright © 2000-2021, MDText.com, Inc.; 2000.
17. Turner AI, Smyth N, Hall SJ, et al. Psychological stress reactivity and future health and disease outcomes: A systematic review of prospective evidence. Psychoneuroendocrinology. Apr 2020;114:104599. doi:10.1016/j.psyneuen.2020.104599
18. Turner-Cobb JM. Psychological and stress hormone correlates in early life: a key to HPA-axis dysregulation and normalisation. Stress. Mar 2005;8(1):47-57. doi:10.1080/10253890500095200
19. Zänkert S, Bellingrath S, Wüst S, Kudielka BM. HPA axis responses to psychological challenge linking stress and disease: What do we know on sources of intra- and interindividual variability? Psychoneuroendocrinology. Jul 2019;105:86-97. doi:10.1016/j.psyneuen.2018.10.027
20. Emmet D, Nuño V, Pierce-Talsma S. OMT to Address the Physiologic Effects of Stress. J Am Osteopath Assoc. Feb 1 2018;118(2):e11. doi:10.7556/jaoa.2018.028
21. Żurowska A, Malak R, Kołcz-Trzęsicka A, Samborski W, Paprocka-Borowicz M. Compression of the Fourth Ventricle Using a Craniosacral Osteopathic Technique: A Systematic Review of the Clinical Evidence. Evid Based Complement Alternat Med. 2017;2017:2974962. doi:10.1155/2017/2974962
22. Field T. Massage therapy research review. Complement Ther Clin Pract. Nov 2014;20(4):224-9. doi:10.1016/j.ctcp.2014.07.002
23. Reeves RR. Diagnosis and management of posttraumatic stress disorder in returning veterans. J Am Osteopath Assoc. May 2007;107(5):181-9.
24. Seffinger MA. The Safety of Osteopathic Manipulative Treatment (OMT). J Am Osteopath Assoc. Mar 1 2018;118(3):137-138. doi:10.7556/jaoa.2018.031
25. Arienti C, Farinola F, Ratti S, Daccò S, Fasulo L. Variations of HRV and skin conductance reveal the influence of CV4 and Rib Raising techniques on autonomic balance: A randomized controlled clinical trial. J Bodyw Mov Ther. Oct 2020;24(4):395-401. doi:10.1016/j.jbmt.2020.07.002
26. Cutler MJ, Holland BS, Stupski BA, Gamber RG, Smith ML. Cranial manipulation can alter sleep latency and sympathetic nerve activity in humans: a pilot study. J Altern Complement Med. Feb 2005;11(1):103-8. doi:10.1089/acm.2005.11.103
27. Miana L, Bastos VH, Machado S, et al. Changes in alpha band activity associated with application of the compression of fourth ventricular (CV-4) osteopathic procedure: a qEEG pilot study. J Bodyw Mov Ther. Jul 2013;17(3):291-6. doi:10.1016/j.jbmt.2012.10.002
28. Curi ACC, Maior Alves AS, Silva JG. Cardiac autonomic response after cranial technique of the fourth ventricle (cv4) compression in systemic hypertensive subjects. J Bodyw Mov Ther. Jul 2018;22(3):666-672. doi:10.1016/j.jbmt.2017.11.013
29. Yu K, Pfotenhauer K, Pierce-Talsma S. OMT for Patients With Sacral Somatic Dysfunction. J Am Osteopath Assoc. Mar 1 2018;118(3):e15. doi:10.7556/jaoa.2018.041
30. Gerhartz B, Bordoni B. Osteopathic Manipulative Treatment: Articulatory Procedure - Sacral Dysfunctions. StatPearls. StatPearls Publishing; 2021.
31. Espi-Lopez GV, Olivia-Pascual-Vaca A. Atlanto-Occipital Joint Manipulation and Suboccipital Inhibition Technique in the Osteopathic Treatment of Patients with Tension-Type Headache. Eur J Ost Clin Rel Res. 2012;7(1):10-21.
32. Jiang W, Li Z, Wei N, Chang W, Chen W, Sui HJ. Effectiveness of physical therapy on the suboccipital area of patients with tension-type headache: A meta-analysis of randomized controlled trials. Medicine (Baltimore). May 2019;98(19):e15487. doi:10.1097/md.0000000000015487
33. Oliveira-Campelo NM, Rubens-Rebelatto J, Martí NVFJ, Alburquerque-Sendí NF, Fernández-de-Las-Peñas C. The immediate effects of atlanto-occipital joint manipulation and suboccipital muscle inhibition technique on active mouth opening and pressure pain sensitivity over latent myofascial trigger points in the masticatory muscles. J Orthop Sports Phys Ther. May 2010;40(5):310-7. doi:10.2519/jospt.2010.3257
34. Field T. Touch for socioemotional and physical well-being: A review. Dev Review. 2010;30(4)doi:10.1016/j.dr.2011.01.001
35. Field T. Massage therapy research review. Complement Ther Clin Pract. Aug 2016;24:19-31. doi:10.1016/j.ctcp.2016.04.005
36. Cerritelli F, Verzella M, Cicchitti L, D'Alessandro G, Vanacore N. The paradox of sham therapy and placebo effect in osteopathy: A systematic review. Medicine (Baltimore). Aug 2016;95(35):e4728. doi:10.1097/md.0000000000004728
37. Licciardone JC, Minotti DE, Gatchel RJ, Kearns CM, Singh KP. Osteopathic manual treatment and ultrasound therapy for chronic low back pain: a randomized controlled trial. Ann Fam Med. Mar-Apr 2013;11(2):122-9. doi:10.1370/afm.1468
38. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. Dec 1983;24(4):385-96.
39. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press; 1983.
40. Vrklevski LP, Franklin J. Vicarious trauma: The impact on solicitors of exposure to traumatic material. Traumatology. 2008;14(1):106-118. doi:https://doi.apa.org/doi/10.1177/1534765607309961

Disclosure

None reported.

MM

Management of Obesity Using Telemedicine During the COVID-19 Pandemic

by Angela A. Wang-Selfridge, DO & Jennifer F. Dennis, PhD

While telemedicine was introduced prior to the pandemic of 2020, the COVID-19 pandemic made it more readily available and more acceptable to both health care professionals and patients.



Angela A. Wang-Selfridge, DO, is at Kansas City University College of Oseopathic Medicine (KCU-COM); Jennifer F. Dennis, PhD, MS, (above) is in the Department of Anatomy, KCU-COM. Both are at the Joplin Campus, Joplin, Missouri.

Abstract

Importance: During the COVID-19 pandemic, telemedicine visits increased to provide safer access to healthcare.

Methods: To evaluate the role of telemedicine in obesity management during COVID-19, we conducted a systematic review to identify barriers in using this approach to patient care.

Conclusion: While necessary, the management of obesity through telemedicine was met with patient-specific and healthcare-specific barriers. Increased awareness of these barriers may allow physicians to better understand patient interactions via virtual medical visits.

Introduction

Telemedicine has played a role in the United States healthcare system for decades now. It was most initially utilized as a means of monitoring astronauts in flight, established by the National Aeronautics and Space Association (NASA) in 1960.[1] In more recent years, it has played a more prevalent role in certain medical specialties, such as radiology, psychiatry, and cardiology than others. It has also allowed for increased inter-specialty communication between healthcare professionals. Its versatility has been demonstrated across different settings as well: ambulatory appointments, emergency visits, hospital follow-up, and most recently, testing and screening for COVID-19.

This article focuses on the use of telemedicine for patients struggling with obesity and its limitations. It is long known that physicians have tried to manage obesity in patients through diet and exercise, then stepping up to medication, and if all else fails, bariatric surgery. However, it is unknown how well these management plans have succeeded during a pandemic that has required virtual medical visits and extended periods of quarantine. This is a particularly important topic to consider because it was found that obesity has been associated with an increased risk of death among hospitalized patients diagnosed with COVID-19.[2] Additionally, obesity has become increasingly common among the population age 50 and younger, thus shifting the severe and fatal COVID-19 cases to the younger population.

Methods

We conducted a systemic review of the literature across the PubMed (MEDLINE) and Elsevier ClinicalKey research databases. Searches were performed between February 1, 2021, and February 28, 2021, by A. W. S. The keywords used to search for relevant articles included telemedicine, telehealth, virtual visits, COVID-19, coronavirus, obesity, and weight. We reviewed articles published between February 1, 2020, and February 1, 2021, and excluded all other articles published outside of that timeframe. The inclusion criteria used for PubMed (MEDLINE) included: free full-text, English language, and humans. The inclusion criteria used for ClinicalKey included: full-text only, articles listed under specialties endocrinology and metabolism, internal medicine, and surgery. Exclusion criteria included: articles outside the scope of the search, articles that included diabetic patients and diabetes management, articles that did not focus on medical management during COVID-19. Using the parameters, 23 articles from the MEDLINE database and 70 articles from the ClinicalKey database were obtained. After exclusion criteria was applied, two articles from the MEDLINE database and three articles from the ClinicalKey database were reviewed and analyzed. Figure 1 illustrates the search process with the inclusion and exclusion criteria described above.

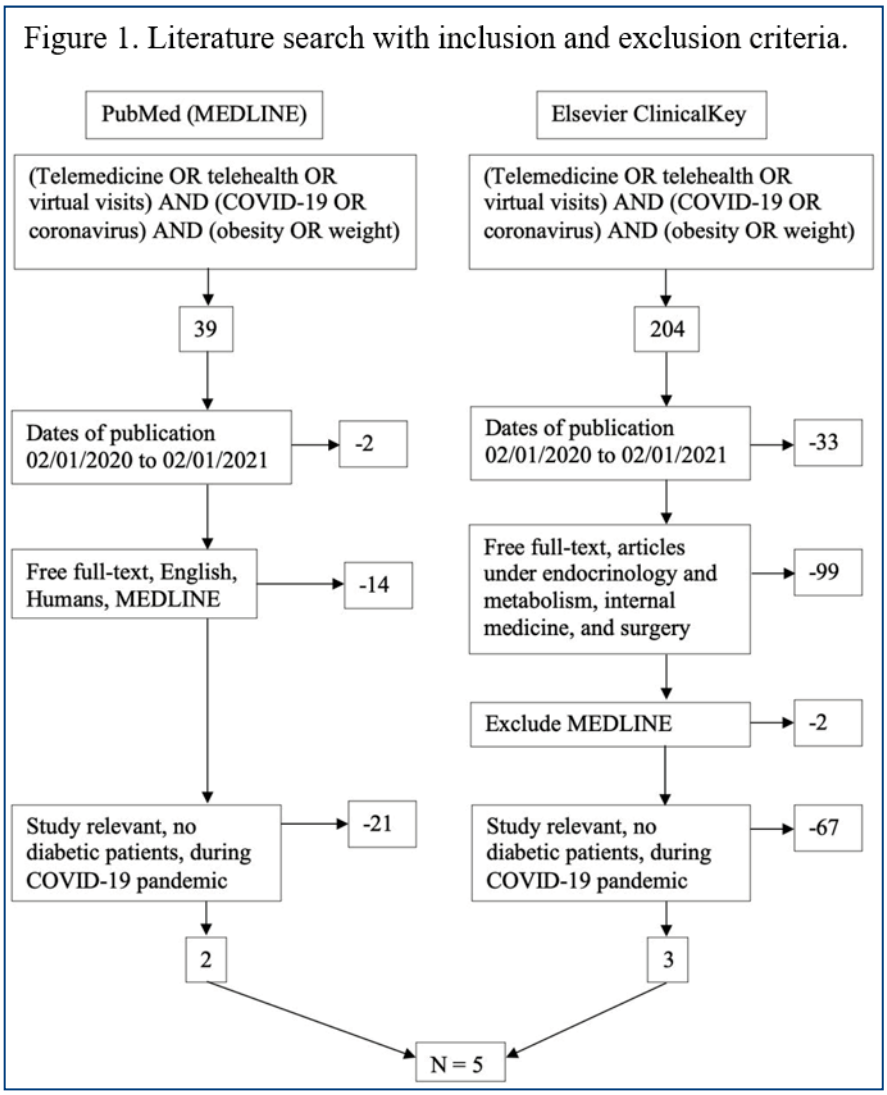
Results

Limitations of telemedicine for visits for obesity management were broken down into two categories: patient-specific barriers and healthcare-specific barriers. Limitations that were included in patient-specific barriers included access to technology and patient acceptance.[3] Although 75% of U.S. adults have internet service at home, this does not account for the unequal distribution across racial minorities, the elderly, those living in rural regions, and those with lower levels of education and income. This is particularly relevant to the management of obesity, as there is a disproportionately higher obese population among certain racial/ethnic and socioeconomic classes.[4] It was found that among the age group of 2-5 years, 16.5% of Hispanic/Latino and 11.6% of Black, non-Hispanic children fall into the obese group, whereas 9.9% of White, non-Hispanic children fall into the same category. These children are also found to have a higher obesity risk in adolescence compared to their healthy weight counterparts. Therefore, children who are impacted by obesity translates into a similar adult population demographic also impacted by obesity. As a result, unfortunately, the same patient demographic who has a disproportionately higher rate of obesity also suffers from more limitations in having access to telehealth.

In comparison, it has been shown that established telemedicine practices have received positive feedback. A Pediatric and Adolescent Weight and Cardiometabolic Clinic in Orono, Maine, had established a weight management clinic with a full interdisciplinary team and IT experts to set up a telemedicine plan for patients in 2015, before the COVID-19 pandemic. It was concluded that the telemedicine services, in fact, reduced barriers to access including reduced travel time, decreasing competing responsibilities, less absence from work, avoidance of inclement weather, and allowing patients to be in a home environment where they are most comfortable.[5] The technological and socioeconomic disparities are briefly touched upon by the author, but the benefits listed contributed a different and interesting perspective in adding telemedicine practices for obesity management as an adjunct to traditional office visits in the future.

In addition to the benefits that the clinic in Orono, Maine, has listed, telemedicine has also been found to be beneficial with regards to increasing access to bariatric surgery programs. Many of the screening process steps for bariatric surgery, questions that patients may have, and initial informational sessions can all be addressed and presented to patients remotely.[6] This also increases the number of participants per session, thus further increasing

Figure 1. Literature search with inclusion and exclusion criteria.



the number of patients who have access to this information. The argument for why traditional office visits have not been as successful with bariatric surgery is due to lengthy process patients have to go through in order to get cleared for surgery, making it a cumbersome and demoralizing process. It has been shown that less than 1% of patients eligible for bariatric surgery actually end up undergoing surgery, and 50% of patients who initiate the process end up dropping out. This is despite the fact that bariatric surgery is one of the most effective methods for treating obesity and its associated comorbidities. Consequently, telemedicine has proven beneficial in this very specific, but unique, avenue of obesity management.

In addition to patient-specific barriers, limitations that were included in healthcare-specific barriers included healthcare provider acceptance, reimbursement, and regulatory barriers. Changes in the healthcare system has also been witnessed to accommodate this prevalent implementation of telemedicine. Previously, insurance companies had restrictions on the types of visits that would receive reimbursements. However, to support the widespread need for virtual visits, Medicare has broadened the scope for which it allows reimbursement for telemedicine visits under the 1135 Waiver.[7] Outside of government-funded healthcare, over 30 states across the country have required private insurance companies to reimburse providers for telehealth services. Additionally, the federal government have lifted regulatory barriers that prohibit communication with patients that may violate the Health Insurance Portability and Accountability Act as well as lifted restrictions on providing care across state lines.[3] This has allowed physicians to communicate with patients via Zoom, Google Hangouts, Apple FaceTime, and more. These changes have eliminated some of the restrictions of the level of care physicians can provide for patients.

Discussion

On a national level, obesity has been viewed as a sign of personal moral failure and is not categorized as a disease.[6] Consequently,

this has limited patient access to care, as well as a patient's desire to seek out care. Additionally, obesity has been shown to affect a disproportionately higher number of certain racial/ethnic groups and those of lower socioeconomic and education status.[4] With the COVID-19 pandemic, patients affected with COVID-19 and who also suffer from obesity, have a higher severity of the disease and fatality.[2] Together, these issues highlight the value of improving obesity management, during the COVID-19 pandemic and after.

The widespread application of telemedicine has both positive and negative impacts on obesity management. Though positive reviews include decreased travel time and less stigmatization of patients seeking bariatric surgery, there are still a number of barriers that need to be corrected to deliver fair and accessible telemedicine healthcare for those in need. This includes overcoming a lack of resources for patients who do not have access to, or do not have knowledge of how to use, the technological aspect of telemedicine. With the increased utilization of telemedicine, it may become a role of the physician's office team to educate patients on how to use technology services and how to understand interactions via a virtual platform. This shift in responsibility will need to be further evaluated in terms of the workflow of a physician's office, the comfort level of the team, feasibility, and simple willingness from both parties. Because obesity is also more prevalent among specific ethnic/racial and socioeconomic groups, reducing the rate of obesity in these patient demographics would help decrease the rate of obesity in general. However, the scope of this approach would have to be further evaluated as obesity has been determined to be a multifactorial and complex health issue.[8,9] We believe that the first step in addressing these issues is recognition, and from there, the limitations can begin to be eliminated.

Conclusion

While telemedicine was introduced prior to the pandemic of 2020, the COVID-19 pandemic made it more readily available and more acceptable to both health care professionals and patients. However, like its counterpart "in-person" practices in medicine, its limitations need to be identified and addressed to further improve delivery of care to patients. More research is needed to identify the barriers that limit patients' access to and use of telemedicine. Before telemedicine can gain further patient acceptance and meet the expectations of the traditional model of healthcare, its barriers need to be understood and eliminated to provide equitable care for patients.

References

1. Hyder MA, Razzak J. Telemedicine in the United States: An Introduction for Students and Residents. J Med Internet Res. 2020;22(11):e20839. Published 2020 Nov 24. doi:10.2196/20839
2. Yu W, Rohli KE, Yang S, Jia P. Impact of obesity on COVID-19 patients. J Diabetes Complications. 2021;35(3):107817. doi:10.1016/j.jdiacomp.2020.107817
3. Mehta P, Stahl MG, Germone MM, et al. Telehealth and Nutrition Support During the COVID-19 Pandemic. J Acad Nutr Diet. 2020;120(12):1953-1957. doi:10.1016/j.jand.2020.07.013
4. Woo Baidal JA, Chang J, Hulse E, Turetsky R, Parkinson K, Rausch JC. Zooming Toward a Telehealth Solution for Vulnerable Children with Obesity During Coronavirus Disease 2019. Obesity (Silver Spring). 2020;28(7):1184-1186. doi:10.1002/oby.22860
5. O'Hara VM, Johnston SV, Browne NT. The paediatric weight management office visit via telemedicine: pre- to post-COVID-19 pandemic. Pediatr Obes. 2020;15(8):e12694. doi:10.1111/ijpo.12694
6. Chao GF, Ehlers AP, Telem DA. Improving obesity treatment through telemedicine: increasing access to bariatric surgery. Surg Obes Relat Dis. 2021;17(1):9-11. doi:10.1016/j.soard.2020.09.012
7. Calton B, Abedini N, Fratkin M. Telemedicine in the Time of Coronavirus. J Pain Symptom Manage. 2020;60(1):e12-e14. doi:10.1016/j.jpainsymman.2020.03.019
8. Ou-Yang MC, Sun Y, Liebowitz M, et al. Accelerated weight gain, prematurity, and the risk of childhood obesity: A meta-analysis and systematic review. PLoS One. 2020;15(5):e0232238. Published 2020 May 5. doi:10.1371/journal.pone.0232238
9. Vrijheid M, Fossati S, Maitre L, et al. Early-Life Environmental Exposures and Childhood Obesity: An Exposome-Wide Approach. Environ Health Perspect. 2020;128(6):67009. doi:10.1289/EHP5975

Disclosure

None reported. **MM**

Integrating Oral Health into Primary Care

by Erinne N. Kennedy DMD & Linda C. Niessen, DMD

Kansas City University

Incorporating an oral exam into the physical evaluation will help identify oral inflammation, infection, and pathology in patients.



Erinne N. Kennedy, DMD, MPH, MMSc, (above) is at Kansas City University College of Dental Medicine (KCU-CDM). Linda C. Niessen, DMD, MPH, MPP, is Vice Provost for Oral Health Affairs, Professor and Dean, KCU-CDM. Both are at the Joplin Campus, Joplin, Missouri.

Abstract

This article provides data on oral diseases as they relate to systemic health conditions. Research continues to identify biologic mechanisms that link oral diseases to systemic disease and vice versa. The Smiles for Life curriculum, developed for physicians, provides a systematic approach for incorporating an oral exam into your physical evaluation. Guidelines for the use of antibiotics for tooth pain and swelling, to prevent infective endocarditis, and for patients for total joint replacements are provided.

Introduction

In the 2000 Surgeon General's Report (SGR) on Oral Health, the first report on oral health promulgated by the Surgeon General, he articulated that oral health is essential to overall health.[1] Since the report, research has continued to support and identify new relationships between oral health and overall health.[1]

Oral diseases, such as periodontal (gum) disease, can have an impact on systemic health through the mechanisms of chronic inflammation and oxidative stress. CDC estimates that more than 45% of all U.S. adults over the age of 30 or 64.7 million adults have periodontal disease, with 30% having moderate periodontitis and 8.5% having severe periodontitis.[2] Smoking is the most significant risk factor for gum disease, however genetics, malnutrition, systemic disease, and local factors can contribute to patients developing gum disease. With more than 45% of U.S. adults having periodontal disease, it is estimated to be the number one cause of inflammation in the body followed closely by obesity.[2]

Obesity effects roughly 42% of U.S. adults. Self-reported data collected through the Behavioral Risk Factor Surveillance System (BRFSS) reported 35% of adults in Missouri were obese.[3,4] Obesity contributes to metabolic disorders such as diabetes mellitus (DM) type II. Research outlines a bidirectional relationship between DM and periodontal disease where treating periodontal disease improves blood glucose control in patients with DM, and well controlled DM improves periodontal health in patients.[5] The link between these two diseases is chronic inflammation and circulating pathogenic bacteria. Treatment options which can improve the oral health of the patient include scaling and root planning therapy to remove the biofilm and infected tissue below the gum surface, and/or periodontal surgery.[5]

Whether chronic inflammation is caused by periodontal disease, obesity, diabetes mellitus, or a combination, inflammation contributes to cardiovascular disease. Cardiovascular disease is the leading cause of death in the U.S.[6] Key risk factors for cardiovascular disease include high blood pressure, high LDL cholesterol, and/or smoking-three key risk factors for heart disease. Research by Bale, Doneen and Vigerust, reports that high-risk periodontal pathogens are a contributory cause of the pathogenesis of atherosclerosis.[7] Linking oral diseases to a patient's overall health helps support risk reduction strategies for patients which include smoking cessation, blood pressure control, and treatment for periodontal disease to decrease pathogenic bacteria and reduce inflammation.

The Smiles for Life Curriculum, developed for physicians, outlines a systematic approach to include an oral exam into the physical examination.The oral screening exam takes less than two minutes and can identify inflammation, infection, and malignancy.[8]

Case Example

Short Case Vignette

A 47-year-old male presents to your clinic for a three-month visit to evaluate a new medication he was prescribed for Type II diabetes mellitus (DM). Contributory medical history includes smoker (27 pack years), hypertension, and uncontrolled Type II DM. He is taking lisinopril, hydrochlorothiazide, insulin, liraglutide, and simvastatin. After your exam he mentions that his tooth is wiggling more when he eats, and he asks you to take a look. When you look inside you see a swelling around a tooth in the back right.

Discussion

The patient case reports a history of DM and hypertension, two out of three risk factors for cardiovascular disease, and signs and symptoms of periodontal disease. During the oral examination, you would expect to see signs of inflammation due to the patient's uncontrolled diabetes mellitus. Oral inflammation associated with chronic periodontal disease will present with red and swollen gingival tissues. Patients may often complain of their gums bleeding easily or it being uncomfortable or painful for them to brush, floss or even chew. With the patient case reporting a mobile tooth, it is likely that the latter is the case, and referral for dental care and treatment of this mobile tooth is recommended.

Odontogenic or tooth-related infections are the most common form of oral infections. Odontogenic infections result in throbbing pain, swelling, and potential purulence around the infected tooth. In this case example, when the swelling and purulence around a tooth is severe, the bone structure around the tooth is lost, making teeth become mobile.

In addition to the extraction of an infected tooth, antibiotics can be used to treat oral infections. To promote antibiotic stewardship, the American Dental Association has released guidelines for both medical and dental clinicians for treating tooth pain and swelling with antibiotics when dental care is and is not immediately available.[9] These guidelines use evidenced-based medicine, and recommend referral patterns for patients with signs of tooth related inflammation and infection. Table 1 illustrates the various published guidelines with recommendations for antibiotic use for prophylaxis and treatment of oral infections.

Prophylactic antibiotics prior to dental treatment are recommended for various systemic conditions such as cardiovascular disease (infective endocarditis) and post total joint replacement. The guidelines promulgated by the American Heart Association support the judicious use of antibiotics in patients with infective endocarditis.[10] In 2017, the American Association of Endodontists updated their guidelines for antibiotic use for oral infections.[11] Similarly, the American Academy of Orthopedic Surgeons developed guidelines for patients with post total joint replacement and have created an online resources for clinicians to help with prescribing prophylactic antibiotics for patients who are immunocompromised.[12]

Fungal infections in the mouth commonly occur among patients in long-term care facilities, with antibiotic therapy, and in patients with an immune deficiency associated with medication or systemic disease. Patient symptoms of an oral

Table 1 Resources for evidenced based use of antibiotics for dental prophylaxis and tooth pain and/or swelling

Resource Type	Dental Organization	Date Released	Citation
Prophylaxis			
Prophylaxis Recommendations for Heart Conditions	American Heart Association	2008	Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. Circulation 2021:Cir0000000000000969
Antibiotic Prophylaxis	American Association of Endodontics	2017	Ashraf F. Fouad, Chair, B. Ellen Byrne, Anibal R. Diogenes, Christine M. Sedgley and Bruce Y. Cha. Antibiotic Prophylaxis 2017 Update [Internet]. American Association of Endodontists; 2017.
Antibiotic Use in Endodontics	American Association of Endodontics	2017	Ashraf F. Fouad, Chair, B. Ellen Byrne, Anibal R. Diogenes, Christine M. Sedgley and Bruce Y. Cha. AAE Guidance on the Use of Systemic Antibiotics in Endodontics [Internet]. American Association of Endodontists; 2017.
Antibiotic Prophylaxis	American Association of Endodontics	2017	Ashraf F. Fouad, Chair, B. Ellen Byrne, Anibal R. Diogenes, Christine M. Sedgley and Bruce Y. Cha. AAE Guidance on Antibiotic Prophylaxis for Patients at Risk of Systemic Disease [Internet]. American Association of Endodontists; 2017
Prophylaxis Recommendations for Prosthetic Joints	American Dental Association	2015	Sollecito TP, Abt E, Lockhart PB, Truelove E, Paumier TM, Tracy SL, et al. The use of prophylactic antibiotics prior to dental procedures in patients with prosthetic joints. The Journal of the American Dental Association [Internet]. 2015 Jan [cited 2019 Jan 29];146(1):11-16.e8.
Editorial on Prophylaxis Recommendations for Prosthetic Joints	American Dental Association	2017	American Dental Association guidance for utilizing appropriate use criteria in the management of the care of patients with orthopedic implants undergoing dental procedures. Journal of the American Dental Association. 2017 Feb;148(2):57–9.
Treatment of Oral Disease			
Antibiotics for the urgent management of symptomatic irreversible pulpitis, symptomatic apical periodontitis, and localized acute apical abscess: Systematic review and meta-analysis-a report of the American Dental Association	American Dental Association	2019	Tampi MP, Pilcher L, Urquhart O, Kennedy E, O'Brien KK, Lockhart PB, Abt E, Aminoshariae A, Durkin MJ, Fouad AF, Gopal P, Hatten BW, Lang MS, Patton LL, Paumier T, Suda KJ, Cho H, Carrasco-Labra A. Antibiotics for the urgent management of symptomatic irreversible pulpitis, symptomatic apical periodontitis, and localized acute apical abscess: Systematic review and meta-analysis-a report of the American Dental Association. J Am Dent Assoc. 2019 Dec;150(12):e179-e216. doi: 10.1016/j.adaj.2019.09.011. PMID: 31761029; PMCID: PMC8098651.
Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: A report from the American Dental Association	American Dental Association	2019	Lockhart PB, Tampi MP, Abt E, Aminoshariae A, Durkin MJ, Fouad AF, Gopal P, Hatten BW, Kennedy E, Lang MS, Patton LL, Paumier T, Suda KJ, Pilcher L, Urquhart O, O'Brien KK, Carrasco-Labra A. Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: A report from the American Dental Association. J Am Dent Assoc. 2019 Nov;150(11):906-921.e12. doi: 10.1016/j.adaj.2019.08.020. PMID: 31668170.
Treatment of Infections in Pediatric Dental Patients	American Association of Pediatric Dentistry	2014	Council on Clinical Affairs. Guideline on Use of Antibiotic Therapy for Pediatric Dental Patients. American Academy of Pediatric Dentistry CLINICAL PRACTICE GUIDELINES [Internet]. 2014 Revised;37(6):289–91.
Recommendations for the non-surgical treatment of periodontal disease	American Dental Association	2015	Smiley CJ, Tracy SL, Abt E, Michalowicz BS, John MT, Gunsolley J, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. The Journal of the American Dental Association [Internet]. 2015 Jul [cited 2019 Jan 29];146(7):525–35.

Candida infection can include a burning sensation, cracked and irritated corners of the mouth, or irritation when a patient wears a denture. Oral fungal infections are treated with topical and systemic antifungal medications.

During the oral examination, you may observe oropharyngeal lesions that have the potential to be malignant. In the above patient case, while the patient didn't report a non-healing lesion or swelling, you noticed in the medical history that the patient has a history of smoking tobacco. Oral and pharyngeal cancers comprise 2.9% of all new cancer cases each year and result in 1.8% of all cancer deaths in 2020. From 2011-2016, the five-year survival rate for oral cancer is 66.2%, among the worst survival rates for all cancers.[13] Risk factors for oral and pharyngeal cancer include the use of alcohol, tobacco, the human papilloma virus (HPV). A key strategy for treating oral malignancy is early detection and referral for care.

Signs and symptoms of oral and pharyngeal cancer may include a non-healing lesion or ulcer in the mouth that is red, white, or red and white in color. Red and white (mixed) lesions present a greater concern. Patients with a difficulty swallowing or a recent change in their voice raise concerns for malignancy. HPV has been identified as a risk factor for oral cancer and currently about 72% of all oropharyngeal cancers are the results of an HPV infection. White, non-smoking males in their 40s and 50s are the most at risk for HPV-related oral cancers.[14] Current health promotion practices include having patients reduce the use of alcohol and tobacco, receive HPV vaccination, and regular screening of all patients for oral cancer, even those who are non-smokers.

Conclusion

Research continues to demonstrate the effect of oral diseases on overall health. Incorporating an oral exam into the physical evaluation will help identify oral inflammation, infection, and pathology in patients. Treating or referring these oral conditions/lesions and implementing risk reduction strategies can improve overall health in addition to improving a patient's oral health.

References

1. U.S. Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General. Bethesda, MD: National Institute of Dental and Craniofacial Research, National Institutes of Health; 2000.
2. Eke PI, Dye BA, Wei L, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 – 2012. 2016;86(5):611-622. doi: 10.1902/jop.2015.140520.
3. Hales CM. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. NCHS Data Brief. 2020;(360):1-8.
4. Adult Obesity Prevalence Maps. Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory. https://www.cdc.gov/obesity/data/prevalence-maps.html. Published 2019. Accessed January 27, 2021.
5. Winning L, Linden GJ. A Review of the Relationship Between Chronic Periodontitis and Diabetes. US Endocrinol. 2018;14(2):80. doi:10.17925/USE.2018.14.2.80.
6. Kochanek KD, Xu J, Arias E. Mortality in the United States, 2019. NCHS Data Brief. 2020;(395):1-8.
7. Bale BF, Doneen AL, Vigerust DJ. High-risk periodontal pathogens contribute to the pathogenesis of atherosclerosis. Postgrad Med J. 2017;93(1098):215-220. doi:10.1136/postgradmedj-2016-134279
8. The Oral Examination. Smiles for Life. https://www.smilesforlifeoralhealth.org/courses/the-oral-examination/. Accessed April 14, 2021.
9. Lockhart PB, Tampi MP, Abt E, et al. Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling. J Am Dent Assoc. 2019;150(11):906-921.e12. doi:10.1016/j.adaj.2019.08.020.
10. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. Circulation 2021:Cir0000000000000969
11. Ashraf F. Fouad, Chair, B. Ellen Byrne, Anibal R. Diogenes, Christine M. Sedgley and Bruce Y. Cha. AAE Guidance on the Use of Systemic Antibiotics in Endodontics [Internet]. American Association of Endodontists; 2017 Published online 2017. https://www.aae.org/specialty/wp-content/uploads/sites/2/2017/06/aae_systemic-antibiotics.pdf
12. American Association of Orthopedic Surgeons. Prevention of Orthopaedic Implant Infection in Patients Undergoing Dental Procedures Evidence-Based Clinical Practice Guideline. https://www.aaos.org/globalassets/quality-and-practice-resources/dental/pudp_guideline.pdf. Published 2012. Accessed June 4, 2021.
13. National Cancer Institute. Cancer Stat Facts: Oral Cavity and Pharynx Cancer. https://seer.cancer.gov/statfacts/html/oralcav.html. Published 2020. Accessed April 12, 2021.
14. Oral Cancer Foundation. Oral Cancer Facts. https://oralcancerfoundation.org/wp-content/uploads/2020/03/Oral-Cancer-Facts-2020-1.pdf. Published online February 17, 2020. Accessed June 4, 2021.

Disclosure

None reported. **MM**

Vaping Associated Cardiac Arrest at School in a Teenager with Anomalous Left Coronary Artery

by Todd A. Glenski, MD & Courtney E. Dorris, BS, Gina M. Patel, MD, Christian M. Taylor, MD & Nichole M. Doyle, MD

1FIRST LITERATURE REPORT

The effects of e-cigarette use on the cardiovascular system are not well known in the pediatric population.



Todd A. Glenski, MD, MSHA, (above), Anesthesiologist, is at Children's Mercy Hospital, Kansas City, Missouri and Clinical Assistant Professor of Anesthesiology, University of Missouri - Kansas City School of Medicine, Kansas City, Missouri (UMKC-SOM KCMO). Courtney E. Dorris, BS, is a Medical Student, UMKC-SOM KCMO. Gina M. Patel, MD, is a Fellow in Pediatric Critical Care, Children's Mercy Hospital, Kansas City, Missouri, and UMKC-SOM KCMO. **Christian M. Taylor, M**D, Anesthesiologist, is at Children's Mercy Hospital, Kansas City, Missouri and Clinical Assistant Professor of Anesthesiology, UMKC-SOM KCMO. Nichole M. Doyle, MD, FASA, Anesthesiologist, is at Children's Mercy Hospital, Kansas City, Missouri and Assistant Professor of Anesthesiology, UMKC-SOM KCMO.

Abstract

The prevalence of electronic cigarette use is increasing at an astonishing pace, particularly in the teenage population. While at school, a healthy 13-year-old male experienced a sudden cardiac arrest after vaping multiple times throughout the day. Workup revealed an anomalous left coronary artery originating from the right sinus of Valsalva. Given this patient's underlying anomalous left coronary artery, we suspect that sympathoexcitatory and arrhythmogenic effects of high dose nicotine from vaping led to his cardiovascular collapse. This is the first published case report of a vaping associated cardiac arrest in a patient of this age.

Introduction

Vaping nicotine containing products is a growing epidemic in teenagers with up to five million using electronic cigarettes (e-cigarettes).[1] With a rise in vaping and high dose nicotine exposure, there have been reported cases of E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) in the pediatric population. The acute and chronic systemic effects of vaping, however, are not well known or reported in pediatrics. Here we present a case of a cardiac arrest in a 13-year-old, with an undiagnosed anomalous left coronary artery, that occurred shortly after vaping while in school. Written HIPAA authorization was obtained from the family for the purpose of this report. This is the first published case report of a vaping associated cardiac arrest in a patient of this age.

Case Presentation

While at school, an otherwise healthy 13-year-old male with no significant past-medical history, experienced a sudden cardiac arrest. At the beginning of gym class, he developed a sensation of heavy pressure in his chest that progressed to lightheadedness and dizziness. The patient then had a witnessed collapse followed by initiation of cardiopulmonary resuscitation (CPR). The patient required several rounds of CPR with two defibrillation shocks from the automated external defibrillator (AED). His heart rhythm was alternating between ventricular fibrillation and polymorphic ventricular tachycardia. After emergency medical services arrived, CPR was continued until the patient had return of spontaneous circulation. On further investigation, it was noted that the

patient had been vaping nicotine containing products immediately prior to going to gym class, as well as vaping one to two times per hour throughout the day.

Upon arrival to the hospital, an echocardiogram and CT angiogram revealed an anomalous left coronary artery originating from the right sinus of Valsalva with an intramural segment (Figure 1). A stress test did not reveal inducible ectopy or ischemic changes. A urine drug screen was negative, except for nicotine and cotinine, a metabolite of nicotine. The patient was stable from a respiratory standpoint excluding a diagnosis of EVALI. During his hospital stay, the patient underwent repair of his anomalous right origin of the left coronary artery by unroofing and resuspension in the left commissure. The surgical procedure went as planned and was uneventful. The patient arrived in the cardiac intensive care unit intubated and sedated on dexmedetomidine and morphine, as well as a milrinone infusion. An epinephrine infusion was subsequently started for hypotension thought to be from vasodilation. The patient was extubated later that day, and all vasoactive medications were weaned off overnight. He was transferred from the intensive care unit to an inpatient floor room the following day.

The patient was later discharged with a wearable cardiac defibrillator device. Genetic testing was inconclusive with no additional recommendations. The patient followed up with cardiology a month later, and a stress test was found to be normal. The patient was cleared to return to sports participation, and it was emphasized that he refrains from vaping nicotine containing products in the future.

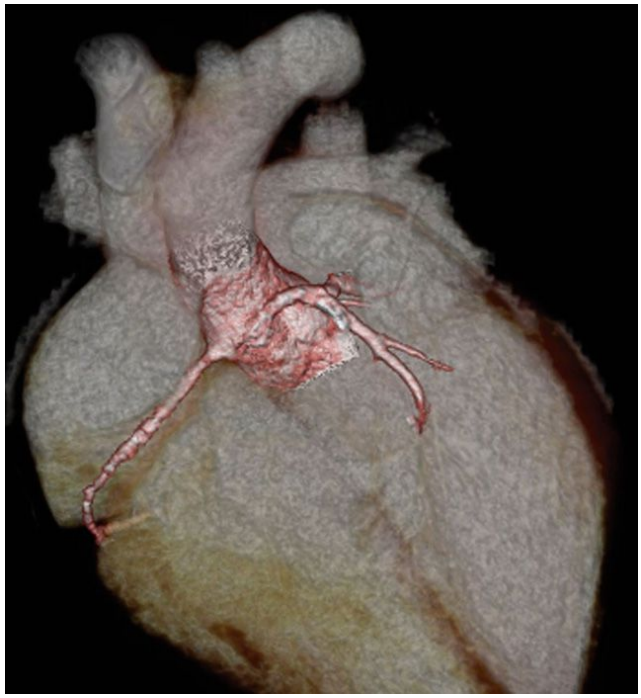


Figure 1. This computed tomography (CT) angiogram shows the right coronary artery coming off towards the left side of the image and the anomalous left coronary artery coming off towards the right side of image branching into the left anterior descending and left circumflex arteries.

Discussion

Since 2011, the prevalence of e-cigarette use has increased at an astonishing pace, including the teenage population. Popular vaping devices are made by JUUL® and Puff Bar®. Due to their discrete and compact profile, these products are used inside and outside of schools, with increased use in school bathrooms and even in classrooms.[2] Between 2011 and 2015, e-cigarette use climbed from 0.6% to 5.3% in middle school children in the United States and from 1.5% to 16% in high schoolers.[3]

Since 2014, e-cigarettes are the most widely used tobacco product among middle and high schoolers.[2] Another source identifies 2014 as the "breakpoint" from traditional cigarette smoking in children and the rapid crescendo of the use of e-cigarette products.[4] From 2017 to 2018, e-cigarette use increased by 77.8% in high schoolers. In 2019, a self-report survey completed by over 19,000 middle and high school students found that 10.5% of middle school students and 27.5% of high school students use e-cigarettes.[1] This sharp incline in vaping is not without potential medical consequences, especially from high levels of nicotine.

In general, sympathetic activation is the most important physiological effect of nicotine. Plasma nicotine levels after vaping are dependent on the generation of electronic cigarette device being used, with most studies looking at the cardiovascular effects after using a first- or second-generation device.[5] The later generation devices like the JUUL® Pod-Mods use nicotine salts instead of alkalinized nicotine which is a more effective delivery method with plasma nicotine levels approaching that of tobacco cigarettes.[6] Newer vaping devices also contain higher nicotine concentrations with up to a 5% nicotine solution

(>50mg/mL), compared to older devices that ranged from 1 to 3% nicotine concentration.[7] Despite a lack of studies using the later generation of devices, studies have shown an acute increase in heart rate and blood pressure which occurred within five to ten minutes secondary to a release of catecholamines.[8] In addition, vaping electronic cigarettes containing nicotine were found to cause electrocardiogram changes specifically increasing the (T_{peak} to T_{end})/ QT ratio, causing abnormal ventricular repolarization which is associated with an increased risk of sudden death.[9] It is important to note that nicotine use has been associated with coronary vasospasm as well.[10]

The prevalence of anomalous left coronary artery (ALCA) arising from the right sinus of Valsalva is extremely rare (0.03%) and is rarely identified in asymptomatic individuals while alive.[11] In ALCA, death often occurs during exercise or with exertion. The proposed mechanism suggests that episodic myocardial ischemia with exertion can result in a lethal arrhythmia and subsequent death. Given this patient's underlying ALCA, we suspect that sympathoexcitatory and arrhythmogenic effects of high dose nicotine via vaping could have led to his cardiovascular collapse at the beginning of gym class. It's noteworthy that the vaping cartridges used by this patient prior to his cardiac arrest did not contain tetrahydrocannabinol (THC), and the cartridges were not tampered with prior to use. In THC-containing vaping products, vitamin E acetate is a common and harmful additive, which has been associated with EVALI.[12]

Conclusion

The effects of e-cigarette use on the cardiovascular system are not well known in the pediatric population. Based on the known adverse effects of nicotine, we suspect that it was the main culprit that caused our patient to suffer a cardiac arrest in the setting of his undiagnosed anomalous left coronary artery. However, due to lack of uniform regulation, the constituents and their concentration in e-cigarettes can vary from product to product. We propose that the adolescent community can benefit from studies looking at the acute and chronic adverse effects of each individual component on the cardiovascular system.

References

1. Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW, Creamer MR, Jamal A, Ambrose BK, King BA. e-Cigarette Use Among Youth in the United States, 2019. JAMA. 2019 Nov 5;322(21):2095–103. doi: 10.1001/jama.2019.18387. Epub ahead of print. PMID: 31688912.

2. Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A, King BA. Vital Signs: Tobacco Product Use Among Middle and High School Students - United States, 2011-2018. MMWR Morb Mortal Wkly Rep. 2019 Feb 15;68(6):157-164. doi: 10.15585/mmwr.mm6806e1. PMID: 30763302.

3. Lippert AM, Corsi DJ, Venechuk GE. Schools Influence Adolescent E-Cigarette use, but when? Examining the Interdependent Association between School Context and Teen Vaping over time. J Youth Adolesc. 2019 Oct;48(10):1899-1911. doi: 10.1007/s10964-019-01106-y. Epub 2019 Aug 24. PMID: 31446585.

4. Creamer MR, Dutra LM, Sharapova SR, Gentzke AS, Delucchi KL, Smith RA, Glantz SA. Effects of e-cigarette use on cigarette smoking among U.S. youth, 2004-2018. Prev Med. 2021 Jan;142:106316. doi: 10.1016/j.ypmed.2020.106316. Epub 2020 Nov 30. PMID: 33272598.

5. MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: what do we know so far? Vasc Health Risk Manag. 2019 Jun 21;15:159-174. doi: 10.2147/VHRM.S175970. PMID: 31417268.

6. Hiler M, Breland A, Spindle T, Maloney S, Lipato T, Karaoghlanian N, Shihadeh A, Lopez A, Ramôa C, Eissenberg T. Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience. Exp Clin Psychopharmacol. 2017 Oct;25(5):380-392. doi: 10.1037/pha0000140. PMID: 29048187.

7. Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market. Tob Control. 2019 Nov;28(6):623-628. doi: 10.1136/tobaccocontrol-2018-054796. Epub 2019 Feb 6. PMID: 30733312..

8. Middlekauff HR, Park J, Moheimani RS. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. J Am Coll Cardiol. 2014 Oct 21;64(16):1740-50. doi: 10.1016/j.jacc.2014.06.1201. PMID: 25323263.

9. Ip M, Diamantakos E, Haptonstall K, Choroomi Y, Moheimani RS, Nguyen KH, Tran E, Gornbein J, Middlekauff HR. Tobacco and electronic cigarettes adversely impact ECG indexes of ventricular repolarization: implication for sudden death risk. Am J Physiol Heart Circ Physiol. 2020 May 1;318(5):H1176-H1184. doi: 10.1152/ajpheart.00738.2019. Epub 2020 Mar 20. PMID: 32196360.

10. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med. 2016 Aug;26(6):515-23. doi: 10.1016/j.tcm.2016.03.001. Epub 2016 Mar 10. PMID: 27079891.

11. Finocchiaro G, Behr ER, Tanzarella G, Papadakis M, Malhotra A, Dhutia H, Miles C, Diemberger I, Sharma S, Sheppard MN. Anomalous Coronary Artery Origin and Sudden Cardiac Death: Clinical and Pathological Insights From a National Pathology Registry. JACC Clin Electrophysiol. 2019 Apr;5(4):516-522. doi: 10.1016/j.jacep.2018.11.015. Epub 2019 Jan 30. PMID: 31000108.

12. Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, Braselton M, Brosius CR, Caron KT, Chambers D, Corstvet J, Cowan E, De Jesús VR, Espinosa P, Fernandez C, Holder C, Kuklenyik Z, Kusovschi JD, Newman C, Reis GB, Rees J, Reese C, Silva L, Seyler T, Song MA, Sosnoff C, Spitzer CR, Tevis D, Wang L, Watson C, Wewers MD, Xia B, Heitkemper DT, Ghinai I, Layden J, Briss P, King BA, Delaney LJ, Jones CM, Baldwin GT, Patel A, Meaney-Delman D, Rose D, Krishnasamy V, Barr JR, Thomas J, Pirkle JL; Lung Injury Response Laboratory Working Group. Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. N Engl J Med. 2020 Feb 20;382(8):697-705. doi: 10.1056/NEJMoa1916433. Epub 2019 Dec 20. PMID: 31860793; PMCID: PMC7032996.

Disclosure

None reported.

MM

The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies

by James J. DiNicolantonio, PharmD & James O'Keefe, MD

Considering that most of the population is deficient in long-chain omega-3s, there is an increased need for educating the public on the importance of increasing marine omega-3 intake. At the same time, background intake of omega-6 polyunsaturated fatty acids also needs to be reduced.





James J. DiNicolantonio, PharmD, (left), and **James H. O'Keefe, MD**, (right), are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri.

Abstract

Up until about 100 years ago, the omega-6/3 ratio has been around 4:1 or less. However, the typical Western diet now provides an omega-6/3 ratio of approximately 20:1 in favor of omega-6. This predisposes to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation. The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of long-chain omega-3s in the diet creates a pro-inflammatory, pro-allergic, pro-thrombotic state. Reducing the omega-6/3 ratio, particularly through reductions in the intake of refined omega-6 seed oil, and increasing the intake of marine omega-3s, either through dietary means or supplementation, may be an effective strategy for reducing inflammation, allergies, and autoimmune reactions.

Introduction

Marine omega-3s have been consumed by our ancestors for millions of years. Estimates indicate that during the Paleolithic era, the intake of the marine omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was approximately 660-14,250 mg/day,[1, 2] compared to just 100-200 mg/day today.[3, 4] Furthermore, the omega-6/3 ratio has increased from around 4:1 during Paleolithic times to 20:1 today.[1, 5]

Over the last 100 years, the intake of the omega-6 fat linoleic acid in the United States has more than doubled.[6] This is primarily due to the increased consumption of omega-6 rich seed oils, such as soybean, corn, and safflower oil, the latter two having an omega-6/3 ratio of approximately 60:1 and 77:1, respectively. Additionally, since the 1950s, there has been an approximate 2.5-fold increase in linoleic acid stored in adipose tissue in the United States.[7] The increase in the omega-6/3 ratio has paralleled the rise in numerous autoimmune, inflammatory, and allergic diseases. Omega-3s are utilized by the body to resolve and lower inflammation, whereas omega-6 polyunsaturated fatty acids are primarily used for increasing inflammation. Thus, the rise in the omega-6/3 ratio over the past 100 years may be driving chronic low-grade inflammatory conditions including autoimmune diseases, allergies and asthma. Table 1 and Table 2 list dietary sources of marine omega-3s and omega-6 fats in the diet.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune condition, whereby the immune system attacks the lining of joints causing joint inflammation and pain. Clinical studies have suggested that omega-3s may play a role in improving rheumatoid arthritis. Indeed, a meta-analysis of 17 randomized controlled trials in humans concluded that omega-3 polyunsaturated fatty acids (PUFAs) are effective in improving symptoms in patients with rheumatoid arthritis, inflammatory bowel disease, and dysmenorrhea.[11] A diet low in arachidonic acid (less than 90 mg/day) has also been found to lower clinical signs of inflammation in patients with rheumatoid arthritis and these effects were enhanced with the addition of a fish oil supplement.[12] At least 11 randomized double-blind placebo-controlled trials have found benefits of fish oil in rheumatoid arthritis including reductions in the need for pain relievers.[13] This may be due to the fact that the EPA/DHA content of immune cells is important for preventing the conversion of the immune system to an inflammatory phenotype and also for reverting chronic inflammatory immune cells back to their native state.

DHA, but not EPA, has been found to reduce the expression of vascular cell adhesion molecule-1 (VCAM-1) and monocyte adhesion to human endothelial cells after inflammatory cytokine stimulation.[14, 15] In young men, when six grams of DHA replaced six grams of linoleic acid (15 grams of DHA-rich alga oil replacing 15 grams of safflower oil) for 90 days the authors reported, "DHA consumption does not inhibit many of the lymphocyte functions which have been reported to be inhibited by fish oil consumption."[16] In other words, DHA does not appear to inhibit immune system function. DHA also lowered prostaglandin E2 (PGE2) and leukotriene B4 production in response to lipopolysaccharide by 60-75% and interleukin-1beta and TNF-alpha release from peripheral blood mononuclear cells by 40-45%.[17] This suggests that DHA calms an overactive immune system, which is at the root of chronic inflammatory disease states and autoimmune conditions. It can take up to 18 weeks to reach maximal DHA content in cells, whereas EPA takes only about six weeks.[18] Furthermore, EPA concentrates largely in circulation whereas DHA concentrates in the cell membranes of brain and heart tissue. Thus, the full benefits of increasing the intake of omega-3s PUFAs may not be realized for months.

Table 1. Dietary Sources of Marine Omega-3[8,9]

Food Source	Grams of EPA/DHA per 3 oz. serving
Salmon roe	2.70
Halibut	2.21
Herring	1.7–1.8
Salmon (wild)	1.0–3.0
Sardines	1.0–1.74
Trout	1.0
Oysters	0.45–1.15
Mackerel	0.35–1.80
Tuna (fresh)	0.25–1.30

Table 2. Dietary Sources of Omega-6[10]

Food Source	Total omega-6 grams per 1-ounce serving
Walnuts	10.8
Pine nuts	9.5
Sunflower seeds	6.5
Sesame seeds	6.0
Brazil nuts	5.8
Pumpkin seeds	5.8
Pecans	5.8
Pistachios	3.7
Almonds	3.4

Ulcerative Colitis and Crohn's Disease

Ulcerative colitis and Crohn's disease are both chronic inflammatory diseases. The main pathological finding is infiltration of neutrophils and mononuclear cells into the affected parts of the intestine.[19] Interluekin-8 (IL-8) is a chemokine and a potent signaling molecule that recruits neutrophils into inflammatory tissues. Compared to normal control subjects, patients with active inflammatory bowel disease have mucosa that contains more IL-8. In one

study, there was a nine-fold increase in IL-8 secretion when smooth muscle cells isolated from the strictures of Crohn's patients were exposed to linoleic acid, which did not occur with oleic acid.[20] Furthermore, linoleic acid activates the arachidonic acid pathways and increases the pro-inflammatory arachidonic metabolites from both lipoxygenase (LOX) (such as leukotriene-B4) and cyclooxygenase (COX) (such as prostaglandin-E2 and thromboxane-B2). Thus, the omega-6 polyunsaturated fatty acid linoleic acid may have proinflammatory effects, particularly in those with inflammatory bowel disease.

In normal cells, oxidized linoleic acid activates Nuclear Factor-Kappa Beta (NF-kB), which is a transcription factor that promotes inflammation.[19] Thus, oxidized linoleic acid may stimulate inflammation in normal healthy intestinal smooth muscle cells. The mononuclear cells and macrophages of Crohn's patients have an increased expression of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1B) and the inflamed mucosa in these patients produces increased amounts of TNF-alpha, interleukin-6 (IL-6) and IL-1B), which likely drives further activation of NF-kB.[19] The suppression of the chronic inflammatory pathway may be why supplementing with fish oil seems to improve these inflammatory/auto-immune conditions.

In Crohn's patients there is increased COX-2 expression in colonic epithelium.[19] The inflamed colon produces large amounts of prostaglandins, thromboxane and leukotrienes. Oxidative stress is also significantly increased in Crohn's cells exposed to oxidized linoleic acid. A combination of oxidative stress and linoleic acid stimulated IL-8 production in both normal and Crohn's cells, whereas linoleic acid alone stimulated IL-8 production in Crohn's cells.[19] Inhibitors of either COX or LOX suppressed the ability of oxidative stress plus linoleic acid to increase IL-8, suggesting that an increase in arachidonic acid metabolites mediate inflammatory responses to linoleic acid. The authors of the study concluded, "These data suggest that dietary restriction of linoleic acid, antioxidant supplementation, and treatment with arachidonic acid pathway inhibitors may be beneficial for treating Crohn's patients."[19]

In summary, the Western diet is now much higher in omega-6 than omega-3 compared to just 100 years ago. This may predispose to chronic inflammatory conditions including autoimmune diseases. Supplementing these patients with marine omega-3s such as EPA and DHA may provide improvements in their condition.

Allergies

The increase in the omega-6/3 ratio occurred in parallel with the rise in the prevalence "hyperallergic" atopic conditions as well as other allergic diseases including rhino-conjunctivitis, allergic asthma, and atopic eczema.[21] The parent omega-3 fatty acid alpha-linolenic acid (ALA) and the parent omega-6 fatty acid linoleic acid compete for the same enzymes. Thus, a high dietary intake of linoleic acid reduces the elongation of ALA into EPA and DHA. Moreover, the bioactive metabolites formed from omega-6 are more inflammatory compared to the omega-3 pathway. Indeed, many of the leukotrienes formed from the omega-6 pathway are implicated in allergic asthma and other atopic diseases. The current imbalance in the omega-6/3 ratio may lead to a "hyperallergic" state through an increase in reactive leukotrienes formed from the omega-6 pathway compared the omega-3 pathway.

The primary contributor to the rise in intake of omega-6 linoleic acid is from the consumption of industrial seed or vegetable oils such as safflower, sunflower, cottonseed, soybean, and corn oil. These omega-6 seed oils provide very high amounts of concentrated linoleic acid. Linoleic acid competes with ALA for elongation but it also is in competition between eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and arachidonic acid (AA) in membrane phospholipids. A low intake of EPA/DHA will lead to an increase in AA and an overproduction of the inflammatory and pro-allergic metabolites such as 2-series eicosanoids and 4-series leukotrienes, respectively, the latter of which can lead to the recruitment and accumulation of mast cells.[22] Moreover, EPA and DHA inhibit cyclooxygenase (COX) and lipoxygenase (LOX); thus, reducing the breakdown of AA and linoleic acid into pro-allergic metabolites while simultaneously boosting anti-inflammatory and anti-allergic metabolites. Importantly, allergic diseases are characterized by a chronic inflammatory state and the anti-inflammatory mediators formed from EPA/DHA such as resolvins and protectins may help to resolve and reduce the

Table 3. Studies of Omega-3s in pregnancy for reducing allergic disease in offspring

Population	Omega-3 Dose	Outcome
98 atopic pregnant women[23]	3,700 mg of long-chain omega-3 PUFAs (56% DHA, 27.7% EPA)/day given at 20 weeks gestation until delivery	Reduced sensitization to eggs at 12 months by 66% and severity of eczema by 91%.
154 pregnant women affected by allergies or having a husband or previous child with allergies[24]	2.7 grams of EPA/DHA/day given at 25 weeks gestation until 3-4 months of breastfeeding	Reduced the risk of food allergy by over 7-fold and lead to a 3-fold reduction in IgE-associated eczema.
533 women with normal pregnancies (30 weeks gestation)[25]	2.7 grams of omega-3 PUFAs from fish oil/day given at 30 weeks gestation	Significant reductions in asthma (-63%) and allergic asthma (-87%) in offspring.
706 pregnant women with a fetus at high risk of developing allergic diseases	900 mg of omega-3 PUFAs from fish oil given at 21 weeks gestation	Reduced atopic eczema and egg sensitization.

inflammatory and allergic state, respectively. Resolvins and protectins are specialized pro-resolving mediators derived from omega-3 fatty acids that have anti-inflammatory effects helping inflammatory conditions return back to normal homeostasis.

Omega-3s in Pregnancy Reduce Allergic Disease in Offspring: Clinical Studies

Randomized controlled trials have found significant reductions in allergic diseases in offspring when long-chain omega-3 PUFAs are provided during pregnancy. One randomized controlled trial in 98 atopic pregnant women showed that compared to olive oil capsules, 3,700 mg of long-chain omega-3 PUFAs (56% DHA, 27.7% EPA) given at 20 weeks gestation until delivery reduced sensitization to eggs at 12 months by 66% and severity of eczema by 91%.[23] Another randomized placebo-controlled trial, this time in 154 pregnant women affected by allergy themselves or having a husband or previous child with allergies, found that 2.7 grams of EPA/DHA given at 25 weeks' gestation until three to four months of breastfeeding reduced the risk of food allergy by over seven-fold and lead to a three-fold reduction in IgE-associated eczema.[24] Another randomized controlled trial in 533 women with normal pregnancies found significant reductions in asthma (-63%) and allergic asthma (-87%) in offspring when 2.7 grams of omega-3 PUFAs from fish oil were given at 30 weeks gestation compared to olive oil.[25] Lastly, a randomized controlled trial in 706 pregnant women with a fetus at high risk of developing allergic diseases found that 900 mg of omega-3 PUFAs from fish oil given at 21 weeks gestation reduced atopic eczema and egg sensitization compared to placebo vegetable oil capsules.[26]

A systematic review and meta-analysis encompassing 10 prospective cohort studies and 5 randomized controlled trials concluded that if pregnant women ingest appropriate amounts of EPA/DHA they may be able to reduce their risk of allergic diseases in their children.[21] Indeed, the authors of the study concluded, "Our systematic review and meta-analysis was suggestive of benefits of increased omega-3 long-chain-PUFAs in the maternal diet and outcomes of childhood allergic disease... increasing omega-3 long-chain-PUFA intake during pregnancy may offer the best opportunity for a primary prevention strategy, decreasing the burden of allergic disease for future generations."[21] Moreover, about 70% of the observational and randomized publications found a reduced incidence of allergic disease symptoms in offspring with increased omega-3 long-chain PUFA or fish intake in pregnancy. Additionally, there were highly significant reductions in "atopic eczema" (-47%), "any positive skin-prick test" (-32%), "sensitization to egg" (-45%), and "sensitization to any food" (-41%) in the first 12 months of life ($p=0.004$, $p=0.006$, $p=0.0004$, and $p<0.0001$, respectively) with increased omega-3 PUFA intake in pregnancy.[21] Thus, ensuring an optimal long-chain omega-6/3 ratio in pregnancy, before the fetal immune system is programed to an allergic phenotype, may be an important strategy to prevent allergic diseases in the offspring.[21] Table 3 summarizes the clinical studies of omega-3s in pregnancy for reducing allergic disease in offspring.

Table 4. Observational data of higher omega-3 intake and lower risk of asthma, eczema and atopic wheeze

Omega-3 Intake	Outcome
Not eating fish at all vs. consistent high fish intake during pregnancy[27]	30% increased risk of asthma in the offspring, 46% increased risk of ever being hospitalized for asthma, and 37% increased risk for ever being prescribed a medication for asthma
Higher dietary omega-6/3 ratio in pregnancy[28]	37% increased risk of allergic rhinitis in the offspring by 5 years of age
A low intake of ALA and total omega-3 PUFAs[29]	67% and 66% increased risk of asthma in the offspring, respectively
7.2 oz. or more of fish per week in pregnancy[30]	43% reduction in the risk of eczema in offspring
Maternal fish intake greater than 2-3 times per week[31,32]	Reduces the incidence of persistent wheeze by 66%, eczema by 37% (in offspring at 1 year), positive skin-prick test to house dust mites by 35% (at 6 years) and atopic wheeze by 45% in offspring at 1 year
Fish intake 1 time per week or more in pregnancy[33]	43% reduction in doctor-confirmed eczema and a 72% in doctor-confirmed hay fever at 5 years

Asthma

Asthma has increased in prevalence over the past several decades, which may be due to a reduction in dietary omega-3 intake. For example, compared with consistently high fish intake in pregnancy, not eating fish at all is associated with a 30% increased risk of asthma in the offspring as well as a 46% increased risk of ever being hospitalized for asthma, and a 37% increased risk for ever being prescribed a medication for asthma.[27] A higher dietary omega-6/3 ratio in pregnancy is associated with a 37% higher risk of allergic rhinitis in the offspring by five years of age.[28] A low intake of ALA and total omega-3 PUFAs in pregnancy is associated with a 67% and 66% increased risk of asthma in the offspring, respectively.[29] An intake of 7.2 oz. or more of fish per week in pregnancy is associated with a 43% reduction in the risk of eczema in offspring.[30] Maternal fish intake greater than two to three times per week has been found to reduce the incidence of persistent wheeze by 66%,[31] eczema by 37% (in offspring at one year) and positive skin-prick test to house dust mites by 35% (at six years).[32] Fish intake was also associated with a reduced risk atopic wheeze by 45% in offspring at one year.[32] And fish intake one time per week or more in pregnancy versus never is also associated with a 43% reduction in doctor-confirmed eczema and a 72% in doctor-confirmed hay fever at five years.[33] Table 4 summarizes the observational data of higher omega-3 intake and lower risk of asthma, eczema and atopic wheeze.

Omega-3s and Asthma: Clinical Studies

One randomized, double-blind, controlled study in 39 asthmatic children (8-12 years-old) of six months compared fish oil capsules plus canola oil and margarine (omega-3 group) versus safflower oil capsules (0.45 grams plus 0.1 grams of olive oil) plus sunflower oil and margarine (omega-6 group).[34] The majority of patients in the study were already on inhaled corticosteroids and beta-agonists. The omega-6 group was asked not to eat fish which translated to the omega-3 group eating more fresh fish vs. the omega-6 group (340 g/month vs. 109 g/month, p=0.0045). The average number of consumed capsules was three out of four in both groups, which equated to 900 mg of EPA/DHA per day (0.18 g EPA and 0.12 g DHA per capsule) in the omega-3 group. The omega-6 group received around 1.35 grams of safflower oil in the capsules on average per day. The changes in plasma phospholipid omega-3 and omega-6 were +3.18% vs. -0.21% at three months and +2.19% vs. 0.05% at six months, respectively. The changes for plasma EPA was +1.98% and -0.11% at three months and +1.2% vs. +0.19% at six months, respectively. Tumor necrosis factor (TNF)-alpha fell significantly vs. baseline in the omega-3 group (-416 $pg \cdot mL^{-1}$) with a slight increase in the omega-6 group (+ 44 $pg \cdot ml^{-1}$) and a trend for a significant difference between the groups (p=0.075). Eosinophil numbers also fell in the omega-3 group from $0.91x10^{9} \cdot L^{-1}$ cells at baseline to $0.74x10^{9}$ $cells \cdot L^{-1}$ at three months

Table 5. Clinical studies testing omega-3s in asthma

Population	Omega-3 Dose	Outcome
39 asthmatic children[34]	More fresh fish vs. the omega-6 group (340 g/month vs. 109 g/month, p=0.0045) plus ~ 900 mg of EPA/DHA per day	The median asthma severity score was lower in the omega-3 group but not significantly less compared to the omega-6 group.
98 patients with obesity and uncontrolled asthma[35]	4 grams/day of omega-3 PUFAs	Significantly reduced asthma-related phone contacts by 66%.

and 0.65 x10^9 cells·L^{-1} at six months, whereas the eosinophil count rose in the omega-6 group from 0.62x10^9 cells·L^{-1} at baseline to 0.70x10^9 cells·L^{-1} at three months and 0.81x10^9 cells·L^{-1} at six months (p=0.11). The continued reduction in TNF-alpha and eosinophil with the intake of omega-3s suggested a reduction in airway inflammation. Additionally, the median asthma severity score was lower in the omega-3 group but not significantly less compared to the omega-6 group.[34] Larger trials of longer duration are needed to conclude if long-chain omega-3s can provide clinical benefits to patients with asthma. The dose of omega-3s used in this study (900 mg of EPA/DHA per day) may not have been optimal for maximal anti-inflammatory effects that higher doses, such as three to four grams of EPA/DHA per day, may have provided.[34]

A recent randomized study in 98 patients with obesity and uncontrolled asthma found that four grams/day of omega-3 PUFAs significantly reduced asthma-related phone contacts by 66%.[35] Despite this benefit the others concluded that omega-3 PUFAs did not improve most asthma-related outcomes (such as leukotriene-E4, forced expiratory volume in one second, and asthma exacerbations at six months). Thus, further studies are required to ascertain the benefits of marine omega-3s in asthma patients. Table 5 summarizes the clinical studies of omega-3s in asthma.

Conclusion

Reducing the omega-6/3 ratio in pregnancy may help to reduce allergic conditions in offspring and may help patients with asthma. Larger clinical studies are required to confirm these benefits particularly in the setting of asthma. It is our contention, that the increase in the omega-6/3 ratio may have contributed to a rise of allergic and autoimmune diseases over the last several decades. Additionally, a high dietary omega-6/3 ratio creates supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation. The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of long-chain omega-3s in the diet puts the population in a pro-inflammatory, pro-allergic, pro-thrombotic and autoimmune-prone state. This pro-inflammatory state may also predispose to cytokine storms during viral infections.

Considering that most of the population is deficient in long-chain omega-3s, there is an increased need for educating the public on the importance of increasing marine omega-3 intake. Supplementation or fortification of foods with marine omega-3s is one way to increase population-wide omega-3 intake. Additionally, increasing the consumption of seafood, such as fatty fish, crustaceans, and shellfish, is another way to increase marine omega-3 intake. At the same time, background intake of omega-6 PUFA also needs to be reduced. In particular, omega-6 seed oils such as soybean, cottonseed, corn, and safflower oil are some of the largest contributors to the omega-6 intake in the Western world. These sources of omega-6 are highly refined and are more susceptible to oxidation compared to whole foods that contain omega-6 PUFAs such as nuts, seeds, vegetables, and eggs. A reduction in the intake of industrial omega-6 seed oils will help reduce the high dietary omega-6/3 ratio and the pro-inflammatory state that ensues.

References

1 Kuipers RS, Luxwolda MF, Dijck-Brouwer DA, et al. Estimated macronutrient and fatty acid intakes from an East African Paleolithic diet. The British journal of nutrition 2010;104:1666-87.

2 Eaton SB, Eaton SB, 3rd, Sinclair AJ, et al. Dietary intake of long-chain polyunsaturated fatty acids during the paleolithic. World review of nutrition and dietetics 1998;83:12-23.
3 Singh RB, Demeester F, Wilczynska A. The tsim tsoum approaches for prevention of cardiovascular disease. Cardiology research and practice 2010;2010:824938.
4 Rodriguez-Leyva D, Dupasquier CM, McCullough R, et al. The cardiovascular effects of flaxseed and its omega-3 fatty acid, alpha-linolenic acid. The Canadian journal of cardiology 2010;26:489-96.
5 Simopoulos AP, DiNicolantonio JJ. The importance of a balanced omega-6 to omega-3 ratio in the prevention and management of obesity. Open Heart 2016;3:e000385.
6 Blasbalg TL, Hibbeln JR, Ramsden CE, et al. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. The American journal of clinical nutrition 2011;93:950-62.
7 Guyenet SJ, Carlson SE. Increase in adipose tissue linoleic acid of US adults in the last half century. Advances in nutrition (Bethesda, Md) 2015;6:660-4.
8 Moyad MA. An introduction to dietary/supplemental omega-3 fatty acids for general health and prevention: part II. Urologic oncology 2005;23:36-48.
9 Arab-Tehrany E, Jacquot M, Gaiani C, et al. Beneficial effects and oxidative stability of omega-3 long-chain polyunsaturated fatty acids. Trends in Food Science & Technology 2012;25:24-33.
10 http://nutritiondata.self.com/. Accessed 8/6/2020.
11 Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007;129:210-23.
12 Adam O, Beringer C, Kless T, et al. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. Rheumatology international 2003;23:27-36.
13 James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. The American journal of clinical nutrition 2000;71:343s-8s.
14 De Caterina R, Cybulsky MI, Clinton SK, et al. The omega-3 fatty acid docosahexaenoate reduces cytokine-induced expression of proatherogenic and proinflammatory proteins in human endothelial cells. Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association 1994;14:1829-36.
15 Weber C, Erl W, Pietsch A, et al. Docosahexaenoic acid selectively attenuates induction of vascular cell adhesion molecule-1 and subsequent monocytic cell adhesion to human endothelial cells stimulated by tumor necrosis factor-alpha. Arteriosclerosis, thrombosis, and vascular biology 1995;15:622-8.
16 Kelley DS, Taylor PC, Nelson GJ, et al. Dietary docosahexaenoic acid and immunocompetence in young healthy men. Lipids 1998;33:559-66.
17 Kelley DS, Taylor PC, Nelson GJ, et al. Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. Lipids 1999;34:317-24.
18 Marangoni F, Angeli MT, Colli S, et al. Changes of n-3 and n-6 fatty acids in plasma and circulating cells of normal subjects, after prolonged administration of 20:5 (EPA) and 22:6 (DHA) ethyl esters and prolonged washout. Biochimica et biophysica acta 1993;1210:55-62.
19 Alzoghaibi MA, Walsh SW, Willey A, et al. Linoleic acid induces interleukin-8 production by Crohn's human intestinal smooth muscle cells via arachidonic acid metabolites. American journal of physiology Gastrointestinal and liver physiology 2004;286:G528-37.
20 Alzoghaibi MA, Walsh SW, Willey A, et al. Linoleic acid, but not oleic acid, upregulates the production of interleukin-8 by human intestinal smooth muscle cells isolated from patients with Crohn's disease. Clinical nutrition (Edinburgh, Scotland) 2003;22:529-35.
21 Best KP, Gold M, Kennedy D, et al. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. The American journal of clinical nutrition 2016;103:128-43.
22 Lundeen KA, Sun B, Karlsson L, et al. Leukotriene B4 receptors BLT1 and BLT2: expression and function in human and murine mast cells. Journal of immunology (Baltimore, Md : 1950) 2006;177:3439-47.
23 Dunstan JA, Mori TA, Barden A, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. The Journal of allergy and clinical immunology 2003;112:1178-84.
24 Furuhjelm C, Warstedt K, Larsson J, et al. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta paediatrica (Oslo, Norway : 1992) 2009;98:1461-7.
25 Olsen SF, Osterdal ML, Salvig JD, et al. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. The American journal of clinical nutrition 2008;88:167-75.
26 Palmer DJ, Sullivan T, Gold MS, et al. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. BMJ (Clinical research ed) 2012;344:e184.
27 Maslova E, Strom M, Oken E, et al. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort. The British journal of nutrition 2013;110:1313-25.
28 Nwaru BI, Erkkola M, Lumia M, et al. Maternal intake of fatty acids during pregnancy and allergies in the offspring. The British journal of nutrition 2012;108:720-32.
29 Lumia M, Luukkainen P, Tapanainen H, et al. Dietary fatty acid composition during pregnancy and the risk of asthma in the offspring. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 2011;22:827-35.
30 Jedrychowski W, Perera F, Maugeri U, et al. Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. International archives of allergy and immunology 2011;155:275-81.
31 Chatzi L, Torrent M, Romieu I, et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. Thorax 2008;63:507-13.
32 Romieu I, Torrent M, Garcia-Esteban R, et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2007;37:518-25.
33 Willers SM, Devereux G, Craig LC, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. Thorax 2007;62:773-9.
34 Hodge L, Salome CM, Hughes JM, et al. Effect of dietary intake of omega-3 and omega-6 fatty acids on severity of asthma in children. The European respiratory journal 1998;11:361-5.
35 Lang JE, Mougey EB, Hossain MJ, et al. Fish Oil Supplementation in Overweight/Obese Patients with Uncontrolled Asthma. A Randomized Trial. Annals of the American Thoracic Society 2019;16:554-62.

Disclosure

JJD is Director of Scientific Affairs at Advanced Ingredients for Dietary Products. JOK is an owner of a nutraceutical company that sells omega-3 supplements. **MM**

A Primer on Chimera Associated Receptor T-Cells

by Sumalatha Muthineni, MD, Katelyn Zink, PharmD & Suman Kambhampati, MD

Dramatic clinical responses and high rates of complete remission have been observed in the setting of CAR T-cell therapy of B-cell malignancies.



Sumalatha Muthineni, MD, Internal Medicine, Katelyn Zink, PharmD, and Suman Kambhampati, MD, Hematology/Oncology, (above), practice at the Sarah Cannon Transplant and Cellular Therapy Program, Research Medical Center, Kansas City, Missouri.

Abstract

Cancer continues to be one of the leading causes of death. Although survival rates have improved with current treatments for hematological malignancies, relapsed and refractory cases have poor prognosis. Immunotherapy against cancer cells offer new hope for curative response in these patients. Of those, Chimeric Antigen Receptor (CAR) T-cells are emerging as promising therapy for hematological malignancies, where T-lymphocytes are genetically engineered with CAR to recognize and eliminate specific tumor cells. The efficacy of CAR T-cell therapy is also being studied in solid tumors. In this review, the basic principles of CAR T-cell therapy are discussed.

Introduction

Cancer is the second leading cause of death. Despite improvements in therapeutic options for malignancies, treatment of refractory and relapsed malignancies is still challenging. Conventional treatments may have curative effect but the side effects caused by these treatments affects quality of life.[1] In order for the cancer cells to survive and proliferate, they must escape the destructive properties of the immune response. Tumor cells can avoid identification and destruction by immune system in different ways, including the ability to down regulate tumor antigen expression and create alternate versions of antigens by mutations or tumor antigen masking, known as immunoediting.[2] Cancer immunotherapy takes advantage of the body's own immune system to battle cancer. Cancer immunotherapies mainly comprise of immune checkpoint inhibitors, adoptive cell therapies, and tumor vaccines.[3] T-lymphocytes play a key role in adaptive immunity by recognizing foreign antigenic peptides presented on MHC molecules by antigen-presenting cells (APC) using T-cell receptor (TCR). The interaction between T-cell and APC recruit's co-receptors, like CD28, leading to activation of signaling cascade then in turn leads to T-cell activation.[4] After T-cell is activated by APC, it starts to proliferate, differentiates into mature effector cell and then migrates to the site of inflammation or infection.[5] Mature CD8+ T cell, when it encounters a cell presenting antigen complementary to its' TCR, release cytotoxic mediators which in turn kills malignant or target cells.

Three major types of T-cell based therapies are known, namely tumor-infiltrating lymphocytes (TILs), TCR and Chimera

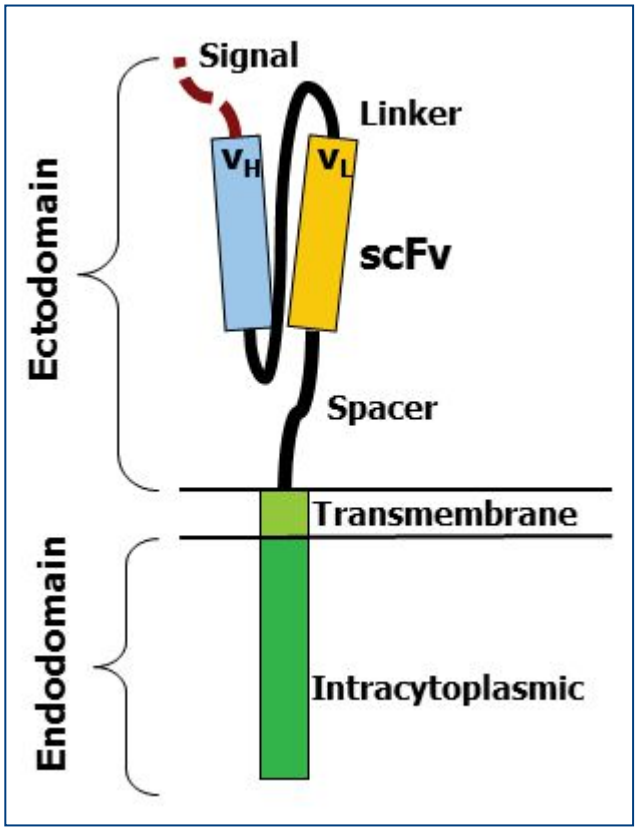


Figure 1. CAR T-cell structure. Source: Research Gate

associated receptor T- cells (CAR T-cells). Based on the property of recognition by TCR, cancer immunotherapy facilitates the adaptive transfer of genetically engineered T-cells and promotes the efficacy of T-cells by mitigating the inhibition of immune checkpoints and expands adaptive immunity.[6] Adaptive cell therapies (ACT) have been used for long time for treatment of various diseases including cancers. ACT is a treatment, where a cancer patients' own T-cells with antitumor activity are expanded in vitro and reinfused into the patient, using autologous tumor-infiltrating lymphocytes.[7] However the process of isolation and expansion of tumor reactive TILs is cumbersome and labor intensive. Therefore genetically engineered T lymphocytes with synthetic receptors to target tumor cells have come into play to overcome these obstacles.[8] CAR T-cell therapy is an innovative technique in immunotherapy for cancer treatment.[9]

What Are CAR T-Cells?

CAR T-cells are T-lymphocytes that are genetically modified to replace the T-cell receptor with synthetic receptors, s-CARs, to recognize and eliminate cancer cells independent of major histocompatibility complex.[10] These synthetic T-cells have both antibody specificity properties as well as regular T-cell functions, such as proliferation, cytokine production and elimination of targeted cells. In 1989, Esshar et al., first described the concept of fusing an immunoglobulin V chain to a TCR constant domain as a CAR, making T-cells MHC unrestricted.[11] This phenomenon allows the modified T-cells to recognize more extensive targets than the natural TCR[9]. It enables T-cell expansion, withstands tumor related immunodeficiency, and avoids tumor escape by HLA down regulation.[12, 13]

Structure

A CAR is a recombinant receptor that comprises of tumor-antigen binding and T-cell activating functions.[14] CARs consist of an extra cellular, antigen-binding domain, an extra cellular hinge region, a transmembrane domain, and an intracellular signaling or T-cell activation domain. Extracellular domain consists of antigen-recognition regions of an antibody, single-chain variable fragment (scFv) that binds specifically to a target molecule expressed on the surface of tumor cells. The hinge region is made of immunoglobulins like CD8, CD28, IgG, and assists in signal transduction. Intracellular signaling domain is the functional part of CAR and it consists of CD3 chain of TCR, which provides the activating signal. Co-stimulatory molecules like CD28, 4-1BB are attached to intracellular domain to improve cell proliferation, survival time in vivo and anti-tumor activity of CAR T-cells[15] (Figure 1).

There are four generations of CAR T-cells, based on their signaling domains. First generation CAR T-cells are made of only one stimulatory domain that is derived from CD3ζ chain or FcRc.[16] First generations CARs were safe, but ineffective due to limited potential for expansion and persistence in vivo.[17] To overcome this, second generation CARs were produced by adding one costimulatory domain to CD3ζ chain, mostly CD28 or 4-1BB to improve cell proliferation, in vivo survival time, cytokine secretion, notably IFN-γ and anti-tumor activity of CAR T-cells.[15]

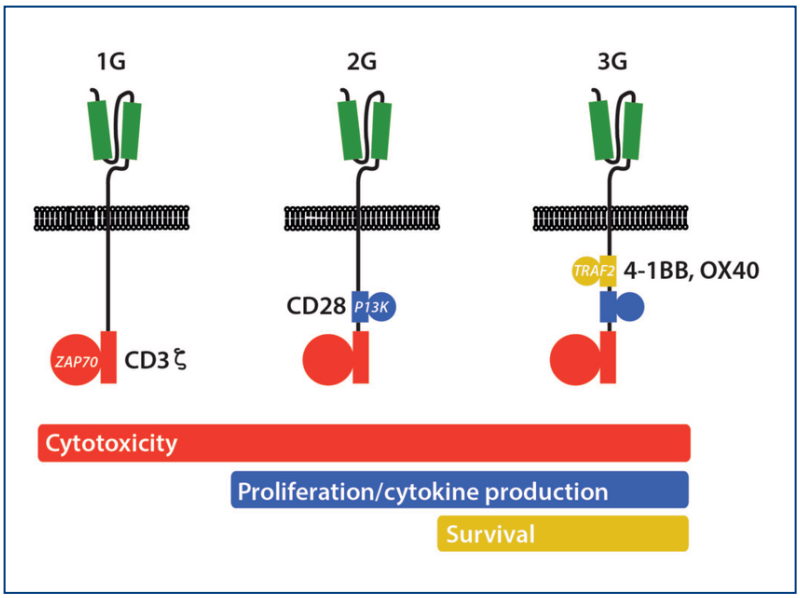


Figure 2.CART generations. Source: Research Gate

Significant anti-tumor responses were seen with second generation CAR T.[18] Third generation CAR T-cells are developed by adding two co-stimulatory molecules to achieve higher potency.[19] Later, fourth generation CAR T-cells, called "T-cells redirected for universal cytokine-mediated killing" (TRUCKs) were developed. These are mainly based on second generation CARs but are engineered with nuclear factor, which induces cytokine expression such as IL-12, 8,9,15, and IL-18 when the cells are activated. This cytokine activation results in prolonged activation of CARs and protects T-cell from activation induced cell death and avoids systemic toxicity.[20] Fifth generation CARs are also in development, again based on second generation CARs but with addition of truncated IL-2 receptor β-chain domain with STAT3 binding site[21] (Figure 2).

Process of Developing CAR T-Cells

CAR T-cell production mainly involves obtaining T-cell from patient, converting them outside the body and reinsertion of the modified cells into human body to target cancer cells.[9] The whole process involves the following steps: T-cell collection by the process of leukapheresis, T-cell activation, T-cell expansion, genetic modification of T-cells by transduction of cells by a vector encoding CAR gene creating CAR T-cells, CAR T-cell culture and expansion ex-vivo, transfuse appropriate dose of the expanded CAR T-cells back into the patient.[15, 22] The entire process from the time of cell extraction to infusion of CAR T-cells into the host takes about three weeks.[9]

Leukapheresis is the first step where T-cells are obtained from the patient, washed and then they are activated with the use of beads, covered in anti CD3 or CD28 monoclonal antibodies or with allogeneic dendritic cells.[23] These activated cells are used for genetic modification. Genetic modification is the process where vectors introduce genetic material in the form of RNA, which is later reversely transcribed into T-cell DNA. It can be done using recombinant viruses, biological nanoparticles and non-viral methods.[24] Gamma retroviral vectors and HIV-based lentiviral vectors are most commonly used for gene transfer system so far.[25] Yet, the cost and expertise needed for production and regulatory requirements are drawbacks to use viral vectors. To prevent these, the transposon system and electroporation of mRNA constructs were introduced. However, transposons require long duration for T-cell culture to produce adequate cell doses and mRNA is unstable, leading to transient CAR expression. Anti Cd3/anti-CD28 monoclonal antibody-coated magnetic beads are used to activate T-cells, and bioreactors are used expand the genetically modified T-cells. Optimal time for ex-vivo expansion appears to be anywhere between one to six weeks.[26] After expansion, the cell culture must be concentrated to appropriate therapeutic dose for the patient. The injectable dose of CAR T-cells varies from $1x\ 10^5$/kg to $1x\ 10^{10}$/kg CAR T-cells or more.[9] Prior to infusion of CAR T-cells into the patient, lymphodepleting therapy in the form of radiation or chemotherapy is recommended to facilitate enhancement of in vivo proliferation and persistence of these T-cells.[27] CAR T-cells after they are infused back into the patient rapidly redistribute throughout the body and

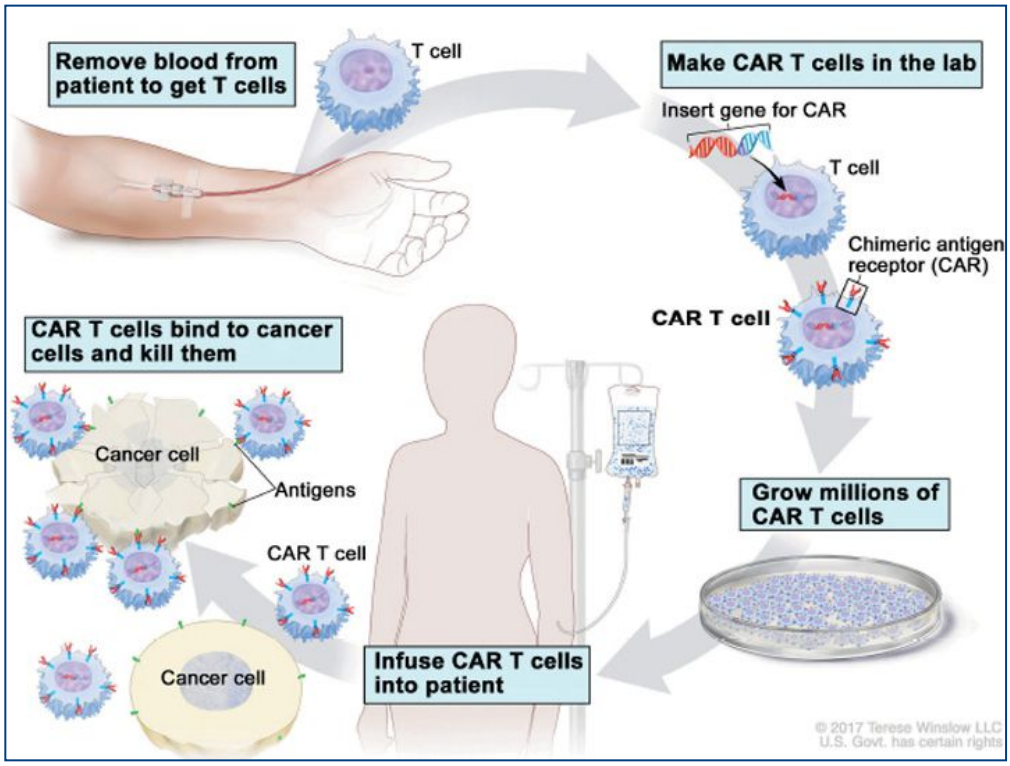


Figure 3. Process of developing CAR-T cells and therapy (used with permission)

re-accumulate at the sites of target recognition.[28] It is believed that the duration of these infused cells in the body provide both continued immunosurveillance and prevents relapse by suppressing the neoplastic clones. After CAR T-cell infusion, typically, patients must be closely monitored for any possible adverse effects or complications in the first few days following transfusion, preferably in hospital setting[23] (Figure 3).

Indications for CAR T-Cell Therapy

CAR T-cell therapy has shown revolutionary results in the treatment of hematologic malignancies, including relapsed and refractory B-cell malignancies, such as B-cell non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). CD19 was chosen as first target because of its broader and higher expression compared to CD20 or CD22 and its' expression is limited to B-cell lineage. Anti-CD19 CAR T-cell therapies have shown promising results in patients with relapsed and refractory B-cell ALL.[18] Since plasma cells do not express CD19, in relapsed multiple myeloma B-cell maturation antigen (BCMA), which is expressed on plasma cells, is chosen as the target. CAR T-cell therapy targeting is showing promising results.[29] Other targets under study are CD20, CD22, CD123, CD30, CD269, and GPC3.[30] In August 2017, Tisagenlecleucel (Kymriah) was approved by FDA for the treatment of relapsed and/or refractory B-cell precursor ALL in children and young adults. Later in October 2017, Axicabtagene ciloleucel (Yescarta) was approved for the treatment of adults with relapsed or refractory large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL).[9] In 2018, Tisagenlecleucel received FDA approval for a second indication in adults with relapsed or refractory DLBCL.[31] In July 2020, a third CAR T-cell therapy, Brexucabtagene autoleucel (Tecartus), was approved by the FDA for the treatment of Mantle cell lymphoma.[30] Lisocabtagene maraleucel (Breyanzi) is another anti-CD19 CAR T-cell product that showed good results in patients with relapsed or refractory DLBCL.[32]

However, the results are not as promising in solid tumors due to various obstacles such as lack of antigen specificity, inefficient trafficking of CAR T-cells to tumor sites, hostile tumor microenvironment, inhibitory cytokines and regulatory T-cells, and the risk of developing on-target/off-tumor toxicities.[33]

Clinical trials are ongoing targeting some tumor associated antigens commonly expressed on solid tumors.[34] Some of the targets for CAR T-cell therapy in clinical trial for solid tumors are listed below in Table 1.

Table 1. Targets for CAR-T cell therapy in clinical trial for solid tumors

Targeted Tumor associated antigens	Soid tumor
Epidermal growth factor receptor (EGFR)	Non-small cell cancer (NSCLC) Epithelial carcinoma
Human epidermal growth factor receptor 2 (HER2)	Ovarian cancer, Breast cancer, Colon cancer Head and neck cancer
Prostate specific membrane antigen (PSMA) PSA	Prostate cancer
carcinoembryonic antigen (CEA)	Pancreatic adenocarcinoma, Breast Cancer Colorectal carcinoma
Carboxy anhydrase-IX (CAIX)	Renal cell carcinoma
Folate binding protein (FBP) Folate receptor-a (FR-a) MUC-CD	Ovarian cancer
Diasialoganglioside (GD2) L1-CAM	Neuroblastoma and Melanoma
AFP GPC3	Hepatocellular cancer
CD133	Glioblastoma Cholangiocarcinoma

Toxicities From CAR T-Cell Therapy

Majority of the side effects from CAR T-cell therapy result from autoimmune response against normal tissues that express the targeted antigen, called on-target/off-tumor toxicities.[35] These toxicities can be immediate or delayed.

Cytokine release syndrome (CRS) is the most common adverse effect, which manifests as systemic inflammatory response, characterized by fevers, hypotension, nausea, vomiting and multiorgan failure in severe cases. CRS is provoked by cytokine release (IL-6, IL-8, IL-10, IFN-g and MCP-1) after activation of CAR T-cells in vivo and the severity correlates with tumor burden and IL-6 levels. It can be mild and self-limited with flu-like symptoms or sometimes life-threatening with multi-organ failure. Severe CRS can be reversible with IL-6 blocking antibody, tocilizumab and corticosteroids.[36] Neurotoxicity, also called CAR–related encephalopathy syndrome (CRES) is the second most common adverse event from CAR T-cell therapy. Endothelial activation and disruption of blood brain barrier were shown as the cause of neurologic toxicity.[37] It manifests as toxic encephalopathy with altered level of consciousness, seizures, aphasia, coma, and cerebral edema. CRES can also be reversible and self-limited in mild cases treated only with supportive care, while anti-epileptics and steroids may be used in severe cases.[38] Both of these toxicities usually occur within the first week of infusion of CAR T-cells. Cytopenias, opportunistic infections, B-cell aplasia and hypogammaglobulinemia are reported as delayed side effects. B-cell aplasia is seen mostly in CD19-targeting CAR T-cell therapy.[36] Further research on CAR T-cell therapy is focused on minimizing toxicity associated with the therapy.

Conclusion

Chimeric antigen receptor T-cell therapy represents a major advancement in personalized cancer treatment. Dramatic clinical responses and high rates of complete remission have been observed in the setting of CAR T-cell therapy of B-cell malignancies. With ongoing efforts, many more approvals are expected in hematological malignancies. Most importantly, through several concerted research efforts the utility of biomarkers are being explored to predict outcomes at earlier time points for patients treated with CAR T-cells. Lastly, by continuing improvements in their safety and outcomes, there is anticipatory excitement that the next-generation of CAR T-cells will continue to challenge the existing armamentarium of commercially available products in blood cancers and beyond, thus leading to further improvements in personalized cancer medicine.

References

1. Ruhlmann CH, Iversen TZ, Okera M, et al. Multinational study exploring patients' perceptions of side-effects induced by chemo-radiotherapy. Radiother Oncol. Nov 2015;117(2):333-337.
2. Song MK, Park BB, Uhm JE. Resistance Mechanisms to CAR T-Cell Therapy and Overcoming Strategy in B-Cell Hematologic Malignancies. Int J Mol Sci. Oct 10 2019;20(20).
3. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T-cell immunotherapy for human cancer. Science. Mar 23 2018;359(6382):1361-1365.
4. Gaud G, Lesourne R, Love PE. Regulatory mechanisms in T cell receptor signalling. Nat Rev Immunol. Aug 2018;18(8):485-497.
5. Masopust D, Schenkel JM. The integration of T cell migration, differentiation and function. Nat Rev Immunol. May 2013;13(5):309-320.
6. Li D, Li X, Zhou WL, et al. Genetically engineered T cells for cancer immunotherapy. Signal Transduct Target Ther. 2019;4:35.
7. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer. Apr 2008;8(4):299-308.
8. Curran KJ, Pegram HJ, Brentjens RJ. Chimeric antigen receptors for T cell immunotherapy: current understanding and future directions. J Gene Med. Jun 2012;14(6):405-415.
9. Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. Front Immunol. 2019;10:2250.
10. Ali N, Haematology F. Chimeric antigen T cell receptor treatment in hematological malignancies. Blood Res. Jun 2019;54(2):81-83.
11. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A. Dec 1989;86(24):10024-10028.
12. Sadelain M. CAR therapy: the CD19 paradigm. J Clin Invest. Sep 2015;125(9):3392-3400.
13. Eshhar Z, Waks T, Gross G, Schindler DG. Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the gamma or zeta subunits of the immunoglobulin and T-cell receptors. Proc Natl Acad Sci U S A. Jan 15 1993;90(2):720-724.
14. Wang Z, Guo Y, Han W. Current status and perspectives of chimeric antigen receptor modified T cells for cancer treatment. Protein Cell. Dec 2017;8(12):896-925.
15. Sadelain M, Riviere I, Riddell S. Therapeutic T cell engineering. Nature. May 24 2017;545(7655):423-431.
16. Lee YH, Kim CH. Evolution of chimeric antigen receptor (CAR) T-cell therapy: current status and future perspectives. Arch Pharm Res. Jul 2019;42(7):607-616.
17. Jensen MC, Popplewell L, Cooper LJ, et al. Antitransgene rejection responses contribute to attenuated persistence of adoptively transferred CD20/CD19-specific chimeric antigen receptor redirected T cells in humans. Biol Blood Marrow Transplant. Sep 2010;16(9):1245-1256.
18. Heyman B, Yang Y. New developments in immunotherapy for lymphoma. Cancer Biol Med. Aug 2018;15(3):189-209.
19. Tang XY, Sun Y, Zhang A, et al. Third-generation CD28/4-1BB chimeric antigen receptor T cells for chemotherapy relapsed or refractory acute lymphoblastic leukaemia: a non-randomised, open-label phase I trial protocol. BMJ Open. Dec 30 2016;6(12):e013904.
20. Chmielewski M, Abken H. TRUCKS, the fourth-generation CAR T-cells: Current developments and clinical translation. ADVANCES IN CELL AND GENE THERAPY. 2020;3(3):e84.
21. Tokarew N, Ogonek J, Endres S, von Bergwelt-Baildon M, Kobold S. Teaching an old dog new tricks: next-generation CAR T-cells. Br J Cancer. Jan 2019;120(1):26-37.
22. Perica K, Varela JC, Oelke M, Schneck J. Adoptive T cell immunotherapy for cancer. Rambam Maimonides Med J. Jan 2015;6(1):e0004.
23. Skorka K, Ostapinska K, Malesa A, Giannopoulos K. The Application of CAR T-Cells in Haematological Malignancies. Arch Immunol Ther Exp (Warsz). Nov 6 2020;68(6):34.
24. Mohanty R, Chowdhury CR, Arega S, Sen P, Ganguly P, Ganguly N. CAR T-cell therapy: A new era for cancer treatment (Review). Oncol Rep. Dec 2019;42(6):2183-2195.
25. Oluwole OO, Davila ML. At The Bedside: Clinical review of chimeric antigen receptor (CAR) T-cell therapy for B cell malignancies. J Leukoc Biol. Dec 2016;100(6):1265-1272.
26. Nagle SJ, Garfall AL, Stadtmauer EA. The Promise of Chimeric Antigen Receptor Engineered T Cells in the Treatment of Hematologic Malignancies. Cancer J. Jan-Feb 2016;22(1):27-33.
27. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol. Mar 22 2012;12(4):269-281.
28. Ritchie DS, Neeson PJ, Khot A, et al. Persistence and efficacy of second generation CAR T-cell against the LeY antigen in acute myeloid leukemia. Mol Ther. Nov 2013;21(11):2122-2129.
29. Huang H, Wu HW, Hu YX. Current advances in chimeric antigen receptor T-cell therapy for refractory/relapsed multiple myeloma. J Zhejiang Univ Sci B. Jan. 2020;21(1):29-41.
30. Han D, Xu Z, Zhuang Y, Ye Z, Qian Q. Current Progress in CAR T-Cell Therapy for Hematological Malignancies. J Cancer. 2021;12(2):326-334.
31. Beyar-Katz O, Gill S. Advances in chimeric antigen receptor T cells. Current Opinion in Hematology. 2020;27(6):368-377.
32. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. Sep 19 2020;396(10254):839-852.
33. Newick K, O'Brien S, Moon E, Albelda SM. CAR T-Cell Therapy for Solid Tumors. Annu Rev Med. Jan 14 2017;68:139-152.
34. Yu S, Li A, Liu Q, et al. Chimeric antigen receptor T cells: a novel therapy for solid tumors. J Hematol Oncol. Mar 29 2017;10(1):78.
35. Zhang Q, Zhang Z, Peng M, Fu S, Xue Z, Zhang R. CAR T-cell therapy in gastrointestinal tumors and hepatic carcinoma: From bench to bedside. Oncoimmunology. 2016;5(12):e1251539.
36. Neelapu SS. Managing the toxicities of CAR T-cell therapy. Hematol Oncol. Jun 2019;37 Suppl 1:48-52.
37. Gust J, Hay KA, Hanafi LA, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR T-Cells. Cancer Discov. Dec 2017;7(12):1404-1419.
38. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. Jan 2018;15(1):47-62.

Disclosure

None reported.

MM

Retinal Degeneration: Short-Term Options and Long-Term Vision for Future Therapy

by Shabnam Majidi, Judith M. Ogilvie, PhD & Colin A. Flaveny, PhD

SAINT LOUIS UNIVERSITY
HENRY AND AMELIA NASRALLAH CENTER FOR NEUROSCIENCE

Continued refinement of the current pool of synthetic ligands will also have to rely significantly on chicken, zebrafish and *in vitro* retinal explant models with eventual validation of these findings in human retinal tissue samples or organoids.



Shabnam Majidi, is in the Department of Pharmacology and Physiology, and Judith M. Ogilvie, PhD, and formerly Colin A. Flaveny, PhD, (above), are in the Department of Biology; all at the Saint Louis University School of Medicine, St. Louis, Missouri.

Abstract

The leading cause blindness is the loss of retinal ganglion cells which connect the retina to the brain. Degenerative retinal diseases include retinal dystrophy, macular degeneration and diabetic retinopathy, which are currently incurable as the mammalian retina has no intrinsic regenerative capacity. By utilizing insight gained from retinal regeneration in simpler species we define an approach that may unlock regenerative programs in the mammalian retina that potentially facilitate the clinical restoration of retinal function.

Introduction

Retinal degeneration is a leading cause of vision loss that currently affects 14 million people globally, and is therefore fraught with major medical, social, and economic ramifications. Identifying novel mechanisms to restore retinal function will be crucial to combating this significant healthcare challenge. No curative treatments are currently available, but in recent years clinical interventions and innovative experimental treatments have made some incremental progress toward partly restoring vision. We first review these innovative treatments. Secondly, we examine a promising strategy for combating retinal degeneration that is founded on retinal repair processes in simpler species that have robust regenerative capacity, such as fish and amphibians. Regenerative capacity in these species is mediated by the activity of a retinal cell type called Müller Glia, which have a comparably limited role in retinal repair in humans and other mammals. We consider our current understanding and assess the therapeutic potential of harnessing Müller Glia plasticity by activating a transcription factor the Tailless-X-Receptor or TLX.

Treatment of Retinal Degeneration

Retinal degeneration is a leading cause of vision loss that currently affects millions people globally.[1] In Missouri alone, over 155,000 people are living with visual disabilities, which has major medical, social and economic consequences.[2] Among Missourians that are able to work, those with visual disabilities are less than half as likely to be employed as those without disabilities. Their household income is 40% less and their poverty rate is 22% higher. Missourians with visual disabilities are 10% less likely to have a high school diploma and 22% less likely to have a bachelor's degree

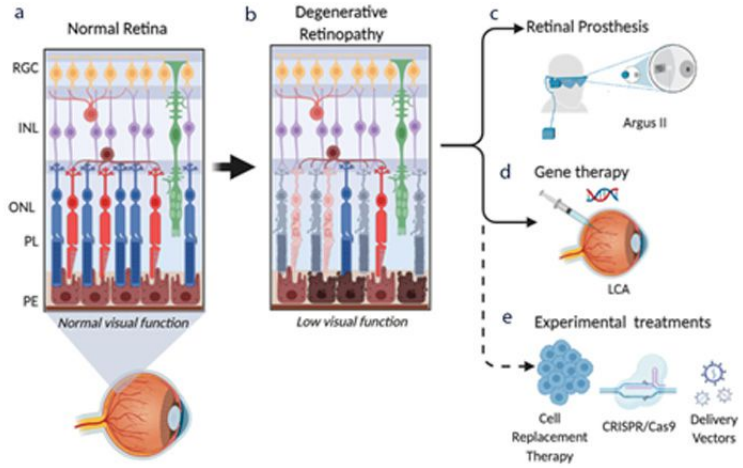


Figure 1. Current and future treatment strategies for rescuing vision loss due to retinal degeneration. (a) Illustration of the normal cellular structure of the retina showing the distinct cell layers. RGC: retinal ganglion cell, INL: inner nuclear layer, ONL: outer nuclear layer, PL: Photo-receptor layer, PE: pigmented epithelium. (b) the diseased retina displaying rod and cone photoreceptor degeneration. (c) An example of a current prosthetic device used to treat retinopathy the Argus II that only partly restores vision. (d) Illustration of recent gene therapy approaches that have restored vision in Leber's Congenital Amaurosis (LCA) patients by rescuing the normal expression of RPE65 gene. (e) Experimental treatments are testing the validity of autologous or endogenous cell replacement therapy, use of refined viral-vector delivery approaches and CRISPR/Cas9 genome editing to stimulate retinal repair. Illustrations made using Biorender.

Vision loss due to defects in the optical pathway are generally treatable today through cataract surgery or corneal transplants. However vision loss due to retinal degenerative diseases or dystrophies continues to increase, in part due to the aging population.[3] Great strides have been made in understanding the causes underlying retinal cell degeneration and yet current therapeutic options remain limited. Two retinal prosthetic devices have been approved by the FDA: the Argus II (Figure 1), placed on the epiretinal surface of the retina, and the subretinal Alpha-IMS.[4] Retinal prostheses convert light signals into electrical signals delivered to the remaining retinal cells to induce neuronal activity. Currently, these devices are only indicated for late-stage retinal degeneration and in many cases only rudimentary vision is recovered.[5] Gene therapy has also been approved for one form of inherited retinal dystrophy called Leber's Congenital Amaurosis (LCA), in which patients have a mutation in the gene RPE65 (Figure 1).[6] A single injection can restore vision to patients with this mutation. However, LCA is a rare form of retinal degeneration, affecting only 1,000-2,000 patients in the United States. In some patients, dietary supplements may slow the progression of degeneration, but they do not halt the inevitable loss of vision.[5] Major advances have been made in understanding the underlying causes of retinal dystrophies and yet current therapeutic options remain limited.

Although currently approved treatments offer limited benefits, they reflect considerable progress in translating basic research to the clinic. Recent advances in technologies such as molecular genetics and multielectrode devices are encouraging for improved prosthetic devices and for a variety of new therapeutic strategies on the horizon such as gene therapy, optogenetics, pharmacotherapies, cell replacement therapy and cell regeneration. Clinical trials with gene therapy for several recessive mutations are underway, some with promising results.[7] Preliminary animal studies are focusing on the potential for using CRISPR/Cas9 genome editing technology to treat causative autosomal dominant gene mutations.[8] In addition, much progress has been made in developing gene delivery vectors. However, gene therapy efforts are hampered by the hundreds of different gene mutations that can cause inherited retinal dystrophies.[9] A novel approach called optogenetics makes use of gene therapy techniques to induce photosensitivity in remaining retinal neurons and could be more widely applicable.[10] Current efforts in this area are focused on increasing neuronal sensitivity to light. The potential for pharmacotherapies, including neuroprotective factors, has grown with our increased understanding of biochemical pathways that are disrupted in inherited retinal degenerations.[11] Progress is also being made in cell replacement therapy, which aims to maintain or

restore vision through the use of either embryonic stem cells or human induced pluripotent stem cells that can be derived from adult tissues (Figure 1). Early clinical trials have shown some promise while also highlighting the challenges in achieving proper repair of existing retinal tissue and the potential for a damaging immune response.[5,11] A new and exciting alternative strategy involves the stimulation of retinal regeneration from a patient's own stem-like cells.

Müller Glia: Retinal Stem-like Cells with Therapeutic Potential

Müller Glia (MG) represent approximately 4-5% of all retinal cells, are the major glial cell type in the retina and the only glial lineage that originates from retinal progenitor cells.[11] Notably, MG are also the last cell type to emerge in the retina and contribute to retinal structure and homeostasis.[12] Although the somas of MG are located in the inner nuclear layer of the retina, their processes span multiple layers. These processes provide structural support by enveloping ganglion axons and controlling ionic balance in the extracellular space.[13] MG cells also support neuron function by releasing trophic factors and recycling neurotransmitters.[14–16] In teleosts and amphibians, MG have a substantial role in retinal regeneration, where MG can reenter the cell cycle and completely regenerate retinal neurons following injury via induction of neurogenic factors.[11,17–19] Therefore, MG in these species have the capacity to promote complete endogenous regenerative repair in the retina. Unfortunately, mammalian MG do not regenerate retinal lineages under normal conditions as seen in simpler organisms.[18,20] Mammalian MG have been shown to display neurogenic potential, but typically contribute to gliosis when stimulated.[21,22] Finding new methodologies to induce MG stem-cell activity, without inducing pernicious inflammation, remains at the forefront of a variety of pre-clinical investigations.[12,23]

The Tailless Receptor (TLX)

One factor, the Tailless-X-Receptor (NR2E1/TLX) may be an important target for unleashing the full potential of MG in the retina. As TLX can pleiotropically regulate proliferative and neurogenic programs, it may be a relevant molecular target to effectively exploit dormant MG plasticity. Since its discovery 25 years ago, TLX, a member of a family of 48 transcription factors called nuclear receptors (NRs), has been shown to be vital to neural stem cell proliferation and neurogenesis.[19,24–32]

TLX displays a tissue-specific pattern of expression that supports its role as a crucial factor in neurogenesis. TLX protein expression is expressed predominantly in the cerebral cortex, basal ganglia, amygdala and retina, but is also detectable in the adrenals, testes, placenta and bone marrow at very low levels.[24,33–36] In the adult human brain, TLX is confined to two highly neurogenic areas: the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricles.[27,37] While embryonic knockout of Tlx has no overt effect on early mouse brain development, adult mice show reduced cerebral hemisphere size.[36,38] Lastly, neural cells isolated from Nr2e1-mutant mice are non-proliferating and fail to self-renew, a capacity that is completely rescued by ectopic expression of Tlx alone.[19,24,35,37] Other studies have shown that TLX is a driver of tumor stem cell self-renewal in gliomas.[33,39] Most of what is known about mammalian TLX expression has been determined through assessing mouse development. Fortunately, human TLX has over 95% homology with mouse Tlx and displays conserved function within the retina.[41] This holds the additional implication that, for TLX, discoveries in mouse models may be reasonably extrapolated to humans.

Rationale for Targeting TLX in the Retina

Studies in mouse models have hinted at a prominent role of TLX in retinogenesis. Interestingly, TLX expression in the adult mammalian retina is downregulated and restricted to MG. Mammalian retinal injury does not typically result in upregulation of the TLX target gene Achaete-Scute Family BHLH Transcription factor 1 (Ascl1). ASLC1 overexpression alone is insufficient to stimulate regenerative

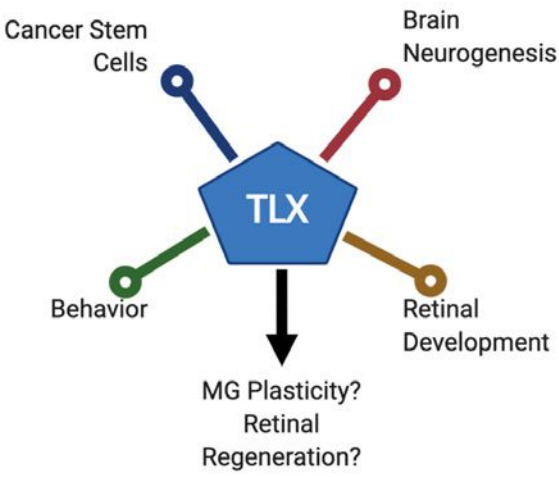


Figure 2. The multitude of functions of the Tailess-X-Receptor. Illustration showing the known roles of TLX in mammalian development and disease. In theory, TLX can be targeted to augment neuronal development and behavior, but mostly importantly holds promise as a target for stimulating retinal repair. Illustration made using Biorender.

programs.[8,9,24,34–36] Conversely, TLX stimulates neuronal stemness through modulation of a number of neurogenic factors known to be induced during retinal repair including Glial Fibrillary Acidic Protein (GFAP).[24,33,45,37–44] In accord with this, we found that TLX activation can stimulate MG proliferation and induce ASCL1 expression. Therefore, TLX could theoretically be targeted to induce stem-like activity in MG. Surprisingly, no published studies to date have focused on targeting TLX in the retina to stimulate regenerative repair. A key step toward targeting TLX in vivo would be the development and use of validated vector delivery systems to activate TLX in MG. Adeno-associated virus (AAV) delivery systems are highly refined tools for transducing ectopic gene expression or facilitating gene transfer. Most importantly, AAV vectos have been used effectively in clinical settings[46–48]. We are currently embarking on the first in vivo studies that use AAV delivery to induce TLX expression in mouse retinal degeneration models. These studies should test the therapeutic potential of TLX, while employing a clinically relevant vector delivery system as opposed to using transgenic models. Future studies will have to incorporate more refined gene editing approaches such as CRISPR/Cas9, which should eventually become widely used in the clinic. Gene editing may be inaccessable to a large subset of patients due to cost and the highly specialized expertise required. The development of drugs that stimulate TLX activity should have comparably broader accessibility and, therefore, should be simultanously pursued. Tlx is embryonically expressed in retinal progenitor cells and is essential for the generation of neuronal lineages as it prevents premature cell-cycle exit.[30,39,40,42] Knockout of Tlx results in optic nerve hypoplasia, retinal degeneration, diminished vascularization in the developing eye, neutrophil infiltration and aberrant misexpression of the retinal ganglion cell factors in the adult retinal MG.[43] Tlx-knockout mice also display poor retinal lamination, retinal dystrophy, disrupted amacrine cell differentiation and aberrant MG function.[30] In mice, ectopic expression of ASCL1 enhances the regenerative response in damaged retinal tissue via MG reprogramming.[18,19,44] ASLC1 overexpression alone is insufficient to stimulate regenerative programs.[18,19,34,44–46] Conversely, TLX stimulates neuronal stemness through pleiotropic modulation of a number of neurogenic factors.[34,43,47–55] In accord with this, we have found that TLX activation can stimulate MG proliferation and induce ASCL1 expression. Therefore, TLX is a potential target for induction of stem-like activity in MG.

The Search for TLX Ligands

TLX has protein sub-domains that are importantly involved in binding ligands, DNA and other coregulatory proteins that allow efficient modulation of target-gene expression. Notably, TLX lacks the AF1-domain found in most NRs that is important for ligand-independent activation, which suggests its activity is tightly controlled by ligands.[56,57] In its unliganded state, TLX typically represses gene expression as it binds to DNA and recruits epigenetic regulators that inhibit gene expression, such as lysine-

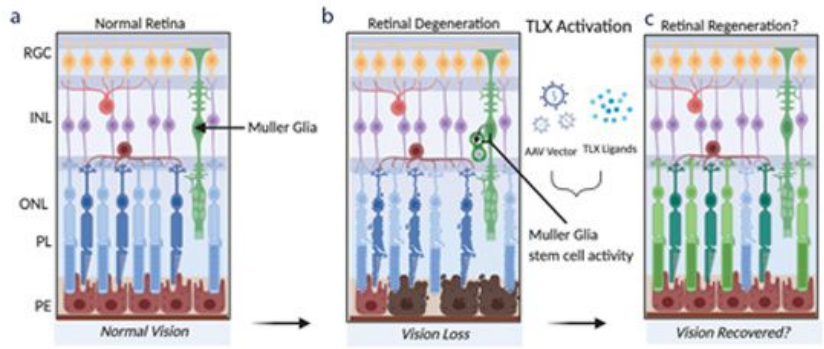


Figure 3. Targeting the Tailless-X-Receptor to activate Müller Glia stem-like activity and induce retinal repair. (a) Structure of the normal retina with Müller Glia indicated. (b) Retinal regeneration as observed in teleost fish and amphibians is mediated by Müller Glia re-entering the cell cycle and generating all cells of the retina. In theory, this activity can be rescued in the human retina by activating TLX, a ligand-binding transcription factor that is exclusively expressed in Müller Glia and has the ability to induce stem-cell activity in neuronal tissue. (c) It is possible that Müller Glia activation could be the key for restoring retinal function. Ongoing research should test this hypothesis. Illustration made using Biorender.

specific histone demethylase, histone deacetylases (HDACs), and the corepressor Atrophin1.[43,48] Another mechanism of TLX regulation involves antagonistic cross-talk with retinoic acid and retinoid-X-receptors (RARs and RXRs); major drivers of terminal differentiation.[58] Conversely, TLX can also indirectly activate gene expression by binding to and blocking SET-2 inhibitory DNA-elements.[58] TLX also stimulates neovascular growth and activates the hypoxia response through DNA binding dependent on independent mechanisms. Due to its potential as a treatment target for neurodegenerative diseases and cancer, significant research efforts have been focused on the identifying effective ways to pharmacologically target TLX (Figure 2).

The lack of a crystal structure for TLX has presented a significant challenge to ongoing attempts to identify synthetic or endogenous ligands. In 2014, the Webb research team created a model of the TLX ligand binding domain (LBD) based on homology with the LBD of RXRα.[57] Through biochemical characterization and differential scanning fluorimetry screening of approximately 20,000 compounds, they identified three compounds as potential synthetic ligands: Ccrp1 (famprofazone), a non-steroidal anti-inflammatory; ccrp2, a ccrp1 analogue with pyrazole and piperazine functional groups; and ccrp3 (dydrogesterone), a progestin analogue.[57] This study does have some controversy regarding the significance of their findings. In particular, the authors claimed that the TLX LBD exists as a homodimer in solution, whereas prior studies indicated monomeric activity. Griffett et al. identified retinoids as potential ligands that regulate TLX activity independent of RAR or RXR. Two TLX agonists, BMS453 and BMS493, and two inverse agonists, CD437 and CD1530, were identified.[59] The authors also claimed that natural retinoids such as all-trans retinal (ATR) may be endogenous ligands for TLX, although at physiologically unattainable concentrations.[59]

In November 2020, a preprint report by Kandel et al. showed that oleic acid may be an endogenous ligand for TLX.[60] This study suggests that oleic acid may convert TLX to an activator of cell cycle and neurogenesis both *in vitro* and *in vivo*. These studies have focused on the role of oleic acid regulation of TLX function in the brain. It would be interesting to explore whether oleic acid similarly functions as a TLX activator in the retina. Neural and retinal stem cells have relatively high levels of mono-unsaturated fatty acids (MUFAs).[61] In addition, recent studies highlight that lipid metabolism may play a critical function in retinal homeostasis and pathology.[62] Furthermore, previous studies in the Penn lab have shown that retinal Müller glial cells were uniquely responsive to fatty acid stimulation in comparison to other retinal cell types in the context of diabetic retinopathy.[63] Nonetheless, the role of oleic acid, specifically, in retinal degeneration and MG cell biology requires further exploration.

Although still in its incipient stages, discovery of new synthetic and endogenous ligands will further enhance our understanding on TLX biology and provide important investigational tools for understanding the therapeutic utility of TLX. In theory, these ligands could be used to alter TLX gene expression, stimulate MG stemness and facilitate retinal regeneration. There are still significant knowledge gaps that need to be filled through further study.

Conclusion

With its expression in MG, TLX has promise as a target for a variety of retinopathies, particularly those that lead to retinal ganglion cell loss. Targeting TLX using synthetic ligands, CRISPR/Cas9 or viral vectors ectopic expression systems may prove to be an effective means of stimulating MG stemness with little off-target effects. Theoretically, activation of TLX alone may prove sufficient to drive MG to replenish RGC populations or even other retinal lineages (Figure 3). This theory, of course, requires thorough testing in pre-clinical models. Even in the absence of direct therapeutic activity, synthetic TLX ligands may also find utility as targeting agents for selective delivery to MG. As is the case with stemness factors, malignant growth as a consequence of TLX activation is an exigent concern. The viablility and pitfalls of targeting TLX must therefore be explored in tandem in pre-clinical models of retinal development and degeneration. Fortunately, a number of bona fide mouse models that recapitulate the pathology of retinal dystrophy and diabetic retinopathy are readily available to evaluate TLX function. Continued refinement of the current pool of synthetic ligands will also have to rely significantly on chicken, zebrafish and *in vitro* retinal explant models with eventual validation of these findings in human retinal tissue samples or organoids. Harnessing the power of these experimental tools should allow us to test the role of TLX in retinal disease and provide important treatments for combating a major cause of blindness.

References

1. Bourne RRA, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: A systematic analysis. Lancet Glob Heal. 2013;1(6). doi:10.1016/S2214-109X(13)70113-X
2. Rodgers HM, Huffman VJ, Voronina VA, Lewandoski M, Mathers PH. The role of the Rx homeobox gene in retinal progenitor proliferation and cell fate specification. Mech Dev. 2018;151:18-29. doi:10.1016/j.mod.2018.04.003
3. Langhe R, Pearson RA. Rebuilding the Retina: Prospects for Müller Glial-mediated Self-repair. Curr Eye Res. 2020;45(3):349-360. doi:10.1080/02713683.2019.1669665
4. Remington LA. Retina: Muller Cells. Clin Anat Physiol Vis Syst (Third Ed . Published online 2012.
5. Stutz B, da Conceição FSL, Santos LE, et al. Murine dopaminergic Müller cells restore motor function in a model of Parkinson's disease. J Neurochem. 2014;128(6):829-840. doi:10.1111/jnc.12475
6. Kubrusly RCC, Panizzutti R, Gardino PF, et al. Expression of functional dopaminergic phenotype in purified cultured Müller cells from vertebrate retina. Neurochem Int. 2008;53(3-4):63-70. doi:10.1016/j.neuint.2008.05.002
7. da Silva BR, Santos LE, de Melo Reis RA, de Mello FG, Ribeiro-Resende VT. Müller Cells Derived from Adult Chicken and Mouse Retina Neurospheres Acquire the Dopaminergic Phenotype. Cell Mol Neurobiol. 2019;39(1):99-109. doi:10.1007/s10571-018-0636-z
8. Pollak J, Wilken MS, Ueki Y, et al. ASCL1 reprograms mouse Müller glia into neurogenic retinal progenitors. Dev. 2013;140(12):2619-2631. doi:10.1242/dev.091355
9. Ueki Y, Wilken MS, Cox KE, et al. Transgenic expression of the proneural transcription factor Ascl1 in Müller glia stimulates retinal regeneration in young mice. Proc Natl Acad Sci U S A. 2015;112(44):13717-13722. doi:10.1073/pnas.1510595112
10. Miyawaki T, Uemura A, Dezawa M, et al. Tlx, an orphan nuclear receptor, regulates cell numbers and astrocyte development in the developing retina. J Neurosci. 2004;24(37):8124-8134. doi:10.1523/JNEUROSCI.2235-04.2004
11. Fischer AJ, Reh TA. Potential of Müller glia to become neurogenic retinal progenitor cells. Glia. 2003;43(1):70-76. doi:10.1002/glia.10218
12. Fischer AJ, Zelinka C, Milani-Nejad N. Reactive retinal microglia, neuronal survival, and the formation of retinal folds and detachments. Glia. 2015;63(2):313-327. doi:10.1002/glia.22752
13. Todd L, Palazzo I, Suarez L, et al. Reactive microglia and IL1β/IL-1R1-signaling mediate neuroprotection in excitotoxin-damaged mouse retina. J Neuroinflammation. 2019;16(1). doi:10.1186/s12974-019-1505-5
14. Hamon A, Roger JE, Yang X-J, Perron M. Müller glial cell-dependent regeneration of the neural retina: An overview across vertebrate model systems. Dev Dyn. 2016;245(7):727-738. doi:10.1002/dvdy.24375
15. Curt JR, Salmani BY, Thor S. Anterior CNS expansion driven by brain transcription factors. Elife. 2019;8. doi:10.7554/eLife.45274
16. Kozareva DA, Moloney GM, Hoban AE, et al. A role for the orphan nuclear receptor TLX in the interaction between neural precursor cells and microglia. Neuronal Signal. 2019;3(1):NS20180177. doi:10.1042/ns20180177
17. Ni N, Zhang D, Xie Q, et al. Effects of let-7b and TLX on the proliferation and differentiation of retinal progenitor cells in vitro. Sci Rep. 2014;4:6671. doi:10.1038/srep06671
18. Sobhan PK, Funa K. TLX-Its Emerging Role for Neurogenesis in Health and Disease. Mol Neurobiol. 2017;54(1):272-280. doi:10.1007/s12035-015-9608-1
19. Lucassen PJ, van Dam A-M, Kandel P, et al. The orphan nuclear receptor TLX: an emerging master regulator of cross-talk between microglia and neural precursor cells. Neuronal Signal. 2019;3(2). doi:10.1042/ns20180208
20. Corso-Díaz X, Simpson EM. Nr2e1 regulates retinal lamination and the development of Müller glia, S-cones, and glycineric amacrine cells during retinogenesis. Mol Brain. 2015;8(1). doi:10.1186/s13041-015-0126-x
21. Jürgens G, Wieschaus E, Nüsslein-Volhard C, Kluding H. Mutations affecting the pattern of the larval cuticle in Drosophila

melanogaster - II. Zygotic loci on the third chromosome. Wilhelm Roux's Arch Dev Biol. 1984;193(5):283-295. doi:10.1007/BF00848157
22. Yu RT, McKeown M, Evans RM, Umesono K. Relationship between Drosophila gap gene tailless and a vertebrate nuclear receptor Tlx. Nature. 1994;370(6488):375-379. doi:10.1038/370375a0
23. Pignoni F, Baldarelli RM, Steingrimsson E, et al. The Drosophila gene tailless is expressed at the embryonic termini and is a member of the steroid receptor superfamily. Cell. 1990;62(1):151-163. doi:10.1016/0092-8674(90)90249-E
24. Hakes AE, Brand AH. Tailless/TLX reverts intermediate neural progenitors to stem cells driving tumourigenesis via repression of asense/ASCL1. Elife. 2020;9. doi:10.7554/eLife.53377
25. Nishimura M, Naito S, Yokoi T. Tissue-specific mRNA expression profiles of human nuclear receptor subfamilies. Drug Metab Pharmacokinet. 2004;19(2):135-149. doi:10.2133/dmpk.19.135
26. Zou Y, Niu W, Qin S, Downes M, Burns DK, Zhang C-LC-L. The nuclear receptor TLX is required for gliomagenesis within the adult neurogenic niche. Mol Cell Biol. 2012;32(23):4811-4820. doi:10.1128/MCB.01122-12
27. Abrahams BS, Kwok MCH, Trinh E, Budaghzadeh S, Hossain SM, Simpson EM. Pathological aggression in "fierce" mice corrected by human nuclear receptor 2E1. J Neurosci. 2005;25(27):6263-6270. doi:10.1523/JNEUROSCI.4757-04.2005
28. Liu H-KK, Belz T, Bock DD, et al. The nuclear receptor tailless is required for neurogenesis in the adult subventricular zone. Genes Dev. 2008;22(18):2473-2478. doi:10.1101/gad.479308
29. Young KA, Berry ML, Mahaffey CL, et al. Fierce: A new mouse deletion of Nr2e1; violent behaviour and ocular abnormalities are background-dependent. Behav Brain Res. 2002;132(2):145-158. doi:10.1016/S0166-4328(01)00413-2
30. Sun G, Cui Q, Shi Y. Nuclear Receptor TLX in Development and Diseases. Curr Top Dev Biol. 2017;125:257-273. doi:10.1016/bs.ctdb.2016.12.003
31. Schmouth J-F, Banks KG, Mathelier A, et al. Retina Restored and Brain Abnormalities Ameliorated by Single-Copy Knock-In of Human NR2E1 in Null Mice. Mol Cell Biol. 2012;32(7):1296-1311. doi:10.1128/mcb.06016-11
32. Ó'Léime CS, Hoban AE, Hueston CM, et al. The orphan nuclear receptor TLX regulates hippocampal transcriptome changes induced by IL-1β. Brain Behav Immun. 2018;70:268-279. doi:10.1016/j.bbi.2018.03.006
33. Zhang C-LL, Zou Y, Yu RT, Gage FH, Evans RM. Nuclear receptor TLX prevents retinal dystrophy and recruits the corepressor atrophin1. 2006;20(10). doi:10.1101/gad.1413606
34. Jorstad NL, Wilken MS, Todd L, et al. STAT Signaling Modifies Ascl1 Chromatin Binding and Limits Neural Regeneration from Muller Glia in Adult Mouse Retina. Cell Rep. 2020;30(7):2195-2208.e5. doi:10.1016/j.celrep.2020.01.075
35. Castro DS, Martynoga B, Parras C, et al. A novel function of the proneural factor Ascl1 in progenitor proliferation identified by genome-wide characterization of its targets. Genes Dev. 2011;25(9):930-945. doi:10.1101/gad.627811
36. Kumari E, Velloso FJ, Nasuhidehnavi A, et al. Developmental IL-6 Exposure Favors Production of PDGF-Responsive Multipotential Progenitors at the Expense of Neural Stem Cells and Other Progenitors. Stem cell reports. 2020;14(5):861-875. doi:10.1016/j.stemcr.2020.03.019
37. Jin SH, Yang JH, Shin BY, et al. Resveratrol inhibits LXRalpha-dependent hepatic lipogenesis through novel antioxidant Sestrin2 gene induction. Toxicol Appl Pharmacol. Published online 2013. doi:10.1016/j.taap.2013.04.023
38. Sun GQ, Yu RT, Evans RM, Shi Y. Orphan nuclear receptor TLX recruits histone deacetylases to repress transcription and regulate neural stem cell proliferation. Proc Natl Acad Sci U S A. 2007;104(39):15282-15287. doi:10.1073/pnas.0704089104
39. Luque-Molina I, Shi Y, Abdullah Y, et al. The Orphan Nuclear Receptor TLX Represses Hes1 Expression, Thereby Affecting NOTCH Signaling and Lineage Progression in the Adult SEZ. Stem Cell Reports. 2019;13(1):132-146. doi:10.1016/j.stemcr.2019.05.004
40. Hu Y, Luo M, Ni N, et al. Reciprocal actions of microRNA-9 and TLX in the proliferation and differentiation of retinal progenitor cells. Stem Cells Dev. 2014;23(22):2771-2781. doi:10.1089/scd.2014.0021
41. Johansson E, Zhai Q, Zeng ZJ, Yoshida T, Funa K. Nuclear receptor TLX inhibits TGF-β signaling in glioblastoma. Exp Cell Res. 2016;343(2):118-125. doi:10.1016/j.yexcr.2016.03.028
42. Qu Q, Sun G, Li W, et al. Orphan nuclear receptor TLX activates Wnt/β-catenin signalling to stimulate neural stem cell proliferation and self-renewal. Nat Cell Biol. 2010;12(1):31-40. doi:10.1038/ncb2001
43. Zhao C, Sun G, Li S, Shi Y. A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination. Nat Struct Mol Biol. 2009;16(4):365-371. doi:10.1038/nsmb.1576
44. Qin S, Niu W, Iqbal N, Smith DK, Zhang C-L. Orphan nuclear receptor TLX regulates astrogenesis by modulating BMP signaling. Front Neurosci. 2014;8(8 APR):74. doi:10.3389/fnins.2014.00074
45. Wu D, Yu S, Jia L, et al. Orphan nuclear receptor TLX functions as a potent suppressor of oncogene-induced senescence in prostate cancer via its transcriptional co-regulation of the CDKN1A (p21WAF1/CIP1) and SIRT1 genes. J Pathol. 2015;236(1):103-115. doi:10.1002/path.4505
46. Lykken EA, Shyng C, Edwards RJ, Rozenberg A, Gray SJ. Recent progress and considerations for AAV gene therapies targeting the central nervous system. J Neurodev Disord. Published online 2018. doi:10.1186/s11689-018-9234-0
47. Koerber JT, Klimczak R, Jang JH, Dalkara D, Flannery JG, Schaffer D V. Molecular evolution of adeno-associated virus for enhanced glial gene delivery. Mol Ther. Published online 2009. doi:10.1038/mt.2009.184
48. Hudry E, Vandenberghe LH. Therapeutic AAV Gene Transfer to the Nervous System: A Clinical Reality. Neuron. Published online 2019. doi:10.1016/j.neuron.2019.02.017
49. Dueva E, Singh K, Kalyta A, LeBlanc E, Rennie PS, Cherkasov A. Computer-Aided Discovery of Small Molecule Inhibitors of Transcriptional Activity of TLX (NR2E1) Nuclear Receptor. Molecules. 2018;23(11). doi:10.3390/molecules23112967
50. Benod C, Villagomez R, Filgueira CS, et al. The human orphan nuclear receptor tailless (TLX, NR2E1) is druggable. PLoS One. 2014;9(6). doi:10.1371/journal.pone.0099440
51. Kobayashi M, Yu RT, Yasuda K, Umesono K. Cell-Type-Specific Regulation of the Retinoic Acid Receptor Mediated by the Orphan Nuclear Receptor TLX. Mol Cell Biol. 2000;20(23):8731-8739. doi:10.1128/mcb.20.23.8731-8739.2000
52. Griffett K, Bedia-Diaz G, Hegazy L, et al. The Orphan Nuclear Receptor TLX Is a Receptor for Synthetic and Natural Retinoids. Cell Chem Biol. 2020;27(10):1272-1284.e4. doi:10.1016/j.chembiol.2020.07.013
53. Kandel P, Semerci F, Bajic A, et al. Oleic acid triggers hippocampal neurogenesis by binding to TLX/NR2E1. bioRxiv. Published online October 29, 2020:2020.10.28.359810. doi:10.1101/2020.10.28.359810
54. Clémot M, Sênos Demarco R, Jones DL. Lipid Mediated Regulation of Adult Stem Cell Behavior. Front Cell Dev Biol. Published online 2020. doi:10.3389/fcell.2020.00115
55. van Leeuwen EM, Emri E, Merle BMJ, et al. A new perspective on lipid research in age-related macular degeneration. Prog Retin Eye Res. Published online 2018. doi:10.1016/j.preteyeres.2018.04.006
56. Capozzi ME, Giblin MJ, Penn JS. Palmitic acid induces müller cell inflammation that is potentiated by co-treatment with glucose. Sci Rep. Published online 2018. doi:10.1038/s41598-018-23601-1

Disclosure

None reported. **MM**



more control

protecting **doctors**
nurses cardiologists
practice managers family physicians
infectious disease specialists
internists **anesthesiologists**
podiatrists nurse practitioners
long term care specialists
neurosurgeons pulmonologists
epidemiologists **oncologists**
pediatricians **general surgeons**
obstetricians & gynecologists
allergists hospital administrators
emergency physicians
urologists geriatricians chiropractors
pathologists immunologists
orthopaedists **radiologists** and more

At ProAssurance, we work to protect medical professionals and support their patient safety efforts with custom healthcare professional liability insurance solutions.

If a malpractice claim is made, we listen and provide experienced counsel, bringing clarity and fair treatment to the claims process.

ProAssurance®
Treated Fairly

Healthcare Professional Liability Insurance

ProAssurance.com


protect
what
matters
most
HOME
866-676-2467
www.msma.biz
rstaggs@msma.biz
MSMA Insurance Agency