Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine January/February 2023

Research Beyond Skin Deep

MU DERMATOLOGY 2023

State of the State's Health
Fentanyl Deaths at Record Levels - Part II
Alzheimer's Disease & Neurocognitive Disorders

MSMA CALL TO ACTION:
SUBMIT PRO-MEDICINE ONLINE TESTIMONY AT MSMA.ORG/ADVOCACY

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

School of Medicine
University of Missouri



Madison Billingsly



Jeffrey Bodeen



Clayton Brinkley



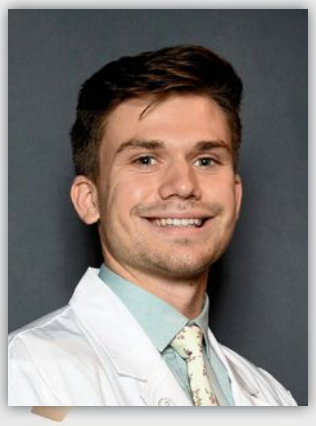
Madison Brune



Brooke Burton



Adam Fehr



Evan Reeves



Ronin Rice



Evadne Rodriguez



Leanna Zelle

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, more than $5,000,000 in MSMA Scholarships have been funded by the Foundation for students at four allopathic and two osteopathic schools of medicine on eight campuses. The Foundation has also facilitated the creation of scholarship funds through a matching grant program.

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

Missouri Medicine

The Journal of the Missouri State Medical Association – Since 1904

Volume 120 | Number 1 | January/February 2023 **www.msma.org/missouri–medicine**

GUEST EDITORIAL

Missouri's Public Health at a Glance
by Paula F. Nickelson, MEd 4

PRESIDENT'S REPORT

Power to Change: Comment on Interoperability and Information Blocking
by **George P. Hubbell, MD** 8

POISONED PILLS REPORT

Part II: Missouri's Fentanyl Poisonings Rise to Record Levels
by **William V. Stoecker, MD, Colin L. Smith, BS** & Elizabeth Connors, MSW 10

PERSPECTIVE

Content Notice: Guidelines to Discuss Suicide on Social Media
by Brianna J. Engelson, MD, **Simone A. Bernstein, MD**, Christine Yu Moutier, MD & **Jessica A. Gold, MD** 15

SCIENTIFIC PERSPECTIVE

Online Teaching Skills During the COVID-19 Pandemic and Beyond: One Curve We Do Not Want to Flatten
by Lacie Bailey, MD & **Emily Hillman, MD** 21

MEDICAL SCHOOL PERSPECTIVE

Team Science and Advancing Research at the University of Missouri
by **Richard J. Barohn, MD** 37

SCIENCE OF MEDICINE | FEATURE SERIES

Research Beyond Skin Deep | Presented by the University of Missouri - Columbia School of Medicine Department of Dermatology

Leprosy (Hansen's disease): An Update and Review
by Andrea Gilmore,MD, **James Roller, MD** & **Jonathan A. Dyer, MD** 39

JAK Inhibitors: A New Weapon in the Skin Care Providers' Arsenal
by Osaigbokan Aihie, MBA & **Jonathan A. Dyer, MD** 45

Infantile Hemangiomas: A Review and Future Opportunities
by Kimberly A. Eisenstein, MD 49

Updates in Cutaneous Oncology
by Jesse Hirner, MD 53

Bugs, Bumps, and Bacteria: The Role of Virtual Collaborative Learning Network in Pediatric Dermatology
by Kathleen Long, MD, Madison Ortega, Robert Pierce, MD, Paula Arinze, MS, Mimi Propst, MD, Lisa Pierce, MD &, Mirna Becevic, PhD 59

Diversity, Equity, and Inclusion Efforts at MU SOM and the Department of Dermatology
by Lydiah Fridah Mpyisi, MS, Kathleen Ann Long, MD & Nkanyezi Ferguson, MD 66

SCIENCE OF MEDICINE | FEATURE REVIEW

Complementary and Alternative Medicine Approaches in Alzheimer Disease and Other Neurocognitive Disorder
by **David Q. Beversdorf, MD, Haley W. Crosby** & **Joel I. Shenker, MD, PhD** 70

SCIENCE OF MEDICINE | MINISERIES

Bridging the Gap: Innovative 'Center for Precision Oncology' in Missouri
by Beth Gustafson, PharmD, Lindsey Douglass, PharmD, Timothy Pluard, MD & Janakiraman Subramanian, MD 79

SCIENCE OF MEDICINE

Relationship Between Weight and Severity of Fibromyalgia
by Karla Núñez-Nevárez, MsC, Alicia López Betancourt, PhD, Vicente Cisneros-Pérez, PhD, Cinthya Nallely Rodríguez-Márquez, Graciela Zambrano Galván, PhD, Abelardo Camacho-Luis, PhD & Martha-Angelica Quintanar-Escorza, PhD .. 83

FROM YOUR ASSOCIATION

Invitation to Annual Convention 3
Correspondence 29
MSMA Members in the News 33
New Members 35

MSMA member names in Table of Contents and throughout the Journal

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, PubMed, ProQuest, and Scopus. Complete issues archived at PubMed Central since 2010. Content appears on EBSCO 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 national media. Manuscripts are submitted from many countries. 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, and 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, P.O. Box 1028, Jefferson City, MO 65102. Annual subscription is included in membership dues; non–members pay $120.

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
Amy A. Cabbabe, MD
Betty M. Drees, MD
David A. Fleming, MD
Arthur H. Gale, MD
Emily A. Hillman, 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: John G. Markley, MD
Cardiology: Jerry D. Kennett, MD
Colon & Rectal Surgery: Erik M. Grossman, MD
Dermatology: Jon A. Dyer, MD
Emergency Medicine: Randall S. Jotte, MD
Endocrinology: Sherry X. Zhou, MD
Family Medicine: Beth E. Rosemergey, DO
Gastroenterology: Sanjay K. Havaldar, 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: Jeffrey F. Scherer, PhD
Toxicology & Addiction Medicine: Douglas M. Burgess, MD
Urology: Elizabeth A. Piontek, MD
Vascular Surgery: Scott W. Kujath, 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 / ©2023 Missouri State Medical Association

Due to the ongoing manufacturing, paper, staffing, and delivery challenges, your issues of Missouri Medicine might arrive later than usual. MSMA regrets any inconvenience.

165th Missouri State Medical Association Annual Convention

March 31-April 2, 2023 | Westin Kansas City at Crown Center, Kansas City, MO

www.msma.org/convention

2023 PRELIMINARY SCHEDULE

PRE-CONVENTION MEETINGS

Friday, March 31

1:00-2:00 pm	MSMA Insurance Agency Board Meeting
2:00-4:00 pm	MSMA Executive Committee Meeting
3:00-6:00 pm	MSMA Convention Registration
4:15-5:15 pm	MSMA General Session
5:30-7:00 pm	Annual Convention Opening Reception
7:00-8:00 pm	WPS/YPS Section Mixer

CONVENTION MEETINGS

Saturday, April 1

6:30 am-5:00 pm	Registration
6:30-7:30 am	MSMA Section Meetings
7:30-8:30 am	Moneta Product Theater Breakfast
8:30-9:30 am	MSMA House of Delegates – 1st Session
9:30-11:30 am	MSMA Reference Committee
9:30-11:30 am	Physicians Health Program Board Meeting
11:00 am-Noon	Caucus Meetings • St. Louis Metropolitan Medical Society • Kansas Medical Society
11:30 am-12:30 pm	Networking Lunch
12:45-1:45 pm	MSMA General Session
2:00-3:00 pm	MSMA General Session
2:00-3:00 pm	MSM Foundation Board Meeting
3:00-4:00 pm	MMPAC Meeting
3:15-4:15 pm	MSMA General Session
4:30-5:30 pm	WPS Section Meeting
4:30-6:30 pm	Medical School Receptions
5:30-6:15 pm	Reception for 50-Year Pin Recipients/ MSMA & MSMA Alliance Past Presidents/ MMPAC Diamond Club
6:30-7:30 pm	MSMA Presidential Inauguration
7:30 pm	MSMA Presidential Reception

Sunday, April 2

7:00-8:00 am	District Breakfasts & Caucuses
8:15 am	MSMA House of Delegates – 2nd Session
After HOD	MSMA Council Meeting



Friday, March 31 • 4:15 pm • Century A - Ballroom Level

Health Equity Opportunities for Doctors and State Medical Associations

Speaker

William Jordan, MD, MPH
Health Equity Policy Director American Medical Association, Chicago, Illinois



Saturday, April 1 • 12:45 pm • Century A - Ballroom Level

The Opioid Epidemic: Striving to Provide Holistic Care to Patients Who Use Drugs

Speaker

Nathan Nolan, MD, MPH, MHPE
Instructor of Medicine - Infectious Disease, St. Louis VA and Washington University School of Medicine, St. Louis, Missouri



Saturday, April 1 • 2:00 pm • Century A - Ballroom Level

Environmental Health: An Overview for Missouri Physicians

Speaker

Elizabeth Friedman, MD, MPH
Region 7 (Missouri, Kansas, Nebraska, Iowa) Mid America-Pediatric Environmental Health Specialty Unit Director, Medical Director, Environmental Health Program; Children's Mercy Hospital, Kansas City, Missouri, Assistant Professor Pediatrics, University of Missouri - Kansas City School of Medicine



Saturday, April 1 • 3:15 pm • Century A - Ballroom Level

Marijuana/Cannabis Guidance for Medical Providers: Follow the Science

Speaker

Roneet Lev, MD, FACEP
Executive Director of Independent Emergency Physician Consortium; Chair of the San Diego Community Response to Drug Overdose Task Force; Former Chief Medical Officer of the White House Office of National Drug Control Policy 2018-2020; Former Chief of Scripps Mercy Hospital/San Diego Emergency Department; Founder and Vice President of IASIC, the International Academy on the Science and Impact of Cannabis

Missouri's Public Health at a Glance

by Paula F. Nickelson, MEd

The public health and healthcare systems must continue to identify methods to address the complex, inter-related factors inclusive of social determinants of health, which impact health outcomes for our neighbors and citizens.

Missouri Department of Health and Senior Services (DHSS) is honored to contribute to *Missouri Medicine* to provide an overview of the 'state of the state's health,' as well as insights into current and anticipated initiatives to improve the health and safety of our citizens. One of the many lessons reinforced by the COVID-19 pandemic was that quality public health data should be used to drive decision-making—whether at the state official level or the individual resident level. While we begin 2023 with room to improve several of our state's public health indicators we are encouraged by upcoming opportunities and engaged partners who are as dedicated as DHSS to changing our trajectory and making a healthier Missouri.



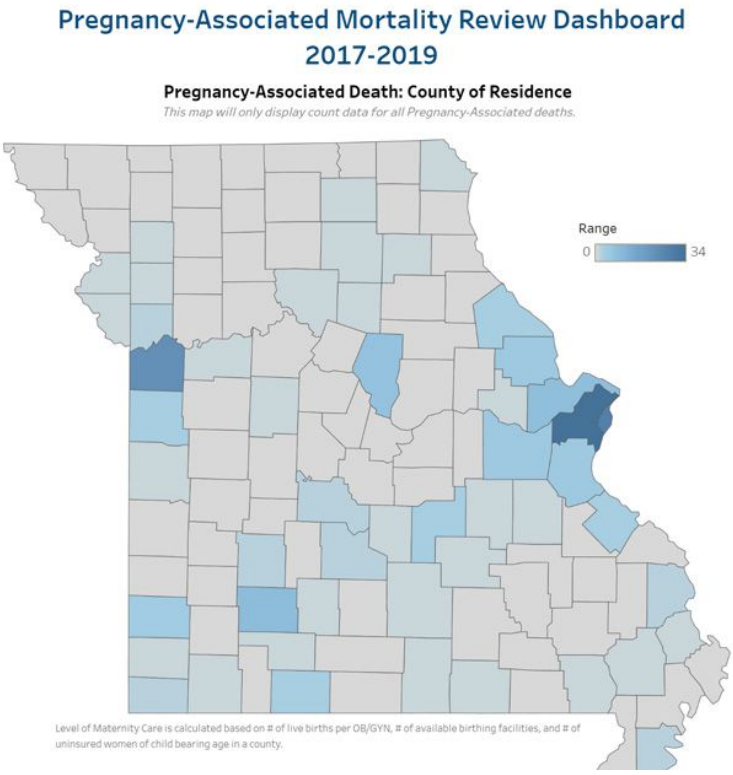
Paula F. Nickelson, MEd, Acting Director, Missouri Department of Health and Senior Services.

Life Expectancy in Missouri: Trends

Life expectancy dropped precipitously in Missouri between 2019 and 2021, mirroring national trends. COVID-19-related deaths, record high opioid overdose deaths, homicides and suicides all contributed to this significant decline. Missouri's life expectancy is 74.6, the lowest calculated in about 40 years. Nationally, life expectancy declined by a similar margin dropping from 78.8 in 2019 to 76.1 in 2021. In recent years, Missouri life expectancy has consistently been about 1.5 years less than the national average and is currently over five years less than Hawaii, which has the longest life expectancy at birth according to the CDC.

Leading Causes of Mortality in Missouri

The impact of the COVID-19 pandemic was apparent in vital statistics collected in 2020 and 2021. COVID-19 was the third-leading cause of death in Missouri for both years following behind heart disease and cancer, which have been the longstanding top two causes of death. COVID-19 death counts were higher than unintentional injuries, chronic lower respiratory diseases and stroke (which ranked fourth through sixth respectively). The total number of Missouri resident deaths increased from 62,155 in 2019 to 73,883 in 2020, an unprecedented increase of almost 19%. The previous highest year-to-year increase was a full century



earlier in 1919 during the Spanish flu pandemic, which resulted in an increase of 13.3%.

Violent deaths affect younger populations at higher rates and have been increasing in Missouri in recent years, an upward trend since 2015. In 2021, the number of homicides decreased by 11%. While a decrease, this rate is still higher than all annual rates experienced from 1999-2019. Suicides experienced a 64% increase in Missouri between 2003 and 2016 but counts have remained relatively stable from 2016-2021.

Maternal Mortality in Missouri

Missouri also experiences high rates of maternal mortality with the 12th highest rate in the United States. Missouri published the first interactive maternal mortality dashboard in the nation, available online at health.mo.gov/data/pamr.

There are multiple policy and programmatic recommendations that the DHSS and partners will be pursuing. They are contained in the "Multi-Year Look at Maternal Mortality in Missouri: 2017-2019 Pregnancy-Associated Mortality Review Annual Report" and are targeted at reducing these tragic statistics.

Obesity: Underlying Factor in Chronic Disease

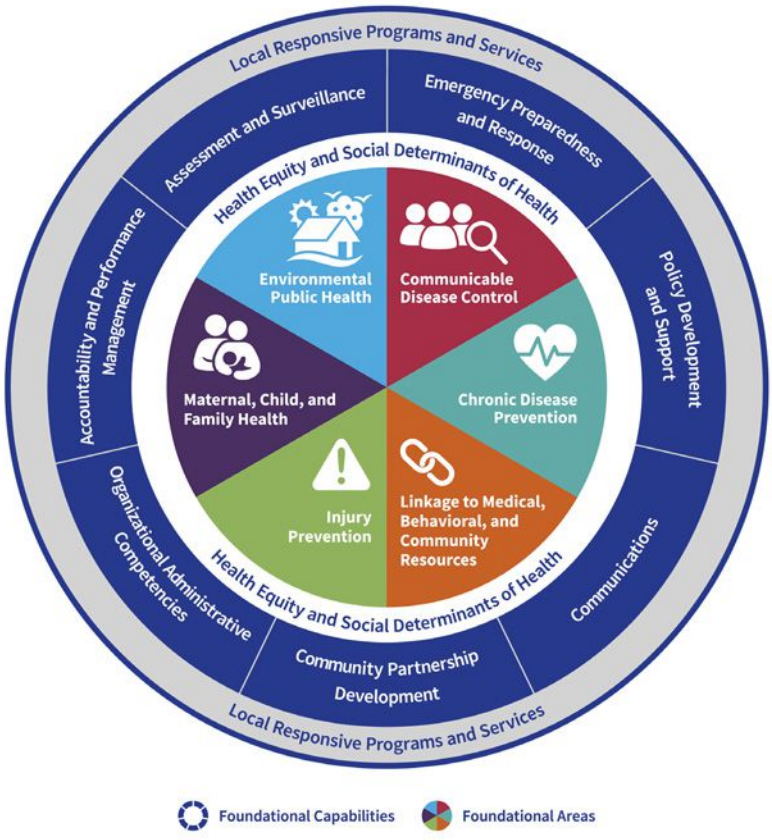
Obesity is one of the fastest growing chronic diseases in the U.S. and is unique in that it is a primary risk factor for virtually all other chronic diseases, including but not limited to diabetes, cardio- and cerebro-vascular diseases, chronic kidney disease and multiple cancers. According to the 2021 Behavioral Risk Factor Surveillance Survey, with an obesity prevalence rate of 37.2% in adults, Missouri continues to outpace the national average of 33.9%. This number jumps to 69.2% when including individuals who are categorized as overweight.

Missouri's Public Health System Under-Resourced: What's Next?

Missouri's public health system has been under-resourced for decades and this must change in order for Missourians' health to improve. With leadership by DHSS, the state's governmental public health system is adopting a new model. The model describes foundational programs and capabilities that must be available to every Missouri resident and in every community to assure the best opportunity for health.

The model described at https://www.healthiermo.org/—the Foundational Public Health Services (FPHS)—aims to assure six core public health programmatic areas are available through every public health agency: chronic disease prevention, communicable disease control, environmental public health,; injury prevention, maternal, child and family health, and linkages to medical, behavioral, and community resources.

With funding from the Centers for Disease Control and Prevention (CDC), DHSS will lead an effort over the next four to five years to conduct a cost analysis for full implementation of the FPHS model statewide, as well as an accountability measure planning effort with a diverse group of stakeholders inclusive of county and state policymakers.



Missouri's Public Health and Healthcare Workforce

Missouri and the entire nation face an unprecedented challenge with the public health and healthcare workforce, across all titles and professional, paraprofessional, support levels, in all areas of the state. Efforts are underway to address these workforce issues, but resolution will take decades and require innovation.

DHSS and the Missouri Division of Workforce Development will co-lead a newly formed Public Health/Healthcare Workforce Commission to continue to address the workforce challenges.

Opioid Misuse, the Impact, and Next Steps

Unintentional injury deaths increased by 48% between 2011 and 2021, by far the largest increase among the top five leading causes of death over this period. Accidental drug overdose, a sub-category of unintentional injury, is the largest driver of this increase.

The state and each county are authorized to receive funding through the opioid settlement, although the funding has been slow to become available for implementation. Planning at the state level for these funds include naloxone distribution, expansion of a statewide Perinatal Quality Collaborative designed to identify methods for practitioners and communities to assure good outcomes for babies born to mothers using opioids, and expansion of Medication Assisted Therapies and other outpatient services for opioid users.

DHSS and Missouri Department of Mental Health approached the CDC and the Substance Abuse and Mental Health Services Administration to co-facilitate a statewide convening to plan for the prevention, treatment and recovery of individuals using and abusing opioids. These meetings occurred in November and December 2022 with a comprehensive, statewide plan forthcoming.

Non-Medical Marijuana Use for Adults: Implementation

With the November 2022 passage of the petition ballot initiative, Missouri became one of twenty-one states allowing non-medical marijuana use for adults. Missouri legalized medical marijuana use four years ago, now one of thirty-seven states to do so. DHSS is responsible to develop, implement, and oversee both medical and adult non-medical use in the state. Further information and updates are available at cannabis.mo.gov.

COVID and ARPA Funding

DHSS is grateful for the American Rescue and Preparedness Act (ARPA) funds, which the Governor and General Assembly dedicated to the expansion of the Missouri State Public Health Laboratory – an integrated approach to

laboratory needs of the Missouri Departments of Health and Senior Services, Agriculture, Conservation, Natural Resources, and Public Health. This represents the first state laboratory in the nation to house scientists interested in the human, animal, and environmental issues and the impact of that intersection to the health of all three. We are excited to lead the way in this effort and look forward to benefits not yet totally foreseen.

DHSS published a public-facing, interactive dashboard in early 2023 allowing community members, policy makers, and stakeholders to understand how the public health COVID-19 funds have been used in their communities and for the betterment of public health and healthcare across the state. To view our success stories at health.mo.gov/funding.

Master Plan on Aging

By 2030, Missouri seniors will comprise more than 25% of Missouri's population—for the first time there will be more older adults than individuals younger than 18 years of age. In 2023, the state will launch planning for a Cabinet-level Master Plan on Aging under leadership from the Governor's Office and DHSS to chart the path forward for public and private investments and initiatives across all disciplines and fields to proactively plan for our aging residents.

DHSS Board of Health

DHSS thanks the members of the State Board of Health for their leadership. Those members include: Sue Allen, Town and Country; Matthew Brandt, MD, Springfield; Jeffrey Coughenour, MD, Columbia; Nick Ragone, St. Louis; and Debra Ann Schumer, Cape Girardeau.



DHSS Chief Medical Officer

Heidi Miller, MD, MSMA member and an internal medicine physician with extensive experience with uninsured, Medicaid and underinsured populations, joined DHSS as the department's first Chief Medical Officer in January 2023. Dr. Miller will provide medical guidance and expertise to DHSS programs, serve as the liaison with medical associations and providers, be instrumental in program and protocol development, and continue to build and implement the vision of an integrated public health and healthcare system.

Forward Together

While many of Missouri's health indicators are not encouraging, there are actionable improvements, which Missourians can and must make starting with investments in our public health system and our public health/healthcare workforce. The public health and healthcare systems must continue to identify methods to address the complex, inter-related factors inclusive of social determinants of health, which impact health outcomes for our neighbors and citizens. Strategic partnerships with fellow state departments, industry associations (inclusive of Missouri Hospital Association, Missouri Primary Care Association, Missouri Health Care Association, and Missouri Area Agencies on Aging), academic partners and disciplinary-specific associations (inclusive of MSMA, Missouri Chapter of American Academy of Pediatrics, Missouri Association of Family Practice Physicians, Missouri Association of Osteopathic Physicians and Surgeons, and Missouri College of Emergency Physicians) make us confident that true progress will occur for Missourians.

DHSS looks forward to our continued partnership with Missouri State Medical Association and the state's medical providers to identify those opportunities for positive and sustained impact.

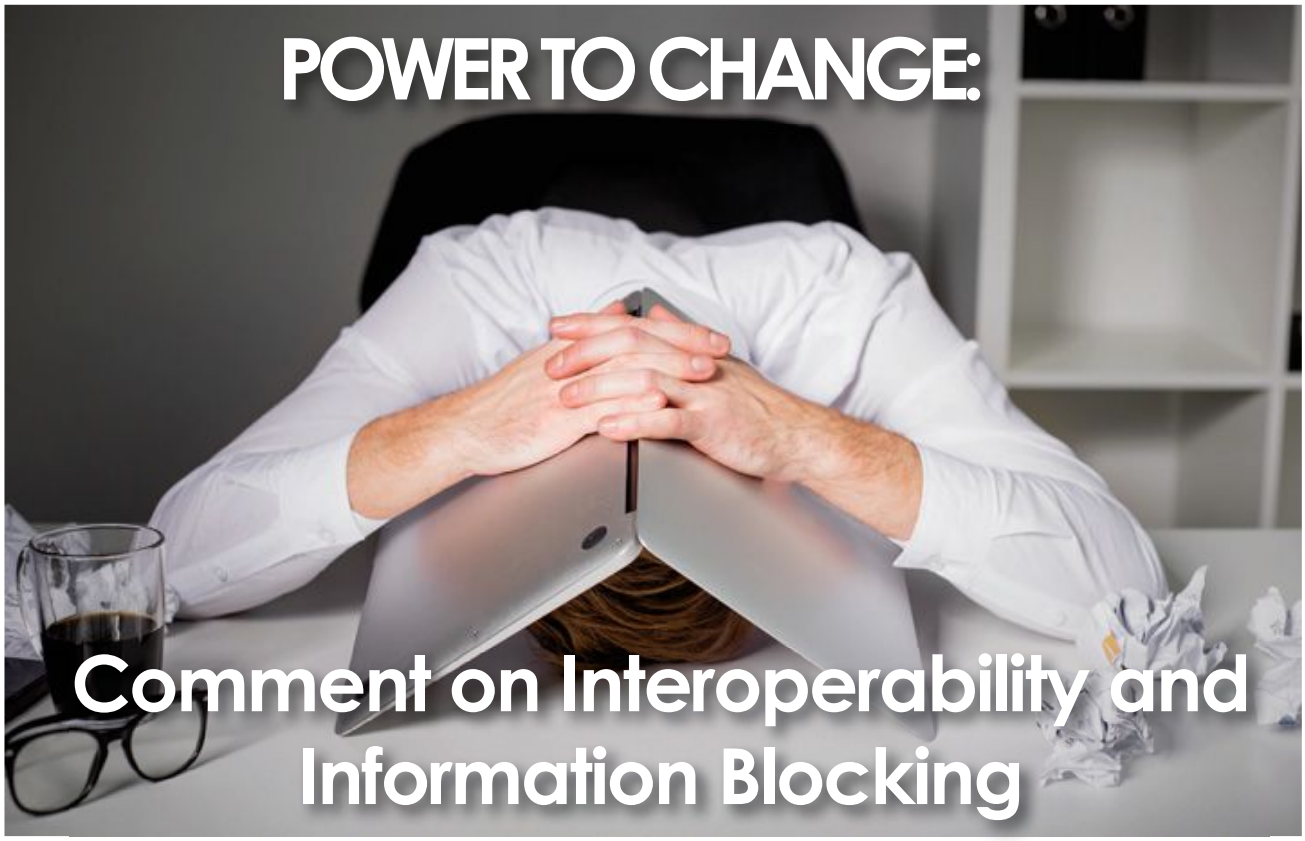
References

1. Centers for Disease Control and Prevention. (2022, Aug. 24). Life expectancy at birth by state. https://www.cdc.gov/nchs/pressroom/sosmap/life_expectancy/life_expectancy.htm

2. Missouri Department of Health and Senior Services (2022, December). Pregnancy-associated mortality review. https://health.mo.gov/data/pamr/

3. Missouri Department of Health and Senior Services (2022, August). A multi-year look at maternal mortality in Missouri, 2017-2019 pregnancy-associated mortality review. https://health.mo.gov/data/pamr/pdf/2019-annual-report.pdf

4. Missouri Public Health Association. (2020). Transforming the future of public health in Missouri. https://www.healthiermo.org/fphs-model **MM**



POWER TO CHANGE:

Comment on Interoperability and Information Blocking

by George P. Hubbell, MD

The 2023 legislative session has begun at the state Capitol. Currently, there are more than 600 bills introduced in the State Senate and nearly another 1,000 in the House of Representatives. They will come close to introducing 2,500 pieces of legislation before the March 1 deadline for both chambers. The reality, that more than 90% will not pass, is somewhat reassuring, and it will keep MSMA staff and our three lobbyists most vigilant for the next five months. A good portion of these affect our practices and patients, and having the most resonant voice as a profession requires our presence.



George P. Hubbell, MS, MD, FACOG, is President of the Missouri State Medical Association for 2022–2023. He is a Obstetrician/Gynecologist from Lake Ozark, Missouri.

Communications come in many ways from MSMA, but the Monday morning publication *Five Things You Need to Know This Week* and the Thursday *Legislative Report* keep you abreast of medically pertinent bills and their movement. When a bill you want to be passionately involved with is on the schedule, your physical presence is most welcome for testimony at the hearing. While in-person testimony matters, now digital or written comments are easy to enter through the www.house.mo.gov and www.senate.mo.gov websites. These are very easy to operate, and your elected officials will welcome your comments and opinions. Let's make loud and present cacophony for those issues near and dear, now so easy and at your fingertips. Watch for your MSMA briefs sent each week via email.

I've been watching interoperability (IT connect and communication in a coordinated way-minimizing effort by the physician end-user) for EHRs nationally. As you know, patient information at the point of care is still not easily available despite billions of dollars and 14 years in the making. Frustration in our ranks exists daily adding significantly to physician burnout that

has risen from 36% pre-pandemic era to 63% post-pandemic, according to a recent survey. This is entirely unacceptable.[1]

The Office of National Coordinator for Health Information Technology (ONC) has been tasked with facilitating patient and physician access to electronic records under the U.S. Department of Health and Human Services (HHS). The ONC certifies EHRs and enforces the current law which to date hasn't been physician or patient centric but favoring the corporate IT industry and its vendors. As a result of the 21st Century Cures Act (CURES) a final rule has been issued and relates to EHR blocking, interoperability, and the ONC certification program.

The Veterans Administration health system (VA) has contracted with a former Missouri IT company, Oracle Cerner, to provide EHR to the government medical systems. Rollout began in 2020 at a contracted cost of $10 billion and cost overruns now estimate the figure at $16 billion to date. At the VA in Spokane, Washington, where the product has been introduced as a pilot, 148 veterans have been harmed and the system has gone down over 50 times, with 11,000 orders for specialty care not processed. The penalty has been a mere $156,750 fine for "loss of functionality.[2]" With the unforeseen delay, the remainder of the 170 hospitals in the VA system won't go live until 2028.[3]

The VA EHR modernization executive director announced her resignation this week and an interim director has been appointed effective February 25,2023. Additionally, a bill has been introduced, HR 592, in the US House of Representatives that in effect would prevent the VA from implementing the Oracle Cerner EHR platform at any other VA facilities until senior clinician approval is met.[4]

This only represents one hospital that mirrors what has happened in many others and with all vendors—not just the VA's. Currently, the comment period for the HSS final rule on interoperability, information blocking, and certification is open through April 17, 2023. If you have comment, it can be made regarding these rule changes by registering at bit.ly/3lH9YtN.

We now spend over half our time behind the EHR screen, creating excessive documentation each day. If ever our comments and feedback need to reverberate, *it is now.* Let's act in the present, we can't go back, but need immediately to involve ourselves with the future.

References

1. Berg, Sara. Burnout high where you practice? AMA News. Jan 24, 2023.
2. Rodriguez, Sarai. Lawmaker Blasts VA over $156K fine for Oracle Cerner system outages. EHR Intelligence. Sept 26,2022.
3. Land, Heather. First VA Medical Center (finally) Goes Live on Cerner EHR as part of $16B Project. Health Tech Oct 26,2020.
4. Hanah Nelson. VA Modernization Program Executive Director to Depart Agency. EHR Intelligence Feb 13, 2023.

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**



Part II

Missouri's Fentanyl Poisonings Rise to Record Levels

by William V. Stoecker, MD, Colin L. Smith, BS & Elizabeth Connors, MSW

Abstract

Missouri's dramatic rise in fentanyl-related overdoses was reported in Part I of this two-part series. In Part II, we report that previous efforts to combat the surge in illicit fentanyl supply from China failed, as Chinese factories shifted production to basic fentanyl precursor chemicals, known as dual-use pre-precursors. Mexican drug cartels now synthesize fentanyl from these basic chemicals and have overpowered the Mexican government. All efforts to reduce the fentanyl supply appear to be failing.

Missouri has implemented harm reduction methods: training first responders and educating people who use drugs in safer practices. Harm reduction agencies are distributing naloxone at unprecedented levels. The "One Pill Can Kill" campaign begun by the Drug Enforcement Agency (DEA) in 2021 and foundations created by bereaved parents aim to educate young people on the extraordinary danger of counterfeit pills.

In 2022, Missouri is at a crossroads, with record numbers of fatalities from illicit fentanyl and new levels of effort by harm reduction agencies to combat the soaring rate of deaths from this powerful narcotic.



William V. Stoecker, MD, MS, (left), is at S&A Technologies and The Dermatology Center, Rolla, Missouri and in the Department of Dermatology, University of Missouri Health Sciences Center, Columbia, Missouri. **Colin L. Smith, BS**, is at the Kirksville College of Osteopathic Medicine, A.T. Still University, Kirksville, Missouri. Elizabeth Connors, LCSW, MSW, CRADC, is at the Missouri Institute of Mental Health, University of Missouri-St. Louis, St. Louis Missouri.

Fentanyl Chemicals from China: Dual-Use Pre-Precursors

In Part I of this two-part series, we reviewed the hazards of fentanyl exposure. The drug is inherently hazardous because of its potency in suppressing neurons that control respiration. Furthermore, there is significant variation of fentanyl toxicity among people due to the variation in genetics that govern its toxic effects (toxicodynamics) and differences in its metabolism (toxicokinetics). In Part II of this series, we review the causes of the unprecedented availability of illicit fentanyl.

In a previous article on fentanyl overdoses, we reported that the main supplier of fentanyl for the illicit drug trade was China.[1] The production and distribution of illicit fentanyl changed dramatically as documented in a Brookings Institution report by Vanda Felbab-Brown.[2] After American diplomatic efforts, the Chinese government changed its policy in 2019, implementing requirements for special government licenses to produce, sell, and export synthetic fentanyl-type drugs, including fentanyl analogs.[3] China's designation of certain drugs for control, placing them on a schedule, had an immediate effect on the flow of drugs from China. Direct mail shipments of fentanyl fell precipitously, declining by 90% between 2018 and 2019.[4] The Chinese government also scheduled two immediate precursors of fentanyl, NPP (N-phenethyl-4-piperidone) and 4-ANPP (4-anilino-N-phenethyl-4-piperidine).[5]

Chinese chemical companies adapted to these regulations by producing nonscheduled precursors. These firms now sell products that enable production of direct fentanyl precursors—so-called "pre-precursors"—many of which are dual-use, meaning that they are also used to produce legal pharmaceuticals.[6] Matthew Donahue of the DEA stated that Chinese traffickers, rather than producing fentanyl, produce "an unlimited and endless supply of precursor chemicals" which are

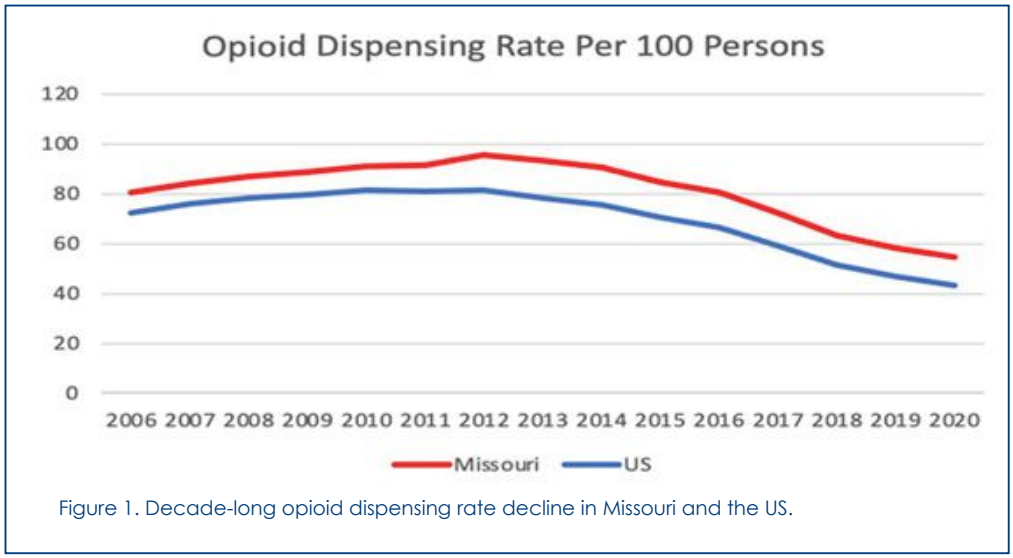


Figure 1. Decade-long opioid dispensing rate decline in Missouri and the US.

sold and distributed to Mexico.[7] Chinese officials have no intent to schedule these pre-precursors, even if they have no legal use today because that might hinder the development of legal uses in the future.[8] Additionally, Chinese manufacturers supply pill presses used by criminal organizations in Mexico and America to make counterfeit pills. Chinese export regulation for these presses remains weak.[9] One diplomat said: "The United States hoped that it could schedule its way out of the opioid epidemic. That has not happened."[3]

Chinese participation in the fentanyl precursor trade goes beyond manufacturing basic fentanyl pre-precursors. Chinese mafia cells have appeared in Mexican smuggling ports, such as Lázaro Cárdenas in Michoacán.[10] These cells facilitate the chemical trade and serve to launder the vast profits of the Mexican drug cartels.[11, 12]

Sinaloa: The Drug Cartel with 100,000 Workers

After Chinese producers expedite the fentanyl pre-precursors to Mexico, the Mexican drug cartels undertake the next steps: manufacturing fentanyl and transporting the drugs via the interstate system to distribution centers in the United States, including Missouri. Two Mexican drug cartels, Sinaloa and Cartel Jalisco Nueva Generación (CJNG), dominate drug trafficking, driving illicit drugs up the interstate directly to Missouri.[13] The unofficial count of 100,000 Sinaloa workers ranks the cartel third in the number of employees among private Mexican firms, behind only Wal-Mart Mexico, and FEMSA, the bottler of Coca-Cola in Mexico.[14]

Estimates of illicit drug export revenues from this trafficking range from $6 billion to $21 billion a year between 2010 and 2018.[15] After China's crackdown on direct mail shipments of fentanyl from China to the U.S., the flow of fentanyl across the Southwest U.S. border from Mexico surged. Fentanyl seizures by the DEA totaled 588 pounds in 2021.[16] The Sinaloa cartel is one of the most powerful criminal organizations in the world and, for over a decade, has been the largest drug cartel in Mexico.[17]

Based in the city of Culiacán, in the state of Sinaloa, the giant cartel was formerly headed by the infamous Joaquin "El Chapo" Guzman. He pioneered the use of drug smuggling through long tunnels under the Southwest U.S. border and was captured three times.[17] After escaping from Mexican prisons twice, his final arrest led to extradition to the U.S., where he serves a sentence of life plus 30 years.[18] Three of El Chapo's sons serve under the new leader of the cartel, Ismael Zambada Garcia. Mexican criminal groups have become quite skilled in chemical innovation and drug production from widely available chemicals. The cartels can produce "meth essentially from 'nothing,'" as an international drug policy official stated.[19] The Mexican cartels recruit advanced chemistry students and recent graduates from Michoacán and Mexico City universities. Cartel chemists can synthesize fentanyl by the Jannsen method, which is more sophisticated than the Siegfried method. DEA's research laboratory reported that 94% of illicit fentanyl analyzed in 2018 was synthesized with the Janssen method. [20]

In the next section, we present data to show that the rise in fentanyl overdoses correlates with the flood of illicit fentanyl and not opioid prescribing patterns. As Greene County Medical Examiner, Tom Van De Berg, stated of the increase in illicit fentanyl available:, "There is just more of it on the street."

Street Drugs, Not Prescription Overdoses, Driving Epidemic

Missouri providers in 2020 wrote 54.4 opioid prescriptions per 100 persons, more than the national average rate of 43.3 prescriptions for opioids (fentanyl included) per 100 persons.[21] Both rates were lower than the corresponding figures for 2019: 58.3 for Missouri and 46.7 for the U.S.,[22] following a long-term decline in opioid prescribing rates (Figure 1).

Five Missouri Counties—Butler, Cape Girardeau, St. Francois, Jasper, and Howell—were at the top of Missouri counties regarding opioid prescription rates (125.4, 102.8, 99.5, 95.8, and 93.7 opioid prescriptions per 100 people, respectively) in 2020. Dunklin County, with the top opioid prescription rate in 2018 (148.6 opioid prescriptions per 100 people), has fallen to half that rate: 74.1 prescriptions per 100 people in 2020.[21] Of the five counties with the highest opioid prescription rates, St. Francois County is the only one that ranks within the top eight counties for overdoses in 2021. St. Louis City, with the highest rate of opioid deaths in the state, ranks below the national average for opioid prescriptions: 42.5 per 100 persons.[21]

Missouri health department statisticians urge caution in comparing these rates, which do not consider the number of pills prescribed or the strength of opioids. The rate is merely the number of prescriptions divided by the population in the county. Doctors in counties with high prescribing rates may be doing a better job regulating prescriptions, for example, writing several prescriptions, each for a shorter period.

The persistent rise in opioid deaths has occurred during a long-term decline in opioid prescriptions. Access to genuine pharmaceutical opioids has declined sharply, while access to counterfeit opioids has become much easier. Some counterfeit opioid users believe that prescription opioids are so challenging to obtain that counterfeit opioids are their only option.[23] While judicious opioid prescribing is essential, decreasing opioid prescriptions alone will not solve this overdose crisis. Harm reduction methods are a more promising approach. In the next section, we discuss recent harm reduction efforts in Missouri.

Harm Reduction Through Education: Safer Drug Use & Avoid Counterfeit Pills

The Connecting the DOTS (Drug Overdose Training and Safety) Project (2019-2023) of the Missouri Institute of Mental Health at the University of Missouri, St. Louis (UMSL-MIMH) was developed by the UMSL-MIMH Department of Addiction Science.[24] The project is funded by Substance Abuse and Mental Health Services Administration of the U.S. Department of Health and Human Services. This project aims to improve overdose prevention and response initiatives across Missouri by providing occupational safety training to emergency first responders in high-impact areas of the opioid epidemic, increasing naloxone distribution for first responders, and improving collaboration between first responders and community-based service providers.

Connecting the DOTS provides a targeted response to nine areas with a high rate of opioid overdoses: Year 1: St. Louis City, Jackson County, and Greene County; Year 2: Jefferson, Clay, and St. Louis Counties; Year 3: Boone, Franklin, and St. Charles Counties.[24] Occupational safety training follows the SHIELD (Safety and Health Integration in the Enforcement of Laws on Drugs) model, customized to each community served, and modified for either law enforcement, fire protection, or emergency medical services audiences.[25] Training content focuses on first responder wellness, overdose scene safety, and community coordination to assist first responders with connecting people who use drugs to available community resources.[26]

The DOTS Project provides naloxone to trained first responder agencies within the nine target counties the project serves. Law enforcement personnel are provided naloxone to carry on hand, while emergency medical service providers are trained to leave behind naloxone kits with overdose survivors or their loved ones. Leave-behind naloxone kits include one box of nasal naloxone, a one-way breathing mask, and educational resources related to addiction and recovery.

The DOTS Project emphasizes a follow-on connection to treatment or harm reduction resources after an overdose encounter. First responders are educated on community coordination efforts, such as the Engaging Patients in Care Coordination (EPICC) project and Community Behavioral Health Liaisons, and how to refer community members to these linkage resources. [28] This enhanced collaboration boosts first responders' ability to connect individuals who overdose to appropriate community care options, thus leading to increased treatment and recovery service referrals following an overdose event.

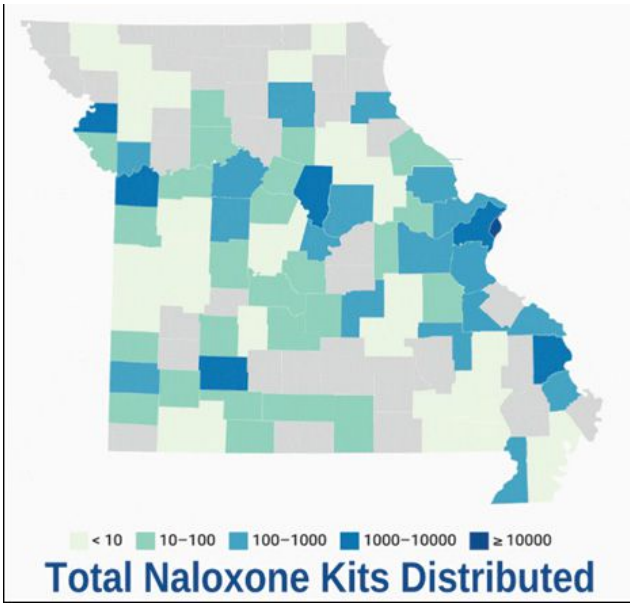


Figure 2. Naloxone kits supplied by grant funding via the University of Missouri-St. Louis - Missouri Institute of Mental Health, 7/1/2020 to 3/31/2022. [27]

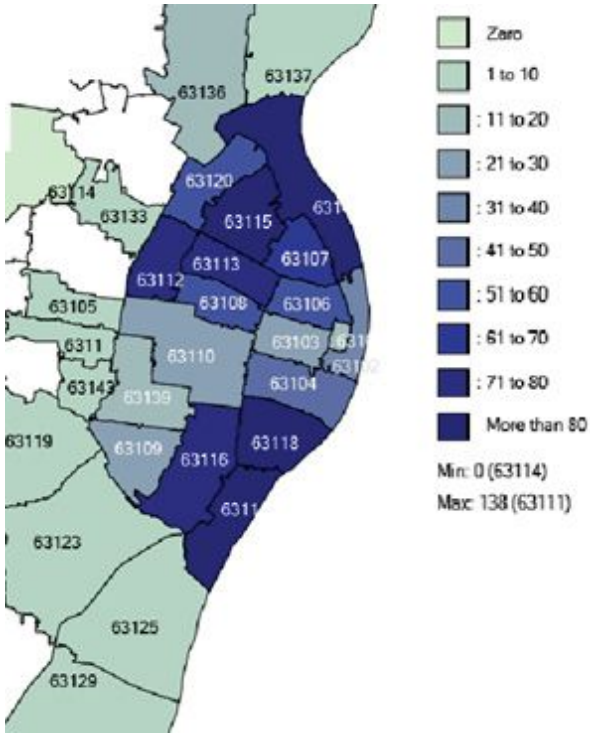


Figure 3. Naloxone administrations in St. Louis City and St. Louis County, 2020-2021.[30]

Preliminary data shows evidence of success through the Connecting the DOTS Project, with pre- and post-training surveys showing increases in first responder intention to refer to supportive services.

The Missouri Institute of Mental Health partnered with NEXT Distro (Needle EXchange Technology Distribution), an online and mail-based harm reduction service designed to reduce opioid overdose deaths and prevent injection-related disease transmission.[29] The partnership delivered 57,193 naloxone kits to Missourians as of March 31, 2022, the majority via street outreach, harm reduction programs, recovery centers, and treatment providers (Figure 2).[30] These efforts have significantly increased the availability of naloxone in Missouri, especially in the areas targeted by the Connecting the DOTS project. Part I of this series showed a high rate of opioid fatalities in many rural counties in Missouri, especially along the Interstate-44 corridor. Figure 2 suggests a need for additional naloxone in rural counties with high rates of opioid fatalities.

The Connecting the DOTS project documented intensive administration of naloxone in St. Louis City and St. Louis County, 2020-2021, Figure 3.[30] Zip code areas near the northern and southern boundaries of the city experienced more than 80 naloxone administrations. Three of the nine Connecting the DOTS service areas, St. Louis City and County and Franklin County, experienced a decrease in fatal opioid overdoses in 2021 vs. 2020, counter to the overall Missouri overdose increase shown in Part I.

Libby and Randy Davis, the parents of Cooper Davis, the teen who died after taking just one-half of a counterfeit pill, remain active in the Cooper Davis Memorial Foundation. Their mission is to spread awareness of the danger of counterfeit pills and educate the community with the hope of saving families from a loss like theirs. “Every life is precious, and we want to prevent others from making that one choice that could have a deadly outcome,” says Libby Davis.[31] The foundation’s electronic billboard on Interstate-70 in Kansas conveys the message, “One pill can kill,” (Figure 4). Despite the efforts of individuals and government agencies, as of the beginning of 2023, Missouri remains in the midst of an unprecedented epidemic of fatal fentanyl encounters.

References

1. Stoecker WV, Bosworth KT, Rottnek F. Missouri’s Fentanyl Problem: The China Connection. .Mo Med. 2020 Jul-Aug;117(4):362-369.
2. Vanda Felbab-Brown. China and Synthetic Drug Control. Brookings Institution, March 2022. https://www.brookings.edu/wpcontent/



Figure 4. Electronic billboard for Cooper Davis on I-70 near Kansas City.

uploads/2022/03/FP_20221107_drug_trafficking_felbab_brown.pdf Accessed January 17, 2023
3. Ibid, p. 3
4. Lauren Greenwood and Kevin Fashola, Illicit Fentanyl from China: An Evolving Global Operation. U.S.-China Economic and Security Review Commission. August 24, 2021.
Illicit Fentanyl from China (uscc.gov) https://www.uscc.gov/sites/default/files/2021-08/Illicit_Fentanyl_from_China-An_Evolving_Global_Operation.pdf Accessed January 27, 2023
5. Felbab-Brown, op. cit., p. 13
6. Felbab-Brown, Ibid, p. 3
7. Matthew Donahue, cited in Lauren Greenwood and Kevin Fashola, "Illicit Fentanyl from China: An Evolving Global Operation," (Washington, DC: U.S.-China Economic and Security Review Commission, August 24, 2021), Illicit Fentanyl from China (uscc.gov) https://www.uscc.gov/sites/default/files/2021-08/Illicit_Fentanyl_from_China-An_Evolving_Global_Operation.pdf Accessed January 17, 2023.
8. Felbab-Brown, op. cit., p. 16
9. Felbab-Brown, op. cit., p. 14
10. Felbab-Brown, op. cit., p. 45
11. Felbab-Brown, op. cit., p. 46
12. Felbab-Brown, op. cit., p. 47
13. Felbab-Brown, op. cit., p. 43
14. Number of workers at top Mexican companies 2021 | Statista https://www.statista.com/statistics/1025815/mexico-number-employees-top-companies/ Accessed January 17, 2023
15. Sources for Velbab-Brown's Mexican cartel earnings estimates, Velbab-Brown p. 46: "Estimating Illicit Financial Flows Resulting from Drug Trafficking and Other Transnational Organized Crimes," (Vienna: United Nations Office on Drugs and Crime, October 2011), https://www. unodc.org/documents/data-and-analysis/Studies/Illicit_financial_flows_2011_web.pdf Accessed January 17, 2017; Beau Kilmer, Jonathan P. Caulkins, Brittany M. Bond, and Peter Reuter, "Reducing Drug Trafficking Revenues and Violence in Mexico: Would Legalizing Marijuana in California Help?" (Santa Monica, CA.: RAND Corporation, 2010), https://www.rand.org/pubs/occasional_papers/OP325.html January 17, 2023; and Gabriel Stargardter, "Mexico's drug cartels, now hooked on fuel, cripple the country's refineries," Reuters, January 24, 2018, https://www.reuters.com/investigates/special-report/mexico-violence-oil/ Accessed January 17, 2023.
16. Border agents reported a 1,066% increase in fentanyl seized in south Texas last year - CNN https://www.cnn.com/2022/01/08/us/fentanyl-seized-south-texas-border-2021/index.html Accessed January 17, 2023.
17. Inside Mexico's Most Powerful Drug Cartel. By Sol Prendido 7/23/2021 BorderlandBeat http://www.borderlandbeat.com/2021/07/inside-mexicos-most-powerful-drug-cartel.html Accessed January 17, 2023.
18. Joaquín "El Chapo" Guzmán -https://en.wikipedia.org/wiki/Joaqu%C3%ADn_%22El_Chapo%22_Guzm%C3%A1n Accessed January 17, 2023.
19. Felbab-Brown, op. cit., p. 15
20. Drug Enforcement Administration. National Drug Threat Assessment. 2019; 1-146. https://www.dea.gov/sites/default/files/2020-01/2019-NDTA-final-01-14-2020_Low_Web-DIR-007-20_2019.pdf Accessed January 17, 2023
21. U.S. State Opioid Dispensing Rates, 2020. https://www.cdc.gov/drugoverdose/rxrate-maps/state2020.html Accessed January 17, 2023.
22. U.S. State Opioid Dispensing Rates, 2019. https://www.cdc.gov/drugoverdose/rxrate-maps/state2019.html Accessed January 17, 2023.
23. Daniulaityte R, Sweeney K, Ki S, Doebbeling BN, Mendoza N. "They say it's fentanyl, but they honestly look like Perc 30s": Initiation and use of counterfeit fentanyl pills. Harm Reduct J. 2022 May 25;19(1):52.
24. Connecting the DOTS: Drug Overdose Trust and Safety https://dotsproject.org Accessed January 17, 2023.
25. The SHIELD training initiative. https://www.shieldtraining.org Accessed January 17, 2023.
26. Overdose scene safety includes instruction on the actual risks of fentanyl powder vs. the perceived risks. Education helps some first responders who believe that fentanyl is so powerful that if they touch an overdose victim, they also risk an overdose.
27. HOSPITAL-INITIATED SUBSTANCE USE PROGRAMMING: ENGAGING PATIENTS IN CARE COORDINATION [EPICC] https://mocep.org/about/epicc/#:~:text=Hospital-Initiated%20Bridge%20Programming%3A%20Engaging%20Patients%20In%20Care%20Coordination,immediate%20connections%20from%20hospitals%20to%20community-level%20treatment%20services. Accessed January 17, 2023
28. Community Behavioral Health Liaisons https://dmh.mo.gov/behavioral-health/treatment-services/specialized-programs/liaisons Accessed January 17, 2023.
29. NEXT Distro is an online and mail-based harm reduction service designed to reduce opioid overdose death, prevent injection-related disease transmission, and improve the lives of people who use drugs. https://nextdistro.org/68. https://dotsproject.org/dots-project/#goal2 Accessed January 17, 2023. In Kansas City and St. Louis, needle exchange programs in clinics remain illegal, technically. Missouri remains one of eleven states which do not allow needle exchange. Needle exchange programs, also known as syringe services programs, have been shown to reduce transmission of HIV and hepatitis and introduce people who use drugs to treatment programs. Syringe Services Programs (SSPs) FAQs | CDC https://www.cdc.gov/ssp/syringe-services-programs-faq.html#reduce-infections Accessed January 17, 2023 Yet legislation to allow needle exchange, sponsored by Sen. Holly Thompson Rehder, R-Sikeston, after passing the Missouri Senate committee in March 2022, has not been approved as of August 2022. .https://missouriindependent.com/2022/03/02/bill-that-would-decriminalize-needle-exchange-programs-passes-missouri-senate-committee/ Accessed January 17, 2023
30. Naloxone administrations in St. Louis City and St. Louis County, 2020 to 2021. https://static1.squarespace.com/static/5dafc3d188f0340df586016b/t/620fba886aa97b407ecb454f/1645197961137/DOTS+Y2+Eval+Brief+%281%29.pdf Accessed January 17, 2023.
31. Personal Communication, Libby Davis, Co-Founder of Cooper Davis Memorial Foundation, July 23, 2022.

Disclosure

None reported.

MM

Content Notice: Guidelines to Discuss Suicide on Social Media

by Brianna J. Engelson, MD, Simone A. Bernstein, MD, Christine Yu Moutier, MD & Jessica A. Gold, MD

Physicians and other health professionals can play a leadership role by following guidelines and amplifying experts. As conversations about celebrities—and even healthcare worker's deaths—populate social media sites, guidelines can help us talk about suicide without endangering the public.

On January 30, 2022, Miss USA 2019 Cheslie Kryst died by suicide. The news of her untimely death spread quickly across all forms of media. Although well-researched media guidelines for safely reporting on suicide have existed for years, journalists broke important rules—such as detailing the method of suicide and including the contents of the note she left.[1,2] Social media activity further amplified this problem. While news outlets shared stories with images and triggering language, individual social media users amplified those stories and expressed shock, grief, and condolences via comments and posts of their own (Figure 1). Such social media activity is concerning because discussions about suicide on social media platforms can perpetuate old myths and stigma, and can potentially lead to suicide contagion.[3,4]



Brianna J. Engelson, MD, (left), is in the Department of Psychiatry, University of Minnesota Minneapolis, Minnesota. **Simone A. Bernstein, MD**, and **Jessica A. Gold, MD**, are in the Department of Psychiatry, Washington University, St. Louis, Missouri. Christine Yu Moutier, MD, is with the American Foundation for Suicide Prevention, New York, New York.

Suicide remains a major public health concern. Nearly half a million lives were lost to suicide between 2010 and 2020 in the United States alone, and the national age-adjusted suicide rate increased by 30% during that time.[5] While the early period of the pandemic saw a 3% decline in the national suicide rate (in 2020), this improvement was not seen in youth and young adults. Suicide was the second leading cause of death among individuals between the ages of 10-14 and 25-34 and the third leading cause of death among individuals between the ages of 15-24 in 2020.[5] Given that these populations use social media more frequently, social media can be utilized as a significant venue for psychoeducation and risk reduction.[6]

Several studies demonstrate an association between population suicide rates, and cultural beliefs about mental health and help seeking.[7] The sheer volume of online discussions broadens the reach beyond one location or population and highlights the importance of safe conversations about suicide; there are 4.48 billion social media users worldwide, and many are not yet informed about how to responsibly communicate about suicide.[8] While guidelines for general media exist, those for social media are limited and not widely known.[1,9] The answer is not to stop talking about suicide, since matters of critical public health concern warrant public education and

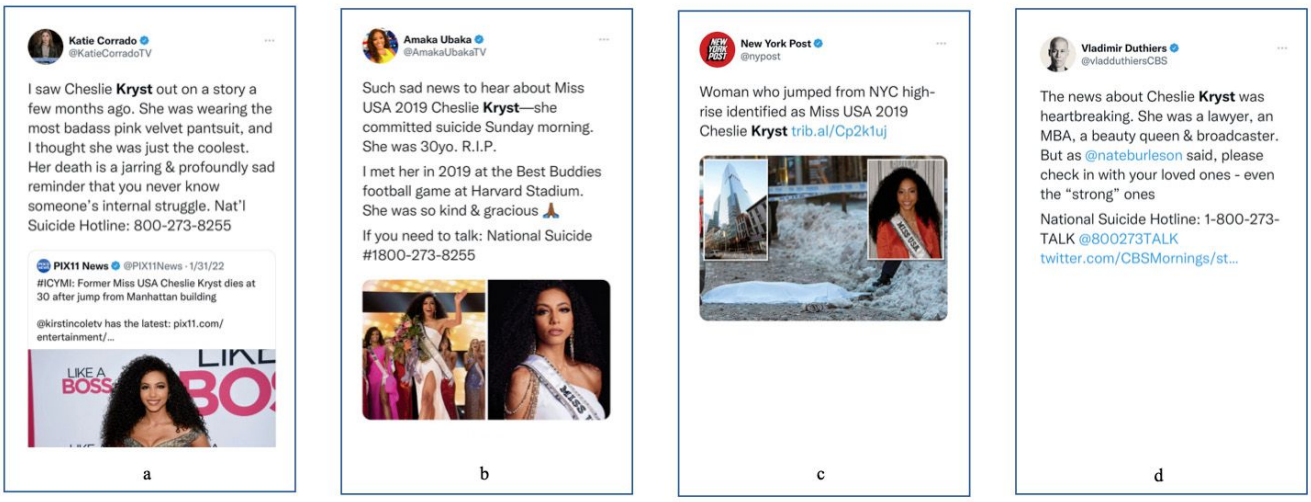


Figure 1. Content Notice: This figure includes some examples of what not to do when posting about suicide on social media. These are example Twitter posts about Cheslie Kryst's suicide **a)** A post from a verified account* for a journalist is an example of further amplifying a news story that does not follow media guidelines for reporting on suicide. While the tweet itself follows guidelines, like including the number for a suicide hotline, the news story does not. **b)** A post from a verified account that uses the phrase "committed suicide" in reference Cheslie's death. Guidelines for reporting on suicide indicate that a phrase such as "died by suicide" should be used instead. **c)** A tweet by the *New York Post* that includes a graphic image. This image, which depicts the method and location of the suicide, is not in compliance with media guidelines for reporting on suicide and may be triggering. News organizations need to monitor their social media postings just as stringently as their articles. **d)** Unlike previous examples, a tweet by a verified journalist that follows recommended guidelines for the discussion of suicide and includes information about suicide prevention.
**a verified account lets people know that an account of public interest is authentic (i.e. not a bot or an automated program that simulates human behavior on social networks). Often, verified accounts are celebrities, journalists, government officials, or people with large followings*

destigmatization—especially as stigma related to mental illness is directly associated with less active help seeking.[10] Instead, we must talk about suicide safely and effectively. Rather than elevating contagion risk, conversations may deepen mental health literacy, increase help seeking behaviors, and instill hope.[4,11]

Why Guidelines Are Needed: The History of Suicide Contagion

Suicide contagion is not a new phenomenon. The Werther effect, as it is widely called, is named after a reported spike in suicides following the 1774 publication of Goethe's *The Sorrows of Young Werther*.[11] More recent examples include upticks in suicide following media reports of celebrity deaths. According to a 2020 meta-analysis, reporting of celebrity suicides is correlated with an increase in the number of suicides by 8-18% in the months following the death, and detailing the method of suicide is associated with an 18-44% increase in the risk by the same method.[12] Though no studies have yet looked at Kryst's death (since Centers for Disease Control and Prevention (CDC) reporting on suicide lags by 12-18 months), when Robin Williams died by suicide in 2014, suicides via the same method increased by 32% in the months following his death.[13] There were concerns after William's death that United States (U.S.) print media only moderately adhered to recommendations including providing details romanticizing suicide.[14]

Because of the very real dangers of particular messaging about suicide, media guidelines for reporting were developed by several government agencies and health organizations, including WHO, CDC, the American Foundation for Suicide Prevention, the American Association of Suicidology, and the Annenberg Public Policy Center in 2001.[15] While adherence to these guidelines is voluntary in the U.S., it is considered so important that the Columbia University School of Journalism has a center devoted to reporting on suicide and the Poynter Institute has also led on this.[16,17] Still, a recent comparison of major news outlets for initial reporting on celebrity suicide found that while articles frequently adhered to

guidelines for what not to do when reporting on suicide (86%), they rarely adhered to guidelines for what to do (26%).[18] It is just as important that guidelines are in place to prevent untoward outcomes, as they are to help promote good ones. For example, news articles that educate readers on risk factors, warning signs, and coping with suicidal struggles have been shown to decrease suicidal thoughts and increase knowledge about suicide prevention, without harmful effects.[19] This is in line with another concept, the Papageno effect, named after the main character in Mozart's 18th century opera The Magic Flute.[11] Papageno feels the only way out of the pain of losing his love is suicide, but before he can act on it, three characters show him other ways to solve his problems. The media, in this sense, can act as the other characters by highlighting stories of resilience, survival, and encouraging help seeking. Currently, guidelines largely focus on traditional forms of news and print media. As the use of social media has risen sharply, the content of posts about suicide on these platforms must be considered as well.[8]

How Information Is Spread: Suicide and Social Media

Social media has become fundamental in the way we share opinions, ideas, and information. News on social media platforms surpassed print newspapers as a form of news consumption in the U.S.[20] Similarly, social media is becoming integral to the way we communicate about mental health. As of June 2022, the #MentalHealth hashtag has generated nearly 40 million public Instagram posts and has been used in millions of TikTok videos, amassing 36 billion views.[21,22] This influx of mental health-related posts undoubtedly helps normalize the discussion of mental illness. Celebrities, influencers, and members of the general public are opening up about their mental health and sharing content that addresses their experiences. But, unlike discussions or disclosures about anxiety (or almost any other health issue), discussions about suicide can lead to serious consequences due to the unique risk of contagion. Social media sites and online forums are common sources of information about suicide, and participation in particular online forums is strongly related to increases in suicidal ideation.[23] However, similar to other forms of media, while inappropriate social media discussions about suicide can be harmful, appropriate conversations can lead to shared knowledge, offerings of support, and a sense of connection—a known protective factor against suicide risk.[24] The difference is a matter of informing the public how to post safely and informatively.

Of note, various policies about suicide exist on common social media platforms. In a recent study titled "Self-Harm Policies and Internet Platforms," Stanford researchers ranked 39 online platforms, including social networks, to identify the clarity in public-facing policies relating to self-harming behavior.[25] They noted considerable variability in the comprehensiveness of public-facing policies. For example, Facebook policies address not only suicide but also suicide notes and live streaming suicide attempts. In contrast, other sites such as Reddit have no policies related to suicide in their primary policy documents. This large variability leaves individual's responsible for providing correct and safe information to the public. Also, as regulations can limit helpful and educational content, it is important to be aware of these policies and adapt. For example, on TikTok, posts that discuss death, dying, or suicide are often removed.[26] To circumvent this, creators use the word "unalive" to raise awareness instead.

As healthcare providers on social media, we must set an example with appropriate messaging. Through role-modeling specific language and providing resources, health professionals can help raise awareness and create change in the evolving discussion about suicide. We can also identify posts that are well written and educational, while gently pointing out problems in others. Our role is perhaps even more important in cases where the person who died is a healthcare worker, such as Lorna Breen, MD, a New York emergency medicine physician who died by suicide in 2020. Dr. Breen's story was featured in news outlets worldwide and healthcare professionals reacted on social media. While this case led to more conversation about, and normalization of, the pandemic's impact on healthcare professionals' mental health, the news was

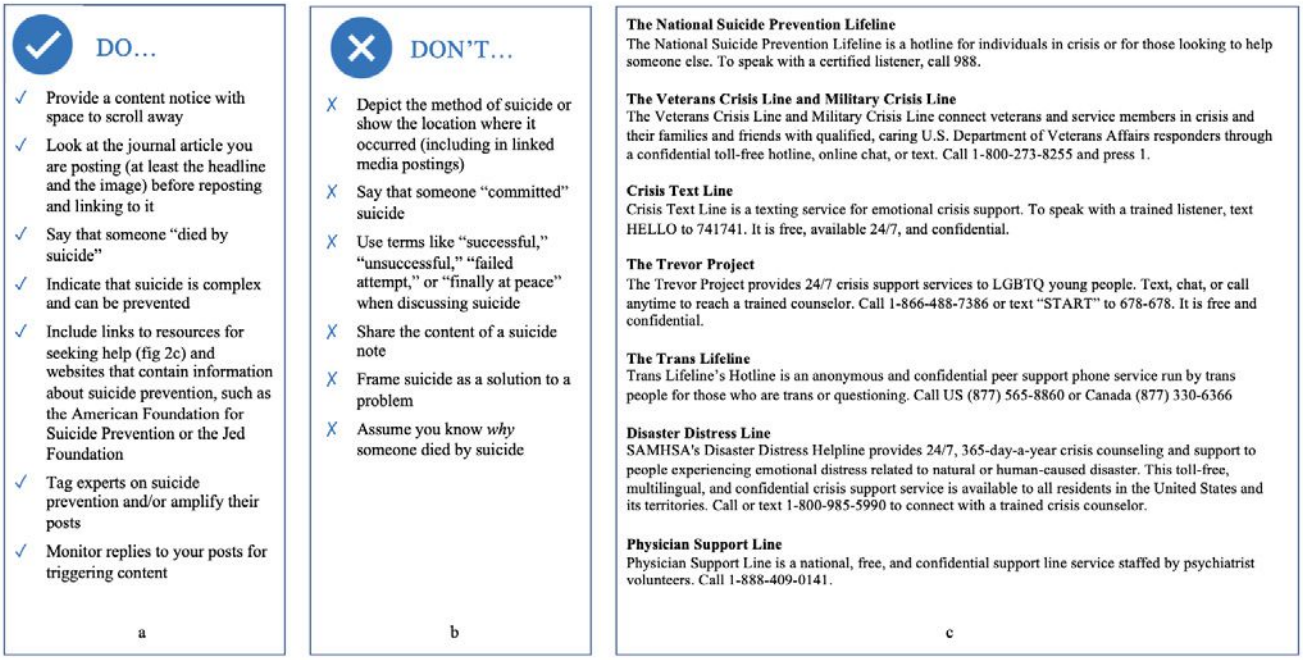


Figure 2. Summary of social media suicide reporting guidelines **a)** Do's of social media posting about suicide **b)** Don'ts of social media posting about suicide **c)** A noncomprehensive list of resources to provide on social media that direct people to help.

discussed dangerously in the media. In fact, a 2021 study found limited adherence to suicide reporting guidelines in the coverage of Dr. Breen's death by top media outlets.[27] Healthcare workers are responsible for accurately and sensitively sharing information about suicide. In this case a more positive focus could be messaging about the systemic issues surrounding physicians during the pandemic and the importance of proactive approaches to physicians' mental health, including suicide prevention efforts and the importance of accessing support and treatment. This shifts the lens from the individual suicide and instead focuses on the broader narrative about suicide prevention.

Proposed Guidelines for Social Media Discussions about Suicide

As far as the authors are aware, there are no formally vetted guidelines created for social media. Guidelines can help ground conversations and lead professionals and creators to discuss suicide safely and more easily. As such, we propose these key strategies to encourage people to responsibly report and discuss suicide on social media (Figure 2).

1. Include a Content Notice

"Triggering" occurs when a person considering suicide or self-harm views material related to someone else engaging in these behaviors and is subsequently drawn closer to their suicidal feelings or acts on their thoughts.[4] A trigger warning (TW), also known as a content notice (CN), is a statement at the beginning of a post that alerts other users to potentially distressing content. Such warnings give space for the reader to "scroll away" or otherwise avoid the content of the post. It also allows users who may have certain words "muted" not to have those posts show up on their feed at all.

2. Limit Details

Details surrounding suicidal behavior may intensify thoughts of suicide in others. For example, sharing personal information or the content of a suicide note can lead to over-identification with the individual who attempted or died by suicide and oversimplification of the events leading to the suicide attempt. This may also lead vulnerable individuals to, consciously or unconsciously, view suicide as a way to draw positive attention to themselves or secure their legacy. Moreover, information about

the method of suicide may suggest a viable means to others. Beyond these more overt cognitive mechanisms for contagion, it's important to remember that on a neurosynaptic level, humans are social creatures that are hard-wired with mirror neurons leading to unconsciously imitative behavior.[28] For individuals with suicide risk factors, detailed descriptions of other's suicidal behavior can draw them closer to their suicidal urges via these neurological and cognitive mechanisms. Therefore, it is best to keep information about the suicide general.

3. Images

Most social media platforms encourage the use of images, photos, and videos. However, images can have unintended consequences, particularly if they portray a person who has died by suicide. Such images may give rise to thoughts of suicide in others via triggering and may make suicide seem more realistic by suggesting viable methods of self-harm. Thus, posting—or reposting—images, photos, video content, or animations that depict the method of suicide or the location where it occurred should be avoided completely.

4. Language

Certain words and phrases can be hurtful, harmful, and further stigmatize suicide. For example, saying that a person "committed" suicide references a time when suicide was considered a crime or a sin. Instead, say that someone "died by suicide"—a recommendation made in the Associated Press Stylebook.[17] Also, consider that suicide should not be described as a desirable outcome. For example, words or phrases such as "successful," "unsuccessful," or "failed attempt" when describing suicidal behavior should be avoided. Avoid inaccurate phrases like "suicide epidemic," since it is not only inaccurate in terms of the rate of increase but implies a prevalence that makes suicide seem like a common behavioral response to stress. Finally, while it may be comforting for loved ones to say that a person lost to suicide is "finally at peace" this can prove dangerous to those who are experiencing suicidal thoughts as such phrasing frames suicide as a solution to a problem.

5. Don't Sensationalize

Acknowledging that there have been numerous suicide attempts at a particular location or "hotspot" can make self-harm seem like a regular, unavoidable, or effective coping strategy for distress. Instead, consider quoting, retweeting, or linking to suicide prevention experts on causes and treatments or linking to the national crisis resources. This may be a way for your account to amplify those who can talk about the issue more in-depth. The goal is to communicate the importance of the issue and encourage coping behaviors without normalizing suicide.

6. Do Not Assume You Know Why Someone Died by Suicide

Suicide is complex and research shows there are always multiple causes, including psychiatric illnesses—that may or may not have been recognized or treated.[29] Other contributing factors include physical illness, financial hardships, loss of relationships, academic performance, substance use, peer influence, and numerous other stressful life events. Avoid stating that suicide was preceded by a single event, like a divorce or job change or even the pandemic. Instead, indicate that many factors, including mental health, physical health, and psychosocial factors may contribute to a person ending their life. Additionally, in situations involving a school, do not resort to blaming the administrators. They are often struggling, too, and may even feel responsible for the suicide despite its multifactorial nature.

7. Comments

Comments on social media posts should be monitored for hurtful remarks and indications that others are considering suicide. Inappropriate and/or insensitive posts should be removed. Users and social media platforms together can monitor posts for inappropriate content and replies can even be limited (for example, allowing replies from followers or "friends" only) when discussing these topics.

8. Provide Messages of Hope

Inform others that suicide can be prevented and link to resources for seeking help, such as crisis lines and websites that contain information about suicide prevention. Promote the universal nature of facing challenges, the importance of opening up about mental health experiences, and connecting

with others for support. Providing access to good information in a sea of misinformation is extremely helpful to people.

Conclusion

Suicide is a national public health crisis, and social media is a powerful tool that can be used to educate the public about it. People may believe that suicide should not be discussed because the topic is "dangerous." However, talking about suicide properly can normalize help-seeking and deepen the public's knowledge about mental health and suicide. Social media guidelines can shape the conversation and allow for accurate, safe, and hopeful messages related to suicide—such as living through struggles and connecting to support or treatment—rather than dangerous posts that can lead to contagion. Physicians and other health professionals can play a leadership role by following guidelines and amplifying experts. As conversations about celebrities—and even healthcare worker's deaths—populate social media sites, guidelines can help us talk about suicide without endangering the public.

References

1. Reporting on Suicide. https://reportingonsuicide.org/. Accessed April 8, 2022.
2. Celona L, Moore T, Fitz-Gibbon J. Fatal NYC jumper identified as Miss USA 2019 Cheslie Kryst. New York Post. https://nypost.com/2022/01/30/fatal-nyc-jumper-identified-as-miss-usa-2019-cheslie-kryst/. Published 2022. Accessed April 8, 2022.
3. Gould M, Jamieson P, Romer D. Media contagion and suicide among the young. Am Behav Sci. 2003;46(9). doi:10.1177/0002764202250670
4. Patel DM, Simon MA, Taylor RM. Contagion of Violence: Workshop Summary.; 2013. http://www.nap.edu/catalog.php?record_id=13489.
5. National Institute of Mental Health. Suicide. https://www.nimh.nih.gov/health/statistics/suicide. Accessed July 27, 2022.
6. Auxier B, Anderson M. Social Media Use in 2021. Pew Research Center. https://www.pewresearch.org/internet/2021/04/07/social-media-use-in-2021/. Published 2021. Accessed July 27, 2022.
7. Reynders A, Kerkhof AJFM, Molenberghs G, Van Audenhove C. Help-seeking, stigma and attitudes of people with and without a suicidal past. A comparison between a low and a high suicide rate country. J Affect Disord. 2015;178:5-11. doi:10.1016/j.jad.2015.02.013
8. Dean B. How Many People Use Social Media in 2022. BackLinko. https://backlinko.com/social-media-users. Published 2021. Accessed April 8, 2022.
9. Social media guidelines for mental health promotion and suicide prevention. Each Mind Matters Resource Center. https://emmresourcecenter.org/resources/social-media-guidelines-mental-health-promotion-and-suicide-prevention. Accessed May 28, 2022.
10. Schnyder N, Panczak R, Groth N, Schultze-Lutter F. Association between mental health-related stigma and active help-seeking: Systematic review and meta-analysis. Br J Psychiatry. 2017;210(4):261-268. doi:10.1192/BJP.BP.116.189464
11. Niederkrotenthaler T, Till B. Suicide and the Media: From Werther to Papageno Effects – A Selective Literature Review. Suicidologi. 2019;24(2):4-12. doi:10.5617/suicidologi.7398
12. Niederkrotenthaler T, Braun M, Pirkis J, et al. Association between suicide reporting in the media and suicide: Systematic review and meta-analysis. BMJ. 2020;368(March):1-17. doi:10.1136/bmj.m575
13. Fink DS, Santaella-Tenorio J, Keyes KM. Increase in suicides the months after the death of Robin Williams in the US. PLoS One. 2018;13(2):1-12. doi:10.1371/journal.pone.0191405
14. Carmichael V, Whitley R. Media coverage of Robin Williams' suicide in the United States: A contributor to contagion? PLoS One. 2019;14(5). doi:10.1371/JOURNAL.PONE.0216543
15. Tatum PT, Canetto SS, Slater MD. Suicide Coverage in U.S. Newspapers Following the Publication of the Media Guidelines. Suicide Life-Threatening Behav. 2010;40(5):524-534. doi:10.1521/SULI.2010.40.5.524
16. Suicide. Dart Center for Journalism and Trauma. https://dartcenter.org/topic/suicide. Accessed April 24, 2022.
17. McBride K. Best practices for covering suicide responsibly. Poynter. https://www.poynter.org/reporting-editing/2018/best-practices-for-covering-suicide-responsibly/. Published 2018. Accessed April 24, 2022.
18. Kenny TE, Goldfinger S, Lewis SP. Examining adherence to suicide reporting guidelines in initial reports on high-profile celebrity suicides. Cris J Cris Interv Suicide Prev. 2020;42(6):488. doi:10.1027/0227-5910/A000741
19. Till B, Arendt F, Scherr S, Niederkrotenthaler T. Effect of Educative Suicide Prevention News Articles Featuring Experts With vs Without Personal Experience of Suicidal Ideation: A Randomized Controlled Trial of the Papageno Effect. J Clin Psychiatry. 2018;80(1):E1-E8. doi:10.4088/JCP.17M11975
20. Shearer E. Social media outpaces print newspapers in the U.S. as news source. Pew Res Cent. 2018. https://www.pewresearch.org/fact-tank/2018/12/10/social-media-outpaces-print-newspapers-in-the-u-s-as-a-news-source/. Accessed April 26, 2022.
21. #mentalhealth. Instagram. https://www.instagram.com/explore/tags/mentalhealth/?hl=en. Accessed June 6, 2022.
22. #mentalhealth. TikTok. https://www.tiktok.com/tag/mentalhealth?lang=en. Accessed June 6, 2022.
23. Dunlop SM, More E, Romer D. Where do youth learn about suicides on the Internet, and what influence does this have on suicidal ideation? J Child Psychol Psychiatry Allied Discip. 2011;52(10):1073-1080. doi:10.1111/j.1469-7610.2011.02416.x
24. Nesi J. The Impact of Social Media on Youth Mental Health. N C Med J. 2020;81(2):116-121. doi:10.18043/NCM.81.2.116
25. Perkins S, Cryst E, Grossman S. Self-Harm Policies and Internet Platforms.; 2021.
26. Suicide & self-harm. TikTok. https://www.tiktok.com/safety/en/suicide-self-harm/. Accessed May 20, 2022.
27. Lynn-Green EE, Jazwińska K, Beckman AL, Latham SR. Violations of Suicide-Prevention Guidelines in US Media Coverage of Physician's Suicide Death During the COVID-19 Pandemic. Crisis. 2021. doi:10.1027/0227-5910/A000778
28. Kilner JM, Lemon RN. What we know currently about mirror neurons. Curr Biol. 2013;23(23). doi:10.1016/j.cub.2013.10.051
29. Turecki G, Brent DA. Suicide and suicidal behaviour. Lancet. 2016;387(10024):1227-1239. doi:10.1016/S0140-6736(15)00234-2

Acknowledgment

The authors would like to acknowledge Dr. Margot Zarin-Pass for her contributions to this article.

Disclosure

None reported. **MM**

Online Teaching Skills During the COVID-19 Pandemic and Beyond: One Curve We Do Not Want to Flatten

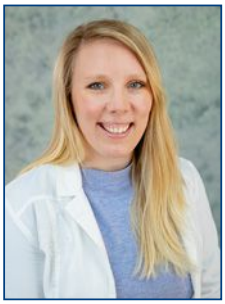
by Lacie Bailey, MD & Emily Hillman, MD

Abstract

The COVID-19 pandemic challenged physicians in academic medicine and clinician-educators in the classroom and at the patient bedside. Medical educators had to pivot overnight—adaptability was essential to providing quality medical education despite government shut-downs, accrediting body recommendations, and institutional limitations on clinical rotations and in-person meetings. Academic institutions faced multiple challenges in making the switch from in-person teaching to online learning. Through those challenges, many lessons were learned. We outline the advantages, challenges, and best practices of delivering medical education virtually.

Introduction

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease (COVID-19) in December 2019, there have been over 265 billion cases with over five million deaths.[1] In the public eye, healthcare workers have been recognized as fighting on the frontlines facing high risk exposures, personal protective equipment (PPE) and staff shortages, and physical and psychological demands.[2,3] Behind the scenes, physicians in academic medicine and clinician-educators have had to balance their clinical and pedagogical responsibilities.[4] The need to create safe learning environments and support learners' wellbeing while adapting to provide quality medical education to the future generation of physicians places a large burden on these educators in the midst of a pandemic.[5]



Lacie Bailey, MD, MS, (left) is a Medical Education and Simulation Fellow and **Emily Hillman, MD, MHPE**, is Associate Professor of Emergency Medicine and Missouri Medicine Contributing Editor. Both are at the University of Missouri-Kansas City School of Medicine, University Health-Truman Medical Center, Kansas City, Missouri.

Medical Education Without Immunity

The challenges of continuing medical education throughout an epidemic or pandemic are not new. During the pandemics caused by H1N1 and H5N1 influenza and severe acute respiratory syndrome (SARS), quarantine measures and school closures resulted in solutions that highlighted the challenges of virtual learning including material and technology costs, time intensity, and personnel resources.[6] The COVID-19 pandemic was no exception and presented multiple challenges for the medical education community.

When the Center for Disease Control and Prevention (CDC) stay-at-home recommendations were implemented throughout the United States between March to May 2020, medical education was turned upside down overnight. In March 2020, the Association of American Medical Colleges (AAMC) withdrew medical students from any patient contact activities.[7] In a survey conducted from April to May 2020, 74.9% of medical students had clinical rotations shortened or canceled due to the COVID-19 pandemic and 93.7% of respondents were not involved with direct patient care.[8] In many institutions, if medical students were allowed to participate in clinical rotations, they were prohibited from caring for patients with respiratory illnesses.[9] By the time medical students from the class of 2020 started residency training, they had not performed a patient physical exam on average for eight weeks.[10]

Simultaneously, residency programs were challenged with balancing resident education, resident safety, and patient safety. Patient volumes decreased, residents were displaced from clinical rotations, and

Table 1: Definitions of Medical Education Terms

Medical Education Term	Definition
Virtual learning/E-learning	Education involving computer and/or internet[31]
Learning Management Systems	Platforms that incorporate communication, content delivery, and assessment used by individual institutions[40]
Problem-based learning	Student-centered activity that utilizes constructed problems that serve as a stimulus for small group to engage in self-directed inquiry and solve problems as a team[40]
Team-based learning	Active learning activity that applies conceptual knowledge through individual work, teamwork, and feedback facilitated by a content-expert[40]
Simulation based education	Utilization of technology to imitate a process or situation for the purpose of education or training[40]
Flipped classroom	Content delivery is done asynchronously prior to didactic session; class time is dedicated to problem solving and questions[40]
Asynchronous learning	Individualized learning away from small or large groups or classroom setting[23]
Free Open Access Medical Education (FOAM)	Free, online medical education resources available anywhere, anytime to anyone[19]
Hidden curriculum	Implicit and unspoken values, behaviors, and norms within an educational setting[40]
Individualized interactive instruction	Asynchronous learning with four components: faculty oversight, evaluation, monitored participation, and effectiveness[18]
Telehealth	Delivery of healthcare or medical education at a distance[30]
Hybrid classrooms	Combination of face-to-face learning and virtual or online learning[14]
Small groups	Interactive activity that includes three components: active participation, face-to-face connection between learners, and purposeful activity[40]
Gamification	Delivery of educational content via game design to engage learners[40]

experiences were limited with residents not being allowed to participate in key hands-on experiences such as performing intubations.[11] Despite these challenges, the Accreditation Council for Graduate Medical Education (ACGME) kept common program requirements the same, meaning that residency programs were held accountable to quickly find alternatives and solutions to continue providing quality medical education.[12,13]

Early Pandemic Pivoting

Fortunately, in the two decades prior to the COVID-19 pandemic, medical education witnessed the successful integration of virtual learning via online modules and learning management systems (Table 1). Problem and team-based learning, simulation-based education, as well as other instructional approaches like the "flipped-classroom" and asynchronous learning were maturing and offered a range of possibilities.[14] Still, there was no wide-spread, ubiquitously implemented online, hybrid, or asynchronous learning in undergraduate and graduate medical education (UME; GME). Core clinical rotations did not have virtual alternatives. Medical school pre-clinical courses and residency didactic conferences remained largely in-person until March 2020.[15]

At the beginning of the pandemic healthcare educators had to find creative ways to deliver the equivalent curricula (lectures, small group sessions, simulations) and clinical experiences virtually.[16] For institutions utilizing traditional didactic lectures or small group work, the content was easily translatable

and transitioning the curricula to a web-based conferencing platform was not particularly difficult. With in-person clinical experiences, this was not the case, pivoting to virtual education was not as easy as a simple "turn and go." Successfully pivoting required creativity and adaptability; clinician-educators had to evaluate what critical knowledge and skills had to be addressed immediately and how that education would be delivered.

The importance of sound curriculum design (aligning learning objectives with intended outcomes and the best educational approach) was critical in guiding curricular decisions during the pandemic shutdown. The perceived risk of in-person meetings was also a consideration, especially early on. Triaging experiences and opportunities became important in ways not seen before. One example at our institution was our varied approaches to emergency airway management education for emergency medicine (EM) residents and medical students rotating on their EM clerkship. For EM residents, it was 1:1 or 2:1 learner to faculty ratio in a simulated environment with an airway task trainer. Medical students received a series of virtual, small-group case-based didactics with no in-person experience. We were able to blend these two approaches for pediatric critical care education: EM residents participated in a virtual simulation where one learner was in-person leading the simulation (following social distancing and risk reduction guidelines), while the remaining learners participated by remotely viewing the simulation, followed by virtual group debriefing after each case.

As the pandemic has waned, medical educators have begun to critically re-evaluate what ideas and innovations should be continued and which ones served a temporary purpose but should be discarded long term. Additionally, new curricular priorities have emerged such as those surrounding health equity and structural racism and the importance of telehealth education.[4] The pandemic also provided the rare opportunity to critically evaluate an entire curriculum and make changes that would have otherwise not been possible.[17]

The recent emergence and evolving maturation of Free Online Access Medical Education (FOAM) and asynchronous learning influenced how some institutions pivoted during the pandemic and will continue to influence how we design and deliver medical education over time.

Here to Stay?
FOAM: Not Just For Your Coffee

Within the past 10 years, the introduction and maturity of FOAM has provided learners and educators a collection of widely available information and resources to learn from. FOAM is often created by content experts and widely available online in various forms, permitting learners and educators access to people, ideas, and information they would not have had exposure to locally.[18] However, FOAM is not curated or peer reviewed. Educators must be aware of and up to date on these resources as they are an important part of a hidden curriculum; in the last study your learner quoted: did s/he read the study or are they reciting the summary of a past podcast or blogger?

Another challenge of FOAM: there is no curricular structure and there is a disproportionate amount of information on topics. As an example, Stuntz and Clontz found FOAM resources failed to cover 100% of topics in any of the 20 sections of core knowledge content for EM physicians as outlined by the American Board of Emergency Medicine (ABEM) in the Model of Clinical Practice of Emergency Medicine (MCPEM).[19]

A critical part of creating online education that includes FOAM is providing the curricular backbone by curating the resources appropriate for the curriculum.[20] An awareness of the limitations of available content is crucial to narrowing down the extensive body of material to applicable and relevant resources for learners to use.[20,21,22] FOAM resources have helped serve as a foundation and can be incorporated into online and asynchronous education, but faculty oversight is key.

Asynchronous Learning

In 2008, the Council of Emergency Medicine Residency Directors (CORD) made an official statement supporting the integration of asynchronous online learning activities into traditional resident didactics.[23] With the acceptance of asynchronous learning as viable, asynchronous materials have been ubiquitously incorporated into residency programs across specialties.[18,23,24] In specialties such as EM up to 20% of required resident didactic hours can be replaced with individualized interactive instruction, which can be synchronous or asynchronous learning, but must meet a variety of requirements including:

faculty oversight, evaluation, monitored participation, and effectiveness.[25] In other words, faculty oversight and accountability is required but without the teacher and learner being in the same place at the same time.[22] This means that listening to podcasts without any other structure, oversight, or evaluation would not meet these criteria.

Asynchronous online activities in this context are content-expert-created resources that learners use outside traditional didactics to enhance knowledge on specific topics. The initial and continued success of asynchronous education within GME is due in large part to its overlapping tenets with adult learning theory: adults are driven by internal motivation, need to know the reason for learning something, approach each learning opportunity with their own set of experiences, must be ready to learn, are problem-centered learners, and are responsible for their own learning.[26] Asynchronous resources have been successful because they are flexible and reduce the amount of time dedicated to synchronous in-person education. This makes them easy to incorporate into busy clinical schedules, can be tailored for individual learners, and provide engaging activities without negatively impacting test outcomes.[22,26]

Transitioning to a virtual curriculum with asynchronous material incorporated with individualized interactive instruction will allow for more individualized learning plans and flexibility with busy clinical schedules.[27] This allows a transition more in-line with adult learning theory within medical education, which has previously been a challenge given institutional culture.[26]

Telehealth

Prior to the COVID-19 pandemic, telehealth was an area recognized as needing curriculum development within UME and GME.[28] Telehealth became a timely solution to the problem of how to reduce the spread COVID-19 while still providing quality patient care. However, there is a significant lack of training within medical education on telehealth best practices.[29] Stovel et al. conducted a review of telemedicine training world-wide and found that there was not a wide breadth of curricula covering telemedicine, the majority focuses on utilizing the technology rather than clinical training.[30] A growing integration of telehealth within all specialties will require more robust training and curriculum development.[29] Many institutions are beginning to capitalize on their new found skills in web-based conferencing and virtual mobilization to explore innovative ways to help learners develop skills in telehealth. As one example, our medical school is exploring permanently transitioning certain standardized patient scenarios from in-person events to telehealth events. This requires standardized patient training, new infrastructures, and curricular adaptations (new objectives and assessments).

The COVID-19 pandemic provided a clear impetus for virtual education, but a framework and infrastructure to sustain an entirely online curriculum wasn't ubiquitously established in the UME and GME milieu. The logistics and processes that encompass delivering high-quality virtual curricula are of equal importance and consideration as the curriculum itself. For long-term sustainability the infrastructures unique to supporting this type of education must be created, department and/or organizational buy-in must be established, and faculty and staff development is necessary.

Virtual Curriculum Logistics

As early as 2008, Ellaway and Masters recognized some of the challenges of implementing virtual learning or "e-learning" in medical education.[31] There is more to virtual curriculum delivery than the educational content alone. Transitioning previously created curricula online requires additional support including "e-logistics and e-administration" which, in the context of virtual learning, refers to the role of trained administrative support staff, policies for attendance, methods to ensure online security/HIPAA compliance, and standards for online logistics like processes for communicating and sharing links, etc.[31]

Gathering institutional and departmental support to build a sustainable infrastructure and process was key at our institution. This means having a few key leaders involved in developing and implementing a proposal, soliciting feedback, and iteratively improving the process.[20] Now that many institutions have had over two years of experience, there are lessons learned and themes that have emerged in the literature regarding virtual curriculum logistics to guide those looking to continue, revise, or establish new virtual curricula.

Initial critical steps include establishing secure and private online connections, choosing a web-

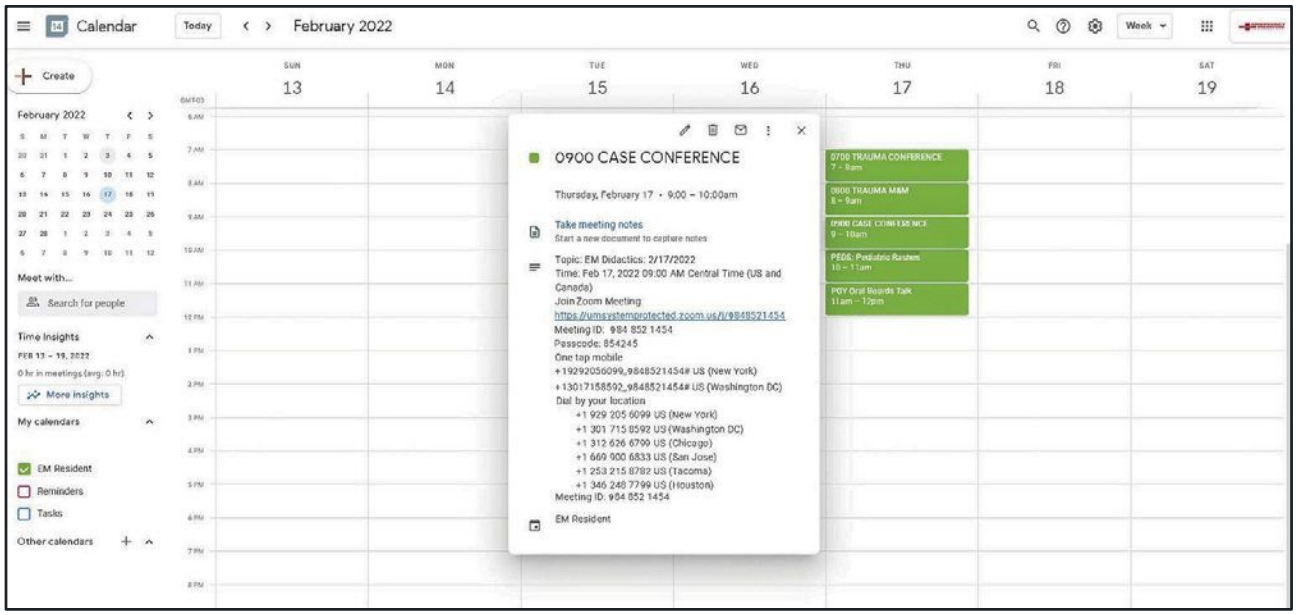


Figure 1: Representative Screenshot Image of a Google Calendar with embedded Zoom links for conference.

based platform (ZOOM, WebEx, Teams, etc.), and establishing processes to communicate this information to learners and faculty in an efficient manner.[20,32] Delivering virtual curricula that involves faculty and learners from multiple institutions (for example between multiple hospital systems and a university) at academic medical centers or programs with learners rotating at multiple healthcare systems has unique challenges. Stakeholders aware of each institution's policies, procedures, resources, and limitations should be involved in planning and implementation to minimize confusion or misinformation and prevent duplication of work. If a program decides to use a Google Education platform but one hospital's information technology (IT) department prohibits access, then the infrastructure may not be sustainable. At each level, establishing teams of invested members including medical educators, faculty, administrators, and learner representatives helps ensure a sound plan and smooth transition.[20]

At our institution, most faculty members are employed by the hospital physician group, while residents are employed by the university. Resident rotations occur across numerous clinical affiliate hospital systems linked only by the shared university. We were able to utilize ZOOM as our delivery platform because it was free through the university and HIPAA compliant with all hospital system standards. As an emergency medicine residency, we utilize a Google Education Workspace and can include ZOOM links for our weekly residency didactics on the Google calendar. Faculty and residents can subscribe to this calendar for easy access from their smartphone. However, to build redundancy, accommodate guest lecturers without access to the residency calendar, or provide an alternative for faculty who were not well versed with navigating the Google Education Workspace, a weekly email with an attached PDF including ZOOM links is provided. Originally ZOOM links were not added to the virtual calendar, but this feature was added based on resident and faculty feedback (Figure 1). An online form for participant attendance was subsequently created to track attendance without requiring manual counts and program administrator attendance. In addition, utilizing the same password protected Zoom link each week reduced participant confusion. These evolutions demonstrate the importance of regular communication among invested individuals including educators, learners, faculty, and administrative assistants.

Once the infrastructure is established and learners and faculty alike know the 'how, when, and where to be,' attention can be shifted back to curriculum content and development. Other considerations include

Table 2: The Foundation of the Future of Virtual Medical Education

Building Blocks	Advantages	Challenges	Best Practices
Curriculum Design	- Allows holistic and critical curriculum review and evaluation[17] - Incorporates new teaching modalities[14] - Incorporates adult learning theory[26]	- There are new curricular priorities (health equity, structural racism, etc.)[4] - No previously implemented online, hybrid, or asynchronous curriculum to build upon[15]	- Use creativity and adaptability to develop innovative solutions[16] - Critically evaluate knowledge and skills to address within the curriculum[17] - Consider accreditation requirements[20] - Perform a needs assessment[17] - Align learning objectives with outcomes and educational approach[17]
FOAM Resources	- Provides access to resources that are otherwise unavailable[18] - Information created by content experts[18]	- Not be curated or peer reviewed[18] - Disproportionate amount of information on certain topics[19]	-Stay up to date on current resources available to learners[19] - Provide faculty oversight for resources used within the curriculum[22]
Asynchronous Activities	- Follows adult learning theory tenets[26] - Does not negatively affect test outcomes[22]	- Must provide key components of individualized interactive instruction to learners[22]	- Follow tenets of individualized interactive instruction (faculty oversight, evaluation, monitored participation, effectiveness)[25]
Telehealth	- Evolving and developing area within UME/GME[30] - Utilizes web-based skills to build curricula[29]	- No standardized curriculum[28]	-Involve practicing physicians and support staff that utilize telehealth in currulum development[30]
Administration and Implementation	- Regular and reliable communication among key individuals[20]	- Multiple areas require attention to move online[31] - Must meet multiple institutional standards across platforms[20]	- Establish secure and private online connections[32] - Create teams to address logistics that involve stakeholders at all levels[20]
Faculty Development	- Faculty development for virtual delivery will have some overlap with in-person teaching skills[37]	- Delivering virtual curriculum requires a different set of teaching skills[35]	- Implement faculty development dedicated to online content delivery and utilization of virtual platforms[35]
Learner Engagement	- Increased satisfaction and improved learning outcomes[14,43]	- Learners may have negative attitudes towards online lectures[38] - Working online there are multiple distractions for learners[39]	-Seek learner feedback as part of program evaluation and planning[38] - Incorporate "flipped-classrooms", small groups, and gamification[14] - Combine case-based learning with technology[14] - Follow online video etiquette[27]

impact of virtual meetings on resident and faculty wellness, faculty development, and increasing learner engagement in the online setting.

Embracing Change

With a career that demands physicians be direct healthcare providers, educators, administrators, and lifelong learners, without taking life outside of work into consideration, the COVID-19 pandemic added an extra component for educators and students to manage in their already busy lives. The uncertainty of a global pandemic causing rapid shift to online learning, not surprisingly, added to learners' physical, psychological, and emotional burden.[33] The flexibility

of online learning and hybrid classrooms offers a solution to combat the increasing demands on time for learners and educators alike. One study showed that depression, anxiety, and burnout decreased during online learning.[34] Though an entirely virtual future is unlikely, the demand for continued online options will be present. For sustainable high quality virtual learning faculty development is key.

Faculty Development

Creativity and innovation are among the most important assets when transitioning to and maintaining a virtual curriculum.[17] For many, transitioning to a virtual curriculum meant faculty development was put on fast-forward. Prior to the pandemic, faculty and educators did not ubiquitously have experience teaching virtually. The availability of individual experts or more robust faculty development programs and resources varied across institutions and departments. For sustainability and long-term success, members of the education team needed to become adept in delivering virtual curriculum and navigating online platforms.[27]

Teaching in an online setting is a skill that is developed over time and must be practiced like any other.[35] Therefore, faculty development must be implemented to continue quality virtual education. In a survey performed by Sarfaraz et al. medical faculty noted that they felt competent in delivering online education; however, they wanted more faculty development sessions and feedback related to virtual teaching.[36] One benefit of faculty development in virtual curriculum delivery is that the content may overlap with in-person teaching skills and educators will benefit in both arenas.[37]

Learner Engagement

Though learner engagement can be a challenge regardless of the faculty teaching skills or the learning environment, student engagement impacts educational quality.[38] Negative attitudes towards online lectures, virtual lecture fatigue, and distractions for learners all result in less learner engagement over digital platforms.[39] In one study, learners noted that more passive sessions resulted in less retention of the educational materials and that the lack of engagement with both peers and faculty made lectures less effective.[38]

Incorporating "flipped-classrooms," small groups, and gamification have all been shown to enhance engagement and can be easily translated into virtual classrooms.[14] The quality of learning in an online environment can be maximized with the combination of case-based learning with technology, such as break out rooms to facilitate small groups learning and online gamification such as Kahoot or Poll Everywhere.

Another important step in optimizing online classroom engagement is setting standards for learners' participation. Having students and residents follow online video etiquette, keeping microphones and cameras on in small groups, and changing their display name to first and last name with title, facilitate learner engagement.[27] In larger groups, where traditional lectures translate well, online video etiquette would include having learners keep their microphone off and camera on and using the chat box for question/answers or interactive online polls.[27]

Ongoing faculty development and enhanced learner engagement are only two of the core components for delivery of successful GME regardless of the platform: in-person or online. As medical education and technology continue to evolve these areas will be crucial for educators to adapt and integrate into future curricula. This paper discussed advantages, challenges, and building blocks to consider when incorporating virtual components within medical education (Table 2).

Next Steps

During the COVID-19 pandemic, there have been many creative and successful solutions to transitioning a medical education curriculum virtually. Medical educators have risen to the challenge despite the lack of ubiquitous training in delivering online curricula. Though there have been many challenges transitioning, the change has offered learning opportunities for the future of medical education. Now is the time to continue to develop and critically evaluate solutions that can be incorporated into curricula and guide a future model of medical education.

References

1. "WHO Coronavirus (COVID-19) Dashboard." World Health Organization. December 7, 2021. https://covid19.who.int
2. Cohen J, Rodgers Y van der M. Contributing factors to personal protective equipment shortages during the COVID-19 pandemic. Prev Med. 2020;141:106263-106263. doi:10.1016/j.ypmed.2020.106263
3. Carey J, Pera A, Balica R. Emotional Fatigue, Psychological Distress, and Clinically Significant Depression Associated with Being a COVID-19

Frontline Healthcare Worker. Psychosociological Issues Hum Resour Management. 2020;8(2):27-36. doi:10.22381/pihrm8220203
4. Keegan DA, Bannister SL. More than moving online: Implications of the COVID-19 pandemic on curriculum development. Med Educ. 2020;55(1):1-3. doi:10.1111/medu.14389
5. Sahi PK, Mishra D, Singh T. Medical Education Amid the COVID-19 Pandemic. Indian Pediatr. 5AD;57(51):652-657. doi:10.1007/s13312-020-1894-7
6. Lim EC, Oh VM, Koh DR, Seet RC. The Challenges of "Continuing Medical Education" in a Pandemic Era. Ann Acad Med Singap. 2009;(38):724-726.
7. "Important Guidance for Medical Students on Clinical Rotations During the Coronavirus (COVID-19) Outbreak." Association of American Medical Colleges. December 7, 2021. https://www.aamc.org/news-insights/press-releases/important-guidance-medical-students-clinical-rotations-during-coronavirus-covid-19-outbreak
8. Harries AJ, Lee C, Jones L, et al. Effects of the COVID-19 pandemic on medical students: a multicenter quantitative study. Bmc Med Educ. 2021;21:14. doi:10.1186/s12909-020-02462-1
9. Rose S. Medical Student Education in the Time of COVID-19. JAMA. 2020;323(21):2131-2132. doi:10.1001/jama.2020.5227
10. McLean ME, Cotarelo AA, Huls TA, et al. UME-to-GME PandEMonium in COVID-19: Large-Scale Implementation of a Virtual ACGME Milestone-Based Curriculum for Senior Medical Students Matched Into Emergency Medicine. J Graduate Medical Educ. 2021;13(6):848-857. doi:10.4300/jgme-d-21-00620.1
11. Edigin E, Eseaton PO, Shaka H, Ojemolon PE, Asemota IR, Akuna E. Impact of COVID-19 pandemic on medical postgraduate training in the United States. Med Educ Online. 2020;25(1). doi:10.1080/10872981.2020.1774318
12. "Coronavirus (COVID-19) and ACGME Site Visits, Educational Activities, and Other Meetings." Accreditation Council for Graduate Medical Education. December 7, 2021. https://www.acgme.org/newsroom/2020/3/updated-coronavirus-covid-19-and-acgme-site-visits-educational-activities-and-other-meetings/
13. "The ACGME Common Program Requirements and COVID-19." Accreditation Council for Graduate Medical Education. January 16, 2022. https://www.acgme.org/newsroom/2020/3/the-acgme-common-program-requirements-and-covid-19/
14. Liu J, Peng W, Zhang F, Hu R, Li Y, Yan W. The Effectiveness of Blended Learning in Health Professions: Systematic Review and Meta-Analysis. J Med Internet Res. 2016;18(1). doi:10.2196/jmir.4807
15. Weber W, Ahn J. COVID-19 Conferences: Resident Perceptions of Online Synchronous Learning Environments. West J Emerg Medicine. 2021;22(1):115-118. doi:10.5811/westjem.2020.11.49125
16. Rolak S, Keefe AM, Davidson EL, Aryal P, Parajuli S. Impacts and challenges of United States medical students during the COVID-19 pandemic. World J Clin Cases. 2020;8(15):3136-3141. doi:10.12998/wjcc.v8.i15.3136
17. Muller D, Parkas V, Amiel J, et al. Guiding principles for undergraduate medical education in the time of the COVID-19 pandemic. Med Teach. 2021;43(2):137-141. doi:10.1080/0142159x.2020.1841892
18. Estes M, Gopal P, Siegelman JN, Bailitz J, Gottlieb M. Individualized Interactive Instruction: A Guide to Best Practices from the Council of Emergency Medicine Residency Directors. West J Emerg Medicine. 2019;20(2):363-368. doi:10.5811/westjem.2018.12.40059
19. Stuntz R, Clontz R. An Evaluation of Emergency Medicine Core Content Covered by Free Open Access Medical Education Resources. Ann Emerg Med. 2016;67(5):649-653. doi:10.1016/j.annemergmed.2015.12.020
20. Taha MH, Abdalla ME, Wadi M, Khalafalla H. Curriculum delivery in Medical Education during an emergency: A guide based on the responses to the COVID-19 pandemic [version 1]. Mededpublish. 2020;9:69. doi:10.15694/mep.2020.000069.1
21. Mallin M, Schlein S, Doctor S, Stroud S, Dawson M, Fix M. A Survey of the Current Utilization of Asynchronous Education Among Emergency Medicine Residents in the United States. Acad Med. 2014;89(4):598-601. doi:10.1097/acm.0000000000000170
22. Wray A, Bennett K, Boysen-Osborn M, Wiechmann W, Toohey S. Efficacy of an asynchronous electronic curriculum in emergency medicine education in the United States. J Educ Eval Health Prof. 2017;14:29. doi:10.3352/jeehp.2017.14.29
23. Sadosty AT, Goyal DG, Hern HG, Kilian BJ, Beeson MS. Alternatives to the Conference Status Quo: Summary Recommendations from the 2008 CORD Academic Assembly Conference Alternatives Workgroup. Acad Emerg Med. 2009;16(s2):S25-S31. doi:10.1111/j.1553-2712.2009.00588.x
24. Wittich CM, Agrawal A, Cook DA, et al. E-learning in graduate medical education: survey of residency program directors. Bmc Med Educ. 2017;17(1):114. doi:10.1186/s12909-017-0953-9
25. "Frequently Asked Questions: Emergency Medicine." Accreditation Council for Graduate Medical Education. Published 2017. Accessed January 16, 2022. https://www.acgme.org/globalassets/pdfs/faq/110_emergency_medicine_faqs_2017-07-01.pdf
26. Taylor DCM, Hamdy H. Adult learning theories: Implications for learning and teaching in medical education: AMEE Guide No. 83. Med Teach. 2013;35(11):e1561-e1572. doi:10.3109/0142159x.2013.828153
27. Regmi K, Jones L. A systematic review of the factors – enablers and barriers – affecting e-learning in health sciences education. Bmc Med Educ. 2020;20(1):91. doi:10.1186/s12909-020-02007-6
28. Papanagnou D, Sicks S, Hollander JE. Training the Next Generation of Care Providers: Focus on Telehealth. Healthcare Transformation. 2015;1(1). doi:10.1089/heat.2015.29001-psh
29. Sakumoto M, Jelinek R, Joshi A. Identification of Gaps in Graduate Medical Education Telehealth Training. Telehealth Medicine Today. 2021;6(3). doi:10.30953/tmt.v6.276
30. Stovel RG, Gabarin N, Cavalcanti RB, Abrams H. Curricular needs for training telemedicine physicians: A scoping review. Med Teach. 2020;42(11):1234-1242. doi:10.1080/0142159x.2020.1799959
31. Ellaway R, Masters K. AMEE Guide 32: e-Learning in medical education Part 1: Learning, teaching and assessment. Med Teach. 2009;30(5):455-473. doi:10.1080/01421590802108331
32. Rivera R, Smart J, Sakaria S, et al. Planning Engaging, Remote, Synchronous Didactics in the COVID-19 Pandemic Era. JMIR Med Educ. 2021;7(2). doi:10.2196/25213
33. Ellison EC, Spanknebel K, Stain SC, et al. Impact of the COVID-19 pandemic on surgical training and learner well-being: Report of a survey of general surgery and other surgical specialty educators. J Am Coll Surg. 2020;231(6):613-626. doi:10.1016/j.jamcollsurg.2020.08.766
34. Papapanou M, Routsi E, Tsamakis K, et al. Medical education challenges and innovations during COVID-19 pandemic [published ahead of print March 21, 2022]. Postgrad Med J. doi:10.1136/postgradmedj-2021-140032
35. Reilly J, Vandenhouten C, Gallagher-Lepak S, Ralston-Berg P. Faculty Development for E-Learning: A Multi-Campus Community of Practice (COP) Approach. Online Learn. 2012;16(2). doi:10.24059/olj.v16i2.249
36. Sarfaraz S, Ahmed N, Abbasi MS, et al. Self-perceived competency of the medical faculty for E-Teaching during the COVID-19 pandemic. Work. 2020;67(4):791-798. doi:10.3233/wor-203332
37. Binks AP, LeClair RJ, Willey JM, et al. Changing Medical Education, Overnight: The Curricular Response to COVID-19 of Nine Medical Schools. Teach Learn Med. 2021;33(3):334-342. doi:10.1080/10401334.2021.1891543
38. Weber W, Ahn J. COVID-19 Conferences: Resident Perceptions of Online Synchronous Learning Environments. West J Emerg Medicine. 2021;22(1):115-118. doi:10.5811/westjem.2020.11.49125
39. Coffey CS, MacDonald BV, Shahrvini B, Baxter SL, Lander L. Student Perspectives on Remote Medical Education in Clinical Core Clerkships During the COVID-19 Pandemic. Med Sci Educ. 2020;30(4):1577-1584. doi:10.1007/s40670-020-01114-9
40. Dent J, Harden R, Hunt D. A Practical Guide for Medical Teachers. 6th ed. Seattle, WA: Elsevier; 2021.

Disclosure

None reported. **MM**

Correspondence

Ketamine: Studies Show Benefit

The beneficial psychotropic properties of ketamine, particularly its antidepressant effect, have been demonstrated in several favorable studies. These are encouraging for both patients struggling with mental illness as well as their treating clinicians. A controversial new trend in ketamine dispensing was noted in a recent Wall Street Journal article[1] and raises our concern as members of the psychiatric community. The article highlights several new, online for-profit companies selling ketamine tablets and lozenges for medically unsupervised use at home.[1] As of January 2023, there is no FDA approved treatment for use of ketamine in any modality (tablet, lozenge, infusion) for any psychiatric condition; rather esketamine, a similar but chemically structured variation of ketamine, is the only FDA approved form of ketamine for treatment of depression and suicidality.[2] Unsupervised ketamine treatment is dangerous, debatable, and extremely worrying.

When the FDA approved esketamine treatment for depression, it also required that treatments be monitored in a structured, clinical environment due its potential for psychomimetic and cardio stimulating effects. While these effects are generally well tolerated and transient, they can potentially be quite distressing on the patient and lead to serious adverse outcomes. During treatments, trained medical staff monitor vital signs, mental status for safety and tolerability as well as discharge readiness for two hours following esketamine administration. Beyond monitoring the patient during treatment, another important safety measure is to ensure the patient has a driver and does not operate a vehicle while under the effects of the medication. These measures are mandated, not optional. Allowing patients to self-administer ketamine unsupervised exposes the patients to serious sequalae including, but not limited to, hypertensive crisis, falls, driving accidents under the influence of a dissociative agent, and misinterpretation of environment or intentions of others while in a dissociative state. These in turn could lead to harm, even death, of the patient or others around them.

Another problem with oral ketamine is its low bioavailability. The bioavailability of oral ketamine (20% to 25%) is significantly lower than that of intravenous ketamine (approximately 100%), and it is also inferior to that of esketamine (approximately 50%). Because of the decreased bioavailability, higher doses of oral ketamine are likely to be required to achieve the desired antidepressant effect, increasing the risk of adverse side effects. There is insufficient data on the bioavailability and pharmacokinetic properties of oral ketamine, raising concerns about its growing popularity in the absence of appreciable evidence-based data to guide prescriptive practices. Aside from the pharmacodynamic properties of oral ketamine, there is a scarcity of data on the efficacy and safety profile of the drug's oral formulation for the treatment of depression or any other mental illness. There have only been a few studies on the use of oral ketamine for depression, with the majority of them being uncontrolled, and the few controlled studies having a small subject size.[3]

Ketamine has promise as another option to offer patients struggling with mental illness. We must continue to exercise caution and follow evidence-based practices to maximize patient outcomes while minimizing risk. Only esketamine has an FDA approval for treatment of depression (or any mental illness). Despite its lack of FDA approval, intravenous ketamine use has considerable favorable evidence when both forms are administrated in a controlled medical environment.[4] Oral ketamine use may prove to be another effective treatment for mental illness, but further study is needed to evaluate the risk to benefit ratio not only in prescribing/dosing but how we administer and monitor the drug. Until then, on line accessed ketamine for home use without proper medical supervision should be discourged.

Robert Sobule, PA-C, CAQ-Psychiatry
Clinical Instructor of Psychiatry and Director of Psychiatric Advanced Practice Provider Fellowships at University of Missouri - Columbia School of Medicine Department of Psychiatry

Muaid Ithman, MD
University of Missouri - Columbia School of Medicine Department of Psychiatry Vice Chair; Associate Professor of Clinical Psychiatry; Medical Director for Interventional Psychiatry; and Associate Medical Director of Missouri University Psychiatric Center

References

1. Abbott B, Hernandez D. Americans take ketamine at home for depression with little oversight. Americans Take Ketamine at Home for Depression With Little Oversight. https://www.wsj.com/articles/ketamine-depression-treatment-mental-health-home-11667059093. Published October 30, 2022. Accessed November 20, 2022.
2. FDA approves new nasal spray medication for treatment-resistant depression; available only at a Certified Doctor's Office or clinic. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified. Published March 5, 2019. Accessed November 20, 2022.
3. Smith-Apeldoorn SY, Veraart JKE, Kamphuis J, et al. Oral Esketamine for treatment-resistant depression: Rationale and design of a randomized controlled trial - BMC psychiatry. BioMed Central Psychiatry. https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-019-2359-1. 4. Published November 29, 2019. Accessed November 21, 2022.
Ithman M, Sobule R, Kundert C, Campbell A, Ehrhardt E. Ketamine Infusions Administered Solely by Psychiatric Staff. Mo Med. 2022;119(2):164-166. https://digitaleditions.walsworth.com/publication/?m=11307&i=742977&p=78&ver=html5. Published Mar-Apr 2022. Accessed November 21, 2022.

From Concerned Physicians to Lawmakers: Legislation Addressing the Teenage Vaping Epidemic

E-cigarettes are the most commonly used tobacco product among middle and high school students.[11] Highly addictive and higher concentrations of nicotine than combustible cigarettes, e-cigarettes are a critical threat to the health and safety of adolescents. Nicotine in particular has serious adverse effects on the developing brain and respiratory system.

The 2022 National Youth Tobacco Survey demonstrates that while the use of e-cigarettes has declined from its 2019 peak, 14.1% of high school students and 3.3% of middle school students still report using e-cigarettes.[6] Of these students, 27.6% reported daily use.[6] Most commonly used e-cigarettes were disposable, one-use devices (57.2% high school students, 45.8% middle school students).[6] More than 84.8% of teenagers report using flavored e-cigarettes, including fruit, candy, dessert, and menthol varieties.[6]

Given the magnitude of this situation and the known long-term effects of e-cigarettes, healthcare providers must look beyond individual counseling to political advocacy in an effort to make widespread change. Federal and state efforts to restrict adolescent use, limit unlicensed e-cigarette sales, and bar marketing to adolescents have thus far been modest, and achieved only limited success.

The U.S. Food and Drug Administration's (FDA's) attempts to regulate e-cigarettes has been slow and resulted in minimal success. In 2016, the FDA asserted that e-cigarettes met the definition of a "tobacco product" under the Tobacco Control Act. Based on that finding, the agency required companies to apply to continue marketing any new or existing e-cigarette products. Out of almost 6.7 million applications, the FDA has denied nearly one million.[10] In one widely covered decision, the agency even denied approval for all JUUL products marketed in the U.S. JUUL immediately filed a lawsuit however, and successfully pushed the FDA to reverse course.

This marketing review process was also used by the FDA to ban all flavors except for tobacco and menthol. This ban only applies to cartridge/pod-based e-cigarettes, so does not cover the increasingly popular disposable and refillable devices. We also know that menthol flavors appeal to teens and could become more attractive if they are all that is available. The tobacco industry has responded by offering more products not covered by the current restrictions.

Congress passed Tobacco 21 legislation raising the minimum legal sales age (MLSA) for tobacco products from 18 to 21 years old. Tobacco 21 provided no exemptions and applied to all tobacco products, including e-cigarettes. States may pass more restrictive laws, but either way, federal law requires states to demonstrate that retailers are complying with the new federal standard. Currently, 40 states have increased their MLSA age to 21 to match the federal law.[16] Missouri is not one of them.

In the absence of robust federal oversight, e-cigarette regulation has largely been left to the states. Seventeen states have no licensing requirements to sell e-cigarettes over the counter.[15] Twenty states have no special tax on e-cigarettes that may discourage use.[15] And e-cigarettes are widely advertised on television and the internet, as only a few states have passed their own marketing restrictions

Missouri does not define e-cigarettes as a "tobacco product." The state MLSA is 18, and legislation to increase that age has not made it out of committee. Missouri does require a

license to sell e-cigarettes, but has no special tax for e-cigarettes/vaping products.[13] Local efforts to impose e-cigarette restrictions have fallen short.

As medical professionals, we have a unique role to play in the health of our communities. We must be mindful of that role in combating the vaping epidemic while we look for ways to advocate not only in our medical facility, but in the halls of political power.

Kristen Jones, DO
Critical Care Fellow, University of Missouri-Kansas City

Gary Salzman, MD
Professor, Department of Internal Medicine, Respiratory and Critial Care, University of Missouri-Kansas City School of Medicine, Missouri Medicine Editorial Board - Pulmonary Medicine

References

1. "2021 Vaping Legislation Update." 2021 Vaping Legislation Updates & the Federal Tobacco21 Law, https://www.billtrack50.com/blog/in-the-news/2021-vaping-legislation-update/.
2. Besaratinia, Ahmad, and Stella Tommasi. "Vaping Epidemic: Challenges and Opportunities." Cancer Causes & Control, vol. 31, no. 7, 2020, pp. 663–667., https://doi.org/10.1007/s10552-020-01307-y.
3. Bhatt, Jayesh Mahendra, et al. "An Update on Controversies in e-Cigarettes." Paediatric Respiratory Reviews, vol. 36, 2020, pp. 75–86., https://doi.org/10.1016/j.prrv.2020.09.003.
4. Chadi, Nicholas, et al. "Understanding the Implications of the 'Vaping Epidemic' among Adolescents and Young Adults: A Call for Action." Substance Abuse, vol. 40, no. 1, 2019, pp. 7–10., https://doi.org/10.1080/08897077.2019.1580241.
5. Commissioner, Office of the. "How FDA Is Regulating e-Cigarettes." U.S. Food and Drug Administration, FDA, https://www.fda.gov/news-events/fda-voices/how-fda-regulating-e-cigarettes.
6. Cooper, Maria, et al. "Notes from the Field: E-Cigarette Use among Middle and High School Students — United States, 2022." MMWR. Morbidity and Mortality Weekly Report, vol. 71, no. 40, 2022, pp. 1283–1285., https://doi.org/10.15585/mmwr.mm7140a3.
7. "E-Cigarettes: Facts, Stats and Regulations." Truth Initiative, https://truthinitiative.org/research-resources/emerging-tobacco-products/e-cigarettes-facts-stats-and-regulations#Regulated.
8. The Lancet Respiratory Medicine. "Vaping in Adolescents and Young Adults: It's Time to Act." The Lancet Respiratory Medicine, vol. 10, no. 9, 2022, p. 811., https://doi.org/10.1016/s2213-2600(22)00303-4.
9. Leventhal, Adam M., et al. "Flavored e-Cigarette Use and Progression of Vaping in Adolescents." Pediatrics, vol. 144, no. 5, 2019, https://doi.org/10.1542/peds.2019-0789.
10. November 15, 2022, et al. "FDA Oversight of e-Cigarettes Gathers Speed." National Cancer Institute, https://www.cancer.gov/news-events/cancer-currents-blog/2022/ecigarettes-zeller-fda-regulation.
11. Park-Lee, Eunice, et al. "Tobacco Product Use among Middle and High School Students — United States, 2022." MMWR. Morbidity and Mortality Weekly Report, vol. 71, no. 45, 2022, pp. 1429–1435., https://doi.org/10.15585/mmwr.mm7145a1.
12. Polosa, Riccardo, et al. "A Close Look at Vaping in Adolescents and Young Adults in the United States." The Journal of Allergy and Clinical Immunology: In Practice, vol. 10, no. 11, 2022, pp. 2831–2842., https://doi.org/10.1016/j.jaip.2022.06.005.
13. "Public Health Law Center." E, https://www.publichealthlawcenter.org/resources/us-e-cigarette-regulations-50-state-review/mo.
14. Sindelar, Jody L. "Regulating Vaping — Policies, Possibilities, and Perils." New England Journal of Medicine, vol. 382, no. 20, 2020, https://doi.org/10.1056/nejmp1917065.
15. "State System E-Cigarette Fact Sheet." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 25 Oct. 2022, https://www.cdc.gov/statesystem/factsheets/ecigarette/ECigarette.html#state-legislative-activity.
16. "State System Tobacco MLSA Fact Sheet." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 25 Oct. 2022, https://www.cdc.gov/statesystem/factsheets/mlsa/Minimum-Legal-Sales-Age.html.

Concerns for Youth Go Up in Smoke

Missouri recently followed 20 other states in legalizing the recreational use of cannabis. Debates frequently centered on perceived medical benefit, relative risk compared to alcohol and the disparate impact cannabis laws have on marginalized communities. Often absent from these discussions was the potential impact on youth. A recent publication looking at substance use over the last 20 years in those aged 6-18 found the substance most commonly associated with misuse/abuse cases flipped from alcohol to cannabis in 2014. This trend continued every subsequent year with widening margins and a drastic increase from 2017-2020. The authors noted the precipitous rise occurred concurrently with the expansion of medical and recreational cannabis states.[1]

While there is much anecdotal information touting the medical benefits of cannabis, a recent review highlighted that this is likely an area where enthusiasm has outpaced science.[2] While strong evidence supporting the panacea of medical benefits is lacking, there is an expanding body of literature demonstrating the association between early use of cannabis and subsequent development of psychiatric conditions. There appears to be a dose dependent relationship between adolescent cannabis use and the development of a psychotic disorder (a particular concern given trends of increased THC concentrations in cannabis products). Furthermore, cannabis use is associated with an earlier onset of psychotic symptoms and increased rates of relapse and hospitalizations.[3] Development of depressive disorders, suicidal ideation, and suicide are all correlated with early use of cannabis.[4]

So where does that leave us as health care providers in the state of Missouri? With decreased perception of harm and increased prevalence of cannabis products we can anticipate increased use among children and adolescents. As such, a multipronged approach is

required to mitigate the negative impacts. Parents and youth should receive education on the potential benefit of abstinence or delaying onset of use as well as the dose dependent association with psychosis. During pediatric visits, there should be increased emphasis around screening measures and early interventions. Individuals who continue to use cannabis products should be provided with education around harm reduction strategies, particularly involving edible forms of cannabis that may have increased appeal to toddlers and young children. There is also a role for advocacy particularly around regulating marketing and advertising to youth. Despite these efforts we have to anticipate a subsequent increased demand for specialized services to address the increased prevalence of cannabis use disorders and other psychiatric conditions.

Douglass M. Burgess, MD

Assistant Professor, Department of Psychiatry, Section of Addiction Medicine, University of Missouri-Kansas City School of Medicine, Missouri Medicine Editorial Board - Toxicology and Addiction Medicine

References

1. Hughes, A. R., Grusing, S., Lin, A., Hendrickson, R. G., Sheridan, D. C., Marshall, R., & Horowitz, B. Z. (2022). Trends in intentional abuse and misuse ingestions in school-aged children and adolescents reported to US poison centers from 2000-2020. Clinical toxicology (Philadelphia, Pa.), 1–8. Advance online publication. https://doi.org/10.1080/15563650.2022.2120818

2. Hill, K. P., Gold, M. S., Nemeroff, C. B., McDonald, W., Grzenda, A., Widge, A. S., Rodriguez, C., Kraguljac, N. V., Krystal, J. H., & Carpenter, L. L. (2022). Risks and Benefits of Cannabis and Cannabinoids in Psychiatry. The American journal of psychiatry, 179(2), 98–109. https://doi.org/10.1176/appi.ajp.2021.21030320

3. Hasan, A., von Keller, R., Friemel, C. M., Hall, W., Schneider, M., Koethe, D., Leweke, F. M., Strube, W., & Hoch, E. (2020). Cannabis use and psychosis: a review of reviews. European archives of psychiatry and clinical neuroscience, 270(4), 403–412. https://doi.org/10.1007/s00406-019-01068-z

4. Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., Ware, M., Marmorstein, N., Cipriani, A., Dendukuri, N., & Mayo, N. (2019). Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. JAMA psychiatry, 76(4), 426–434. https://doi.org/10.1001/jamapsychiatry.2018.4500

MM



Today – Do more of what you love

Mercy, one of the 25 largest U.S. health systems, serves millions annually with nationally recognized quality care and one of the nation's largest Accountable Care Organizations. Mercy is a highly integrated, multi-state health care system including more than 40 acute care, managed and specialty (heart, children's, orthopedic and rehab) hospitals, convenient and urgent care locations, imaging centers and pharmacies. Mercy has 900 physician practices and outpatient facilities, 3,400 Mercy Clinic physicians and advanced practitioners, as well as more than 40,000 co-workers serving patients and families across Arkansas, Kansas, Missouri and Oklahoma.

To find out about Physician and Advanced Practitioner openings across the Mercy System, please contact:
Stephen Liebetrau | Physician Talent Scout
314-363-4049 | stephen.liebetrau@mercy.net
Or go to https://careers.mercy.net

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

MSMA Members in the News

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

Missouri Medicine Announces New Editorial Board Members

Missouri Medicine announces new Editorial Board members. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.

Erik M. Grossmann, MD, is the new Editorial Board member for Colon and Rectal Surgery. Dr. Grossman is Associate Professor of Surgery, Department of General Surgery, and Chief of the Division of Colorectal Surgery at the University of Missouri-Columbia School of Medicine. He has more than two decades of experience as a surgeon who focuses on patients with intestinal problems.



Dr. Grossman replaces **Jose M. Dominguez, MD,** who is retiring after nearly a decade in this position. Dr. Dominguez has written numerous articles on colon and rectal surgery for *Missouri Medicine*, and we wish him the best in his future.



Sherry X. Zhou, MD, PhD, is the new Editorial Board member for Endocrinology. Dr. Zhou is an endocrinology, diabetes, and metabolism specialist and practices at Mosaic Life Care at St. Joseph. She is Board Certified in Internal Medicine and completed her Internship at Temple University School of Medicine in Philadelphia, Pennsylvania.

Dr. Zhou replaces **Howard M. Rosen, MD**, who represented Endocrinology on the board for nearly 15 years and is retiring. *Missouri Medicine* thanks Dr. Rosen for his service.



Jeffrey F. Scherer, MA, PhD, an MSMA Affiliate member, is the new Editorial Board member for Statistics and Methodology. He is in the Department of Family and Community Medicine at the Saint Louis University School of Medicine, and also with the St. Louis Center for Health Outcomes Research.

He replaces **Christopher R. Carpenter, MD, MSc,** who has represented Statistics and Methodology for five years, and is leaving Missouri for a position at the Mayo Clinic in Rochester, Minnesota, as Vice Chair of Implementation and Innovation. We wish him the best in his new position.



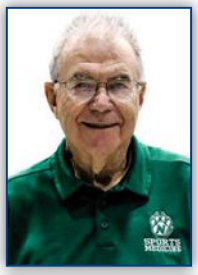
Douglas M. Burgess, MD, is the new Editorial Board member for Toxicology and Addiction Medicine. Dr. Burgess is a Psychiatrist with University of Missouri-Kansas City in the Section of Addiction Psychiatry. He works at University Health-Behavioral Health, and is a researcher at the Center for Behavioral Medicine in Kansas City, Missouri. He replaces **Evan S. Schwarz, MD**, who coordinated several theme series on addiction medicine and emergency medicine, and we thank him for his service.



Scott W. Kujath, MD, FACS, FSVS, is the new Editorial Board member for Vascular Surgery. He practices at Midwest Aortic & Vascular Institute in North Kansas City. He replaces Jonathan M. T. Bath, MD, and we thank Dr. Bath for his service.

MSMA Members in the News

The Missouri Academy of Family Physicians presented several awards at its recent Annual Meeting. Recipients of the 2022 Distinguished Service Award included MSMA members **Patrick Harr, MD**, a retired Family Physician from Maryville; **Peter Koopman, MD**, a Clinical Family and Community Medicine professor at the University of Missouri-Columbia; and **Keith Ratcliff, MD**, a Family Physician at Mercy Clinic Four Rivers Family Medicine in New Haven. The award honors those who have demonstrated long-time dedication to the MAFP and the specialty of Family Medicine.









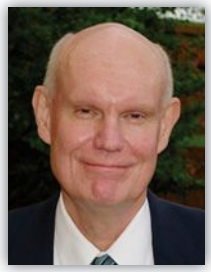
Also at the Annual Meeting, MSMA member **Charlie Rasmussen, DO**, was named the MAFP 2022 Family Physician of the Year. Dr. Rasmussen is in solo practice at Table Rock Family Medicine and Obstetrics in Branson.



The St. Louis Metropolitan Medical Society installed several MSMA members to leadership positions at its February 11 Annual Meeting and Installation Dinner. **M. Laurin Council, MD**, the 2023 President, is a professor of Dermatology at Washington University School of Medicine who was installed by George Hubbell, MD with guest MSMA EVP Jeff Howell. Also taking office were, above from left to right: **Kirsten Dunn, MD**, President Elect; **Richard Wieder, MD**, Vice President: and **Robert Brennan, Jr., MD**, Secretary/Treasurer. **Erin Gardner, MD**, accedes to Immediate Past President. MSMA members **Dee Anna Glaser, MD**, and **George Mansour, MD**, were elected to three-year terms as Councilors.







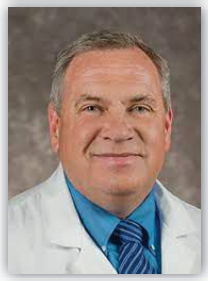








Kansas City Magazine has named North Kansas City Hospital and Meritas Health physicians as 2022 Top Doctors, right from top: **C. Craig Satterlee, MD**, Orthopedic Surgery; **Scott Kujath, MD**, (pictured on page 33), and **Karl Stark, MD**, Vascular Surgery; **Adrian Delaney III, MD**, Family Medicine; and **Justin Albani,**









NEW MSMA MEMBERS!

* = Medical Student

** = Resident/Fellow

Amy Abdalla*
Khalid Abdalla, MD – Internal Medicine – Kansas City
Brooke Adams, DO – Internal Medicine**
Hannah Adams*
Ankita Aggarwal, MD – Internal Medicine**
Ramia Ahmed, DO – Internal Medicine**
Sara Ahmed, MD – Neurology**
Mohammad Al Bataineh, MD – Internal Medicine**
Ariel Almquist, MD – Anesthesiology**
Bilel Amor, MD – Pediatrics**
Gabriel Anders, DO – Pulmonary Critical Care – Sedalia
Sandra Antigua Jimenez, MD – Neurology**
Anju Antony, MD – Anesthesiology**
Tun Tun Aung, DO – Internal Medicine**
Martin Azzam, MD – Dermatology**
Suhaib Bajwa*
Morgan Banker*
Stephanie Barata-Kirby, MD – Obstetrics & Gynecology**
Sanket Basida, MD – Internal Medicine**
Brandon Bautista*
Abigail Beach*
Anne-Taylor Beck, MD – Dermatology**
Elliott Bell, MD – Family Practice**
Lydia Bennett, MD – Emergency Medicine**
Marylin Besong, MD – Anesthesiology**
David Beversdorf, MD – Neurology – Rocheport
Deesha Bhojwani, MD – Internal Medicine**
Mohamed Bilal Hardawala, MD – Neurology**
Tyler Boyd, MD – Internal Medicine**
Niravkumar Brahmbhatt, MD – Internal Medicine**
Jordan Brown, MD – Diagnostic Radiology – St. Louis
Stephanie Cain, MD – Anesthesiology**
James Campbell, MD, DVM – Neurology**
Tarrin Casey, MD – Emergency Medicine**
Tyler Casey, MD – Anesthesiology**
Benjamin Casterline, MD, PhD – Dermatology**
Edward Charbek, MD – Pulmonary Critical Care – Ballwin
Miles Charles*
Nichelle Chastain*
Fizah Chaudhary, MD – Internal Medicine**
Bonnie Chen, MD – Otolaryngology**
Shreeya Chugh, MD – Pediatrics**
Anne Chumbow*
Kiran Chunduri, MD – Radiology – St. Louis
Sydney Cobb*
Leslie Cockerham, MD – Infectious Disease – Wauwatosa
Emma Cooper, MD – Family Practice**
Rachel Couch, DO – Pediatrics**
Abrea Cridlebaugh, MD – Family Practice**
Cole Crossman*
Jordan Cruz, MD – Anesthesiology**
Karen Dale*
Wylie de Vera, MD – Family Practice – Kansas City
Brooke Dean, MD – Family Practice**
Pablo Delgado, MD – Radiology – Lee's Summit
Krupa Desai, DO – Anesthesiology – St. Louis
Katie Detmer, MD – Neurology**
Lakshmi Digala, MD – Neurology**
Julia Dmowska, MD – Otolaryngology**
Jessica Doran, MD – Pediatrics**
Brent Dudenhoeffer, MD – Family Practice**
Peter Egwom, MD – Internal Medicine**
Shannon Ejiofor, DO – Internal Medicine**
Lindsey Ellis, MD – Obstetrics & Gynecology**
Allison Engelbrecht, MD – Obstetrics & Gynecology**
Kristen Ewing, MD – Anesthesiology**
Darian Fard, MD – Internal Medicine**
Mary Faurot, MD – Obstetrics & Gynecology**
Amanda Faust*
Keith Ferguson, MD – Pulmonary Disease – Gendale
Salvador Fernandez, MD – Internal Medicine**
Timothy Foreman, MD – Anesthesiology**
Mustafa Gandhi, MD – Internal Medicine**
Greg Gaskey, MD – Internal Medicine**
Adessya Gausper*
Victor Georgiev, MD – Internal Medicine**
Cameron Gilbert, MD – Internal Medicine**
Megan Gillespie, MD – Otolaryngology**
Andera Gillespie, MD – Otolaryngology**
Mitchell Guenther, MD – Diagnostic Radiology – Overland Park
Mackenzie Guinio-Zorkin, MD – Obstetrics & Gynecology**
Katie Guymon, DO – Pediatrics**
Nanuli Gvazava, MD – Internal Medicine**
Daniel Hafez, MD – Neurological Surgery – St. Louis
Ken Hainsworth, DO – Anesthesiology**
Josh Hall, DO – Pediatrics**
Sana Hasan, MD – Internal Medicine**
James Higgins, MD – Neurology**
Bryce Hoelscher, MD – Neurology**
Margaret Hua*
Alison Huckenpahler, MD – Psychiatry – St. Louis
Amanda Hull, MD – Obstetrics & Gynecology**
Garret Hupman*
Chloe Hutchison*
Khoi Huynh*
Kiet Huynh, MD – Internal Medicine**
Faith Ibu, MD – Emergency Medicine**
Max Isaac, DO – Internal Medicine**
Dalia Ishaq, MD – Pediatrics**
Anne Jacob, MD – Family Practice – St. Louis
Eric Jaqim, MD – Anesthesiology**
Nilesh Jambhekar, MD – Internal Medicine**
Tanner Jeppesen, DO – Anesthesiology**
Chris Joyce, MD – Internal Medicine**
Cassondra Kambeitz, MD – Obstetrics & Gynecology**
Harleen Kaur, MD – Neurology**
Olivia Keller-Baruch, MD – Emergency Medicine**
Brian Kenkel, MD – Diagnostic Radiology**
Asma Khan, MD – Neurology**
Sarah Khan*
Zalan Khan, MD – Neurology**
Pawani Kher, MBBS, MD – Pediatrics**
Gebran Khneizer, MD – Internal Medicine – St. Louis
Nina Kiekhaefer, MD – Family Practice – Jefferson City
Samantha Kos*
Daniel Kowalczyk, MD – Emergency Medicine**

MSMA MEMBERS IN THE NEWS

Beth Kreutzer, MD – Emergency Medicine**
Lara Krusniak, MD – Internal Medicine**
Gilbert Kukielka, MD – Interventional Cardiology – Cape Girardeau
Nicolas Kuyper, MD – Emergency Medicine**
Adam Larey, MD – Family Practice
Flora Laurent*
Tiffany Lehman*
Shaun Lencki, MD – Obstetrics & Gynecology – Springfield
Amy Liepert, MD – Critical Care Surgery**
Abby Lombardi, DO – Obstetrics & Gynecology**
Karstan Luchini*
Annamarie Lukish*
Nicholas Lukish*
Daniel Lyon, DO – Family Practice**
Terrance Mabry, MD – Internal Medicine**
Andres Madrid, MD – Emergency Medicine**
Chris Mandler, DO – Internal Medicine**
Matthew Mardis, MD – Anesthesiology**
Stephen Markham*
Julie Marshall, MD – Anesthesiology – Columbia
Michelle Maskeri, MD – Pediatrics**
Eric May, MD – Anesthesiology – Kansas City
Matthew McCarthy*
Anna McCurdy*
Tyler McGrew, MD – Anesthesiology**
Jane McKelvy*
Lauren McLean, DO – Internal Medicine**
Sam McNair, MD – Family Practice**
Ashir Mehra, MD – Neurology**
Tejas Mehta, MD – Neurology**
Ritika Menon*
Nicole Meyer, MD – Pediatrics**
Mandalyn Mills, DO – General Surgery – St. Joseph
Lindsay Miner, MD – Diagnostic Radiology – Kansas City
Jonathan Misch, MD – Internal Medicine**
Daniel Mitchell, MD – Obstetrics & Gynecology**
Sushmita Mittal, DO – Internal Medicine**
Lauren Moberley*
Maryam (Maz) Molahassani, MD – Emergency Medicine**
Anna Mori-Kreiner*
Stephen Morris, MD – Orthopedic Sports Medicine – Bolivar
Wael Mourad, MD – Family Practice – Overland Park
Suhanna Mutti, MD – Internal Medicine**
Grayson Mynatt, DO – Family Practice**
Urja Nagadia, MD – Internal Medicine**
Sowjanya Naha, MD – Sleep Medicine**
Yak Nak*
Ethan Naquin*
Peter Nathan, MD – Emergency Medicine**
Colbert Nelson, DO – Family Practice**
Haley Nelson*
Nicole Neville*
My Linh Nguyen*
Thai Nguyen, MD – Internal Medicine**
Erin Nischwitz*
Kelechi Nwabara, MD – Internal Medicine**
Sarah O'Hanlon*
Kyle Ohman, MD – Emergency Medicine**
Iwalewa Olowoporoku, MD – Neurology**
Landon Olson, DO – Pediatrics**
Lauren Ostler, MD – Obstetrics & Gynecology**
Ebony Page-Phillips – Emergency Medicine**
Hannah Pang*
Jay Patel*
Ryan Peach, DO – Family Practice**
Adam Perez*
Joshua Petro, DO – Internal Medicine**
Julianne Pietras, DO – Pediatrics**
Amber Pinson-Hilkemeyer, DO – Internal Medicine**
Kate Pitz, MD – Obstetrics & Gynecology**
Airika Poivre, MD – Family Practice**
Dinanath Praveen Attele, DO – Neurology**
Patrick Probst, MD – Urology**
Jacob Quick, MD – General Surgery – Osage Beach
Swathi Radhakriishnan, MD – Internal Medicine**
Anam Rahman, DO – Internal Medicine**
Elly Ranum, MD – Pediatrics**
Michelle Rastegar, MD – Anesthesiology**
Antony Rawindraraj, DO – Internal Medicine**
Sushanth Reddy, DO – Internal Medicine**
Austin Reed, DO – Internal Medicine**
Asha Ricciuti, MD – Hematology/Oncology – Saint Louis
Justin Roberts, DO – Hematology/Oncology – Farmington
Shomita Rode, MD – Internal Medicine**
Aruna Rokkam, MD – Oncology – Leawood
John Rolfes*
Hafsa Safdar, MD – Internal Medicine**
Manal Salim, MD – Pediatrics**
Jaime Santos, Jr., MD – Family Practice – St. Louis
Taher Sapatwalla*
Allayna Sapatwalla*
Shelby Schuh, DO – Internal Medicine**
Christine Schwartz, MD – Internal Medicine**
Brooke Scieszinski, MD – Anesthesiology**
Jeremy Seiler*
Ishani Shah, MD – Internal Medicine**
Sarah Shah, MD – Pediatrics**
AJ Shamloo, DO – Emergency Medicine**
Bhavya Sharma, MD – Otolaryngology**
Sergey Shealy-Sorin, MD – Family Practice – Springfield
Mary Beth Shenk, MD – Dermatology**
Joel Shenker, MD PhD – Neurology**
Nicholas Sheridan, MD – Emergency Medicine**
Elizabeth Sherman, MD – Family Practice**
Rakesh Shetty Rajalbandi, MD – Neurology**
Joe Shin, MD – Internal Medicine**
Alex Shinn, DO – Internal Medicine**
Michael Simmons, MD – Otolaryngology – Jefferson City
Shurti Sinha, MBBS, MD – Pediatrics**
Parker Smith*
Roma Sobieski, MD – Family Practice**
Shahhan Spall, MD – Neurology**
Aaron Stafford, DO – Pediatrics**
Jordan Stauffer, DO – Internal Medicine**
Chris Steadman, MD – Anesthesiology**
Grace Stephan, MD – Family Practice – Kansas City
Dakota Stevenson, MD – Neurology**
Alaina Studt, MD – Family Practice**
Conner Sutton, MD – Family Practice**
John Swift*
Annelise Swords*
David Tabagari, MD – Internal Medicine**
Johnathan Tadlock*
Karanvir Takhar*
Mackenzie Taychert, DO – Internal Medicine**
Molly Thompson, DO – Family Practice**
Quynh Tran*
Christopher Von Tungein, DO – Internal Medicine**
Sai Supriya Vuda*
Natalie Walter, MD – Emergency Medicine**
Mitchell Wattles, MD – Orthopedic Surgery – Creve Coeur
Katelyn Weith*
Preston Wheeler, MD – Pediatrics**
Christine White, DO – Family Practice**
Ellen Willhoit*
Cedric Windom, II, DO – Pediatrics**
Samantha Winstead, MD – Internal Medicine/Pediatrics**
Randi Winter, MD – Dermatology**
Luke Witte, MD – Dermatology**
Andruw Wittels *
Daniel Woolery, DO – Internal Medicine – Sedalia
Lance Workman, MD – Family Practice**
Andrew Wright, DO – Family Practice**
Kevin Xiao, MD – Otolaryngology**
Juan Carlos Yanez-Siller, MD – Otolaryngology**
Chris Yang, MD – Emergency Medicine**
Betul Gok Yavuz, MD – Internal Medicine**
Anudeep Yelam, MD – Nerology**
Kai Yuan Felix Yew, DO – Internal Medicine**
Araya Zaesim, MD – Dermatology**
Qasim Zaidi, MD – Orthopedic-Spine – St. Louis
Wendy Zhang*

School of Medicine
University of Missouri

Team Science and Advancing Research at the University of Missouri

by Richard J. Barohn, MD

The MU School of Medicine is a pioneer in medical education from its founding as the first publicly supported medical school west of the Mississippi River to the creation of its patient-based learning curriculum.

At the University of Missouri School of Medicine, we are driven by a mission that at first glance seems straightforward but is actually inherently complex: saving and improving lives through exemplary education, research, and patient care.

Over my last two and a half years at MU, I have been able to see firsthand the strides we make every day to save and improve lives, particularly through the development of live-saving research.

One of our areas of focus has been team science and laying the foundation for collaborations that will benefit Missourians. Our one-of-a-kind Roy Blunt NextGen Precision Health building is home to the kind of equipment, teams and infrastructure that I am certain will lead to new breakthroughs in medicine (Figure 1).

In just over a year since the NextGen building opened, 34 faculty have established their labs in the building and 28 faculty are occupying wet lab space. Researchers are able to utilize unique tools and infrastructure, such as dedicated clinical research space; the only 7T MRI in the state thanks to our partnership with Siemens Healthineers; and cutting-edge electron microscopy technology through collaboration with Thermo Fisher.

Having an infrastructure in place that promotes unparalleled collaboration allows us to recruit outstanding clinicians and researchers. We recently welcomed Dave Arnold, MD, from Ohio State University to serve as the new NextGen Executive Director, and we anticipate an additional six to 10 faculty joining NextGen by this summer. We will be building out our future home for reproductive health and neurosciences teams and opening our Clinical Translational Science Unit. Through strategic recruiting initiatives in place at Mizzou, we have been busy recruiting physician and laboratory scientists who are involved in leading edge research as well as in the delivery of exceptional patient care.

The 7T MRI has literally been a "magnet" to attract leading scientists from around the country who came to MU in large part because of our amazing equipment, building, and team science approach. Melissa Terpstra, PhD, (from University of Minnesota), Ai-Ling Lin, PhD, (from University of Kentucky), and Jullie Pan, MD, (from University of Pittsburgh) are all nationally renowned imaging scientists who utilize



Richard J. Barohn, MD, is the Executive Vice Chancellor for Health Affairs/Hugh E. and Sarah D. Stephenson Dean of the University of Missouri School of Medicine, Columbia, Missouri.

the 7T MRI and work with our embedded screening scientist, John Grinstead, PhD, to continually advance imaging science.

With the arrival of Michael Chicoine, MD, and Bo Lu, MD, PhD, we now have national leaders in neurosurgery and radiation oncology on our campus. The transformation of neurosurgery and radiation oncology to become new departments is part of our strategy to make MU, our medical school, and the academic health system a leader in these key areas. Dr. Chicoine specializes in brain tumors, and Dr. Lu does research in the effects of radiation on the immune system. Both are internationally known experts.

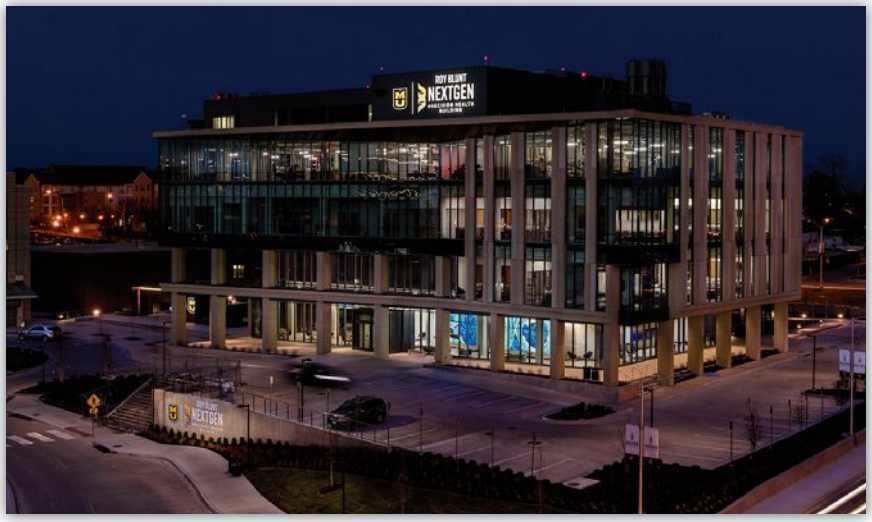


Figure 1. The Roy Blunt NextGen Precision Health building is a state-of-the-art facility at the University of Missouri that is available to all UM System researchers. It is located adjacent to MU Health Care hospitals and the Harry S. Truman Memorial Veterans' hospital.

We have great researchers who are working to arm clinical teams with ways to improve care. For example, Esma Yolcu, PhD, and Haval Shirwan, PhD, (a husband-and-wife research team recruited from University of Louisville, Kentucky), are making amazing progress in their quest to cure Type 1 diabetes as they test a cell transplant treatment that does not require immunosuppressive medications (Figure 2). If successful, it could mean the end of multiple daily insulin injections for the millions across the globe who battle Type 1 diabetes.



Figure 2. MU researchers work on a Type 1 diabetes project by testing a cell transplant treatment that does not require immunosuppressive medications.

Research like this carries the potential to save and improve lives in very tangible and practical ways. This is precisely why team science and research are core components of our mission.

An increased emphasis on team science and recruitment is enabling us to expand our clinical offerings to truly benefit our community and people across our state. We are working to offer a new bone marrow transplant program under the leadership of Gerhard Hildebrandt, MD, who serves as director of Ellis Fischel Cancer Center. Our cancer center and the people who work there are crucial to fueling our ability to care for Missourians.

I am thrilled that we have recently entered into a new research collaboration with Siteman Cancer Center, based at Barnes-Jewish Hospital and Washington University School of Medicine in St. Louis. A major focus of our collaboration with Siteman involves scientists at both of our institutions teaming up on research projects and jointly pursuing competitively funded research grants, including those supported by the NCI of the National Institutes of Health. The collaboration also will enhance efforts in cancer prevention.

Research and team science are just two key components of our mission. The MU School of Medicine is a pioneer in medical education from its founding as the first publicly supported medical school west of the Mississippi River to the creation of its patient-based learning (PBL) curriculum. Our faculty and staff at the MU School of Medicine continually strive for excellence, just as we have done over the last 150 years of our medical school's history. **MM**

Leprosy (Hansen's disease): An Update and Review

by Andrea Gilmore,MD, James Roller, MD & Jonathan A. Dyer, MD

School of Medicine
University of Missouri

Clinicians with suspected cases of Hansen's disease are encouraged to reach out to our faculty for questions, input, teleconsultation, and/or clinical evaluation as part of our ongoing research studies on Hansen's disease in the state of Missouri.



Andrea Gilmore, MD, and **James Roller, MD,** are in the Department of Dermatology, University of Missouri-Columbia School of Medicine. **Jonathan A. Dyer, MD,** (above) is the Philip C. Anderson Chair and Professor Departments of Dermatology and Child Health, also at University of Missouri-Columbia, Columbia, Missouri.

Abstract

Leprosy (Hansen's disease) is caused by infection with bacilli of the *Mycobacterium leprae* complex. It is considered an exotic and rare diagnosis in Missouri. Past leprosy patients diagnosed locally have typically acquired it in areas of the world where leprosy is endemic. However, a recent case in a native Missourian that appears to be locally acquired suggests that leprosy may now be endemic in Missouri, possibly due to the expanded range of its zoonotic vector, the nine-banded armadillo. Health care providers in Missouri should be aware of how leprosy manifests and suspected cases referred to centers such as ours for evaluation and early institution of appropriate treatment.

Introduction

Leprosy (Hansen's disease) is caused by infection of susceptible individuals with acid-fast bacilli (AFB) of the *Mycobacterium leprae* complex (*M. leprae* and *M. lepromatosis*). These rod-shaped AFB were first described by Gerhard Hansen in 1873.[1] *M. leprae* are slow growing organisms that replicate preferentially in macrophages, endothelial cells, and Schwann cells. They are obligate intracellular organisms and do not grow in artificial media cultures. Their ideal growth occurs between 27-33°C. *M. lepromatosis* is more recently described as an etiologic agent, though its clinical course may be indistinguishable from infection caused by *M. leprae*.[2]

Humans are the primary vector for *M. leprae*. In the Americas the nine-banded armadillo (Dasypus novemcinctus) is recognized as a zoonotic reservoir for the bacteria.[3] Like humans, armadillos can develop the full clinical presentation of leprosy including extensive peripheral nerve involvement.[4]

Importantly more recent work has detected *M. leprae* in additional species, including chimpanzees,[5] and it is possible additional species capable of infection by *M. leprae* may be identified. *M. lepromatosis* has been detected in red squirrels in the UK.[6, 7] The mechanism of transmission of *M. leprae* has been somewhat obscure historically due to variability in host susceptibility to infection and a very long potential incubation period. Respiratory secretions are likely the most common route of transmission. Skin contact and vertical transmission are also possible infection mechanisms. The incubation period is quite



Figure 1. A roadkill nine-banded armadillo photographed on Stadium boulevard outside of Faurot Field, University of Missouri, Columbia, Mo.



Figure 2. Typical clinical findings of tuberculoid leprosy. Hypopigmented patches with loss of sensation.
(Photo courtesy of the University of Missouri collection)

broad, with estimates ranging from three to five years for tuberculoid leprosy up to 9 to 12 years for lepromatous leprosy. Longer incubation periods have been described. Importantly, most individuals (up to 90% of the population) appear immune or resistant to *M. leprae* such that most who are exposed do not acquire the infection.

Risk Factors

Notable risk factors for the acquisition of leprosy include close exposure to individuals with lepromatous/multibacillary leprosy, exposure to armadillos,[8] immunosuppression/immunodeficiency, and genetic predisposition (which is poorly understood). A recent review noted that the World Health Organization (WHO) program targeting elimination of leprosy is based solely around eliminating human to human transmission and does not account for the potential of spread via zoonotic vectors. Recent publications suggesting a role for armadillos in zoonotic transmission of leprosy in the U.S.[3] and the notable increasing range of armadillos in the U.S. over the past several decades due to human induced environmental change[9] (Figure 1) suggest that zoonotic vectors cannot be ignored in addressing the spread of leprosy. Traditionally, in Missouri, leprosy has presented in patients who have immigrated from or spent significant time in endemic areas (such as those who have served in the military). However, recent cases of suspected autochthonous transmission in Missouri suggest zoonotic transmission is already occurring in our state (Dyer JA manuscript submitted). Missouri physicians must now consider the possibility of leprosy occurring in local patients with no notable history of foreign travel.

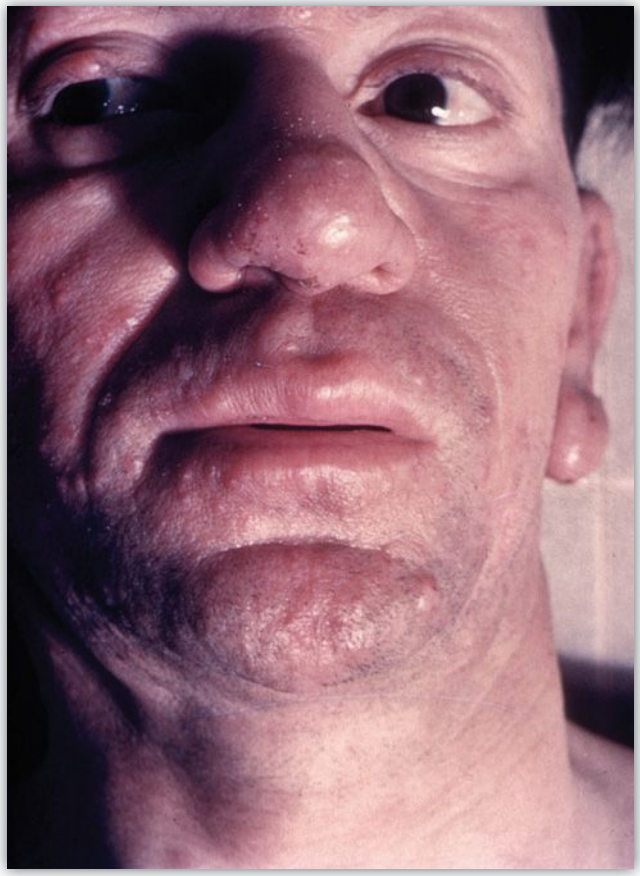
Clinical Features

There are two main classification systems for the clinical presentation of leprosy that guide management and treatment: 1) the Ridley-Jopling classification combines both clinical features, histopathology, and the bacteriologic index (BI); and 2) the WHO classification system is based on the BI or the number of skin lesions. These systems attempt to account for the wide variability in the clinical manifestations of *M. leprae* infection. The bacteriologic index (BI) is the density of bacilli in a slit-skin smear (SSS) examination (if SSS is not available then number of skin lesions is used as a surrogate). In the WHO classification system patients are classified as paucibacillary leprosy (PB) if they have very few (one to five) skin lesions and multibacillary (MB) if they have more than five skin lesions. A positive BI classifies patients as MB. The Ridley-Jopling system categorizes leprosy patients along a spectrum between tuberculoid leprosy (TT) and lepromatous leprosy (LL). The term "polar" is used to describe patients with all the classical

features of TT or LL, indicating that the patient is at the polar end of one side of the clinical spectrum. This system accounts for the clinical variability by including borderline designations for those patients that do not exhibit all the "polar" features of either TT or LL.[2] The individual patient's cell mediated immune response plays a great role in where along this spectrum individual patients fall.

The most common clinical presentation of leprosy is hypopigmented or erythematous patches that exhibit associated loss of sensation (Figure 2). Neural involvement occurs very early in the process and assessing for altered sensation can expedite the diagnosis. Clinical findings are determined by the type of immune response mounted by the patient. TT patients have a vigorous cell mediated immune response (Th1) which impairs proliferation of the bacilli. TT patients have a less severe disease course, often having only a few (or single) hypopigmented well-defined skin lesions (macules or patches/plaques) that show decreased or absent sensation and often loss of hair. TT skin lesions tend to appear erythematous in fair skinned patients and hypopigmented in patients with darker skin types. Borderline patients are unstable in their immune response. Many patients eventually fall into this clinical category.[11]

LL patients seem to lack a true cell mediated immune response, allowing the leprosy bacilli to spread widely. Patients may manifest with widespread anesthetic erythematous to brawny indurated papules and plaques. These may be diffuse or focally localized over certain areas of the body. Some scaling may be noted in more involved areas. With time skin infiltration leads to the development of the classic "leonine facies" (Figure 3a). Decreased sweating, hair loss, and anesthesia of involved areas is typically noted. Involved digits and limbs may demonstrate ulceration and distal resorption due to ongoing chronic injury (Figure 3b). Multiple additional organs can be involved, including the adrenal, kidney, testes, and others. Testicular atrophy can lead to gynecomastia in affected males.





Figures 3a and 3b. Typical clinical findings of lepromatous/ multibacillary leprosy.

A-top. Erythematous, indurated granulomatous patches and plaques with facial infiltration and leonine facies.

B-bottom. Taught acral skin with distal digital resorption and ulceration due to loss of sensation
(Photo 3a courtesy of the University of Missouri collection)

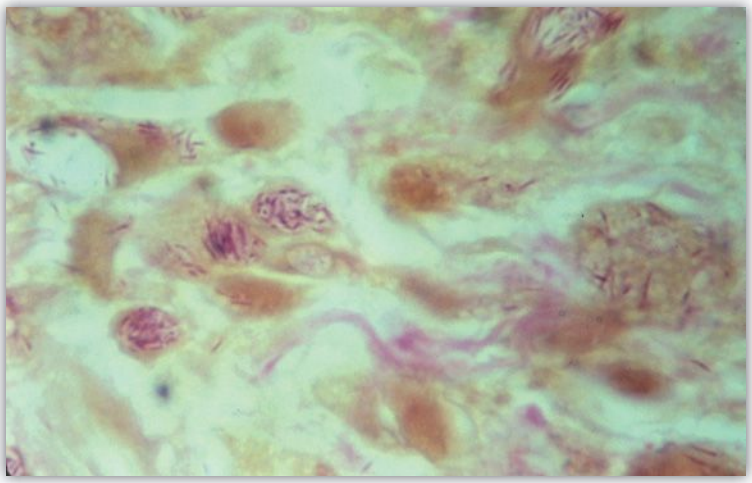


Figure 4. A positive slit skin smear from a patient with multibacillary leprosy. Acid fast bacilli (AFB) are visible. Groups of organisms (globi) are present.

Ocular

Ocular involvement occurs in over 70% of leprosy patients and assessing its presence and severity is important for patient management. Blindness may result in ~5%. There can be direct damage to the ocular nerves (ophthalmic and/or facial) and/or invasion of the anterior ocular chamber by the bacilli. Lagophthalmos (decreased eyelid closure) is the most common clinical finding, with other findings, such as corneal abrasion or ulceration, related to impaired sensation.

Mucosal Involvement

Nasal mucosal involvement is quite common in LL, likely because it is one of the main transmission sites for the bacillus. Oral mucosal lesions are nonspecific but may eventually ulcerate.[2, 11]

Diagnosis

The diagnosis of leprosy is based on clinical findings along with results of a SSS or skin biopsy. Importantly, a recent review highlighted that failure to consider leprosy in the differential diagnosis for patients is often the greatest impediment to making the diagnosis. Leprosy would not be a diagnosis typically considered for granulomatous skin eruptions in patients from Missouri, but it now must be considered a possibility, even in patients with a negative travel history. In a patient with a suspicious skin eruption, a thorough history, including all travel, should be taken. Loss of or decrease in sensation in a hypopigmented or erythematous skin patch should raise concern for leprosy.

Nerve enlargement and/or muscle weakness in the nerve distribution may also be seen. Only peripheral nerves are involved, commonly the ulnar or peroneal nerve in more advanced cases. Patients may exhibit absent sensation throughout the areas supplied by the affected nerve. Sensation may be assessed using monofilaments identical to those used to screen for diabetic neuropathy (monofilament testing was initially developed to assess and screen leprosy patients and was only later adapted to assess other forms of neuropathy). SSS exam should be performed. While SSS are often negative, in positive cases it is quite helpful. The most active lesions should be targeted although high yield anatomic sites (often cooler areas of the body such as the earlobes) can also be sampled. Instructions for performing a proper SSS exam may be found on the website of the National Hansen's Disease Center (NHDC: https://www.hrsa.gov/hansens-disease/diagnosis/skin-smears). Confirmatory skin biopsy with polymerase chain reaction (PCR) studies to screen for *M. leprae* complex DNA are more commonly used. Patients with TT typically exhibit epithelioid granulomas, lymphocytic infiltration around adnexae and nerves, and very few (often absent) AFB on histologic examination. In LL histocyte collections are diffuse and not organized. Histiocytes with foamy cytoplasm (Virchow cells) with large numbers of AFB are typical. Clumps of bacilli are called globi (Figure 4). AFB within peripheral nerves in a biopsy specimen is diagnostic. While skin biopsy is not necessary for diagnosing leprosy it can be a valuable adjunct study in these patients.[2, 10, 11]

Polymerase Chain Reaction

Polymerase chain reaction (PCR) is used to support the suspicion of a clinical diagnosis of leprosy. PCR is highly sensitive in patients with a positive BI, however in those with negative BI it can be much more variable.

Table 1. Differential diagnosis of leprosy subtypes:

Leprosy subtype	Differential diagnostic considerations
Tuberculoid; Indeterminate	Pityriasis alba; post-inflammatory hypopigmentation; vitiligo; segmental vitiligo; tinea versicolor; nummular eczema
Borderline tuberculoid	Granuloma annulare; interstitial granulomatous dermatitis; disseminated granuloma annulare; sarcoidosis; erythema annulare centrifugum; tinea corporis
Mid-borderline and borderline lepromatous	Necrobiosis lipoidica; granuloma annulare; necrobiotic xanthogranuloma; gummatous syphilis; Sweet's syndrome; lichen planus; ichthyosis vulgaris; parapsoriasis; mycosis fungoides; mastocytosis; morphea
Lepromatous	Alternative cutaneous mycobacterial infections (tuberculosis; M. marinum; M. avium-intracullare…etc); deep fungal infection (sporotrichosis; blastomycosis; chromoblastomycosis; lobomycosis); leishmaniasis; erythema elevatum diutinum; xanthogranulomas; trichoepitheliomas; verrucous lesions.
Isolated neural	Peripheral nerve sheath tumor

Adapted from: Moschella SL, Garcia-Albea V. Differential diagnosis of leprosy. In: Scollard DM, Gillis TP, eds. International Textbook of Leprosy. Available at: https://www.internationaltext bookofleprosy.org/. Accessed August 12, 2022

The National Hansens Disease Program (NHDP) performs these free of charge (contact information at end of article).

Additional Diagnostic Procedures

Nerve conduction studies may be utilized to assess the degree of nerve involvement and treatment response. Ultrasound of high yield peripheral nerves has been increasingly utilized in recent decades to objectively measure nerve thickening in suspected cases.[11]

Differential Diagnosis

The differential diagnosis for leprosy is broad and includes several innocuous conditions (Table 1). Assessing sensation in involved areas in any cutaneous eruption where leprosy is in the differential is critical to minimize delays in diagnosis and treatment of affected patients. However, neural involvement can be subtle, especially in early cases, and skin biopsy can be helpful. In Missouri patients eventually diagnosed with leprosy had been previously diagnosed with pityriasis alba, post-inflammatory hypopigmentation from eczema, granuloma annulare, cutaneous sarcoidosis, and diabetic neuropathy with ulceration among other diagnoses.[12] Anesthesia of the involved areas was often a clinical clue.

Immune Reactions

Immune reactions to the *M. leprae* bacilli are one of the major causes of morbidity and even mortality in leprosy patients. The sudden activation of a more pronounced immune response can lead to significant inflammatory reactions, often involving infected nerves and worsening existing nerve damage. In severe cases it can lead to great morbidity or even death. Development of these immune reactions may prompt patients to seek medical care, often for the first time. Clinicians should be aware of how such reactions can manifest. There are three main types of leprosy reactions, Type 1 reactions, type 2 reactions, and the rare Lucio phenomenon. They are considered medical emergencies though there is a great range in their severity. Early recognition and treatment is mandatory for limiting morbidity.[10]

Type 1 reactions (T1R) manifest as subacute to acute inflammation of the skin and nerves. They result from a sudden increase in cell-mediated immunity and delayed-type hypersensitivity to antigens from the *M. leprae* complex bacilli. These reactions can occur at any time, including long after treatment has

ceased. They occur in 30-50% of patients. Involved skin areas become red and edematous. Swelling of the limbs and face may occur. T1R are the main cause of nerve damage in leprosy patients and may present with sudden worsening of nerve palsies, paresthesia, foot drop and facial palsy. Diagnosis of these reactions is clinical, and they may be the reason for initial presentation of the patient. Systemic corticosteroids are the mainstay of therapy.

Type 2 reactions (T2R; erythema nodosum leprosum (ENL)) present as recurrent outbreaks of superficial and deep painful erythematous nodules. These may progress to ulceration with purulent discharge (mimicking erythema induratum). It is more common in LL patients. Lesions often occur on the extremities. Histopathology from an early lesion (first 24-72 hours) may show a neutrophilic infiltrate which can help confirm the diagnosis. Systemic symptoms may accompany the outbreaks such as fever, arthralgia, neuritis, malaise and lymphadenitis. ENL episodes are typically one to three weeks in duration. If present for more than six months it is considered chronic ENL. A high BI is a notable risk factor. Mild cases may respond to nonsteroidal anti-inflammatory drugs (NSAIDs) but any nerve involvement should prompt the use of systemic corticosteroids. Thalidomide is a drug of choice for ENL but is hard to obtain and expensive.

Lucio phenomenon is rare in the U.S., occurring in patients with diffuse LL. It is a thrombotic reaction characterized by the development of purpuric and discolored skin lesions that become necrotic and heal with atrophic scars. Histopathology can be helpful in the diagnosis [10,11]

Conclusion

Leprosy is considered a rare and exotic diagnosis, something the clinician will see only once or twice in a career. Recently patients with suspected autochthonous acquisition of leprosy in Missouri have been identified. This is not surprising considering the rapid expansion of the range of nine banded armadillos, the classic zoonotic vector for leprosy, due to human induced environmental change. In fact it is to be expected and has been anticipated in our department for the past decade. High clinical suspicion is key to the early diagnosis of leprosy. Recognizing the various clinical presentations of leprosy and assessing clinically suspicious lesions for loss of sensation is within the scope of all providers. At the University of Missouri our Dermatology Department has partnered with the Division of Infectious Disease and Department of Neurology to form the Missouri Hansen's Disease Resource Center. Clinicians with suspected cases of Hansen's disease are encouraged to reach out to our faculty for questions, input, teleconsultation, and/or clinical evaluation as part of our ongoing research studies on Hansen's disease in the state of Missouri. Our Dermatopathology lab can process SSS and skin biopsies and perform all staining necessary for these evaluations. We have several ongoing projects investigating the prevalence of Hansen's disease and its transmission in our state.

Resources

- Missouri Hansen's Disease Resource Center: c/o University of Missouri Department of Dermatology; phone: 573-882-8578; fax: 573-884-5947; email: dyerja@health.missouri.edu
- National Hansen's Disease Resource Center: https://www.hrsa.gov/hansens-disease
- International Textbook of Leprosy: Free, comprehensive, and up to date online resource: Scollard DM, Gillis TP, eds. International Textbook of Leprosy. Available at: https://www.internationaltext bookofleprosy.org/. Accessed August 12, 2022.

References

1. Hansen, GA. On the Etiology of Leprosy, British and Foreign Medico-Chirurgical Review, 55 (1875): 459-89.
2. Maymone, M., Venkatesh, S., Laughter, M. et al. Leprosy: Clinical aspects and diagnostic techniques. J Am Acad Dermatol 2020;83:1-14.
3. Truman RW, Singh P, Sharma R, et al. Probable zoonotic leprosy in the southern United States. N Engl J Med. 2011;364: 1626-1633.
4. Pena MT, Lahiri R, Ebenezer GJ et al. The Armadillo as a Model for Leprosy Nerve Function Impairment: Preventative and Therapeutic Interventions. Front. Med. 2022;9:879097.
5. Hockings,KJ, Mubemba,B.; Avanzi,C et al. Leprosy in wild chimpanzees. Nature. 2021; 598:652–656.
6. Meredith A, Del Pozo J, Smith S, Milne E, Stevenson K, McLuckie J. Leprosy in red squirrels in Scotland. Vet Rec. 2014; 175:285-286.
7). Avanzi C, Del-Pozo J, Benjak A, et al. Red squirrels in the British Isles are infected with leprosy bacilli. Science. 2016; 354:744-747.
8. da Silva MB, Portela JM, Li W, et al. Evidence of zoonotic leprosy in Para, Brazilian Amazon, and risks associated with human contact or consumption of armadillos. PLoS Negl Trop Dis. 2018;12:e0006532.
9. Taulman, JF and Robbins, L. Range expansion and distributional limits of the nine-banded armadillo in the United States: an update of Taulman & Robbins (1996). Journal of Biogeography. 2014; 41:1626–1630.
10. Maymone, M., Venkatesh, S., Laughter, M. et al. Leprosy: Treatment and management of complications. J Am Acad Dermatol 2020;83:17-30.
11. Scollard DM, Gillis TP, eds. International Textbook of Leprosy. Available at: https://www.internationaltext bookofleprosy.org/. Accessed August 12, 2022
12. Westblom, TU and Roller, JA. Leprosy in Missouri. Mo Med. 1987;84(11):699-701.

Disclosure

None reported. **MM**

JAK Inhibitors: A New Weapon in the Skin Care Providers' Arsenal

by Osaigbokan Aihie, MBA & Jonathan A. Dyer, MD

School of Medicine
University of Missouri

The rapid explosion in the discovery, development, approval, and use of JAK inhibitors has revolutionized the field of dermatology.



Osaigbokan Aihie, MBA, (above), is a third-year medical student in the Department of Dermatology, University of Missouri-Columbia School of Medicine. **Jonathan A. Dyer, MD,** is the Philip C. Anderson Chair and Professor Departments of Dermatology and Child Health, also at University of Missouri-Columbia, Columbia, Missouri.

Abstract

A number of chronic skin diseases, such as vitiligo and alopecia areata, are historically resistant to or respond poorly to treatment. Additionally, disorders such as atopic dermatitis and psoriasis have subtypes that are inadequately treated by current medications. Lastly, in the field of dermatology there are a number of conditions, some genetic (such as Darier's disease and Hailey-Hailey disease) and others caused by aberrant inflammatory responses (macrophage-driven conditions such as sarcoidosis and autoimmune conditions such as localized scleroderma) where effective treatments have been limited to date. A new class of anti-inflammatory medications that inhibit the Janus Kinase-Signal transducer and activator of transcription pathway (JAK-STAT) show great promise in providing new and effective treatment of these formerly recalcitrant conditions. This brief review will cover inhibitors of the JAK-STAT pathway (JAK inhibitors) currently approved for use in treating dermatologic diseases including several very recently approved medications. It will also touch on additional conditions under study or where early reports of efficacy are promising.

Introduction

The Janus Kinase-signal transducer and activator of transcription (JAK-STAT) pathway is a critically important pathway for intracellular cytokine signaling through type I and type II cytokine receptors. Cytokines signaling through this pathway include IL-4, IL-5, IL-6 , IL-23, and interferon alpha and beta.[1,2] These cytokines cause inflammation and contribute to the pathogenesis of many autoimmune and dermatological conditions.[1,3] The JAK proteins are bound to the intracellular domain of cytokine receptors and are phosphorylated upon ligand binding to those receptors. The activated JAK proteins, in turn, phosphorylate the STAT proteins causing them to dimerize, translocate into the nucleus of cells, and then regulate gene transcription.[1, 4, 5] There are four JAK kinases (JAK1, JAK2, JAK3 and TYK2) and seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) that bind to the intracellular domain of specific cytokine receptors, allowing for the development JAK inhibitors with various isotype specificities for regulation of distinct inflammatory conditions.[1,3,6]

JAK Inhibitors

The future promise of JAK inhibitors for dermatologic

therapy was demonstrated by oclacitinib, which was approved in 2013 for treating pruritus caused by atopic and allergic dermatitis in dogs. Oclacitinib inhibits primarily JAK1 (over JAK2 and JAK3) and has an excellent safety profile. However, though there are reports of its efficacy in treating pruritus in humans due to atopic dermatitis (AD), it is not approved for human use.[7]

Table 1. JAK inhibitors FDA approved for dermatologic indications

JAK inhibitor	Targets	Indications	FDA approval
Ruxolitinib	JAK 1/ 2	Vitiligo Atopic dermatitis (topical)	2022 2021
Tofacitinib	JAK 1/3	Psoriatic arthritis Alopecia areata Sarcoidosis Granuloma annulare	2017 NA NA NA
Baricitinib	JAK 1/ 2	Alopecia areata	2022
Upadacitinib	JAK 1	Psoriatic arthritis Atopic Dermatitis	2021 2022
Abrocitinib	JAK 1	Atopic Dermatitis	2022
Ritlecitinib	JAK 3	Alopecia areata	NA
PF-06651600	JAK 3	Alopecia areata	NA
Deucravacitinib	TYK 2	Psoriasis	2022

The first JAK inhibitors approved for use in humans were ruxolitinib (JAK1 and JAK2 inhibitor and approved in 2011 for treatment of myelofibrosis) and tofacitinib (JAK1 and JAK3 inhibitor and approved 2012 for second line treatment of rheumatoid arthritis).[8,9,10] More recently there has been an explosion in the number of JAK inhibitors approved for a variety of dermatologic conditions (Table 1).[11-13]

Atopic Dermatitis (AD)

AD is a very common inflammatory skin disease in the United States with a prevalence of at least 13% in children and 7% in adults. More than a third of those affected exhibit moderate to severe disease. [11,14,15] Management of AD is stepwise, starting with topical therapies such as moisturizers, topical corticosteroids, and calcineurin inhibitors for mild to moderate cases. Phototherapy is an effective treatment for cases not responding to topical treatments. More recalcitrant or severe cases of AD often require systemic therapies including immunosuppressants like methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine. While these agents can be effective in treating AD, their utility is limited due to the need for frequent lab monitoring, variable efficacy, and potential serious side effects.[11] Recently the biologic agents dupilumab and tralokinumab received FDA approval for treating moderate to severe and recalcitrant AD. Dupilumab and Tralokinumab are both human monoclonal antibodies that interfere with signaling of IL-4 and IL-13, by binding to the cytokine receptors.[11,16,17] Dupilumab is approved for children older than six months of age and adults while tralokinumab is approved for adults 18 years and older.[11]

The potential for JAK inhibitors to effectively treat AD has been recognized since the approval of oclacitinib for canine use. In 2021, the FDA approved topical ruxolitinib for the treatment of mild to moderate atopic dermatitis following the TRuE-AD clinical trial that showed safety and efficacy of the medication for over 1,200 patients 12 years of age and above. Abrocitinib and upadacitinib also demonstrated efficacy in treating atopic dermatitis (AD) and both received FDA approval in 2022 as oral AD therapies.[11] A recent meta-analysis of Phase 2 and 3 RCTs with at least eight weeks of treatment for moderate to severe AD attempted to compare the efficacy of JAK inhibitors against each other as well as anti-IL4/13 agents and suggested benefit from higher dosages of JAK inhibitors.[11,18] Many JAK inhibitors exhibit favorable pharmacokinetics with rapid onset and short-half lives, allowing rapid discontinuation if adverse effects develop.[11]

Psoriasis

Psoriasis is a chronic skin condition involving keratinocytes, dendritic cells, and several cytokines that mediate inflammation, with IL-12 and IL-23 being the major players.[1,13] IL-23 production by dendritic cells stimulates Th17 cells to differentiate and release proinflammatory cytokines including IL-17 and TNF-alpha utilizing JAK2/Tyk2 pathway.[1] The JAK inhibitor tofacitinib was approved in 2017 for the treatment of psoriatic arthritis but not isolated cutaneous plaque psoriasis.[1] Tofacitinib showed promise in several Phase III clinical trials with patients achieving up to 75% reduction in Psoriasis Area and Severity Index (PASI 75) after taking 5mg and 10mg of the drug twice daily. Better results were noted at the higher dose.[13] Other JAK inhibitors studied in psoriasis include baricitinib and deucravacitinib. Baricitinib showed significant improvement in patients with chronic plaque psoriasis

compared to placebo in a phase II b clinical trial but has shown no additional benefit when compared to tofacitinib.[19] Deucravacitinib has shown more promise. Deucravacitinib is a first-in-class, oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor and directly opposes IL-12/1L-23 signaling.[13,20] The drug was found to be superior to placebo and apremilast in a phase III clinical trial with patients achieving PASI 75 after 16 weeks of treatment. The most common adverse reactions were upper respiratory tract infections, increases in blood creatine phosphokinase levels, herpes simplex reactivation, mouth ulcers, folliculitis and acne/folliculitis. It was approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in September 2022.[20]

Alopecia Areata

Alopecia areata is a common autoimmune condition exhibiting chronic non-scarring hair loss mediated by CD8 T-cells and upregulation of the JAK-STAT dependent cytokines, IL-15 and IFN-γ.[13,21]

In 2014, a case report describing a patient with both alopecia and psoriasis who experienced complete regrowth of scalp and body hair (including eye lashes and eyebrows) while using tofacitinib to treat psoriasis was received with great excitement.[22] This triggered an explosion of studies describing positive results with both topical and systemic use of a variety of JAK inhibitors in the treatment of alopecia areata. It was a momentous event when, in early 2022, baricitinib became the first oral agent to receive an FDA indication for the treatment of alopecia areata in patients 18 years and older.

Many clinical trials are currently underway examining JAK inhibitors for the treatment of alopecia areata including tofacitinib (Phase 4), ritlecitinib (Phase 2A), and PF-06651600 (Phase 3).[21] It is quite likely that there will be a number of FDA approved agents within the next few years to choose from. Currently the drugs are approved for patients 18 years and older. There is a desperate need for studies of these agents in younger patients (6-18 years of age) when alopecia areata has profound and long-lasting impacts on patient's quality of life and wellbeing.[23]

Vitiligo

Vitiligo is a chronic autoimmune condition characterized by CD8+ T-cell mediated destruction of melanocytes. Vitiligo is considered one of the autoimmune skin diseases that is most recalcitrant to treatment. Current standard of care typically utilizes topical corticosteroids and calcineurin inhibitors with variable efficacy. Phototherapy and excimer laser therapy are also used but vary in their treatment response and are cumbersome for patients.

Several initial reports suggested efficacy of JAK inhibitors in treating vitiligo, including a case report of a patient who had complete repigmentation of areas on the hands, forearms and face while using tofacitinib.[13] Another report described a case series of ten patients with vitiligo who noted improvement with concomitant JAK inhibitor and phototherapy.[24]

This led to a randomized double blinded, multicenter study with topical ruxolitinib where 50% of patients achieved a f-VASI 50 (improvement of facial Vitiligo Area Scoring Index by 50%) compared to 3% in the placebo group.[25] These promising results stimulated expansion of the work into the Phase 3 TRuE-V clinical trials (TRuE-V1 and TRuE-V2) to evaluate the safety and efficacy of ruxolitinib 1.5% cream vs. placebo in treating vitiligo in patients 12 years of age and older. More than 600 patients participated in the studies which reported similar results to those seen previously, ~30% F-VASI75 at 24 weeks (vs 8-13% in placebo) and ~50% F-VASI75 at 52 weeks. Almost one-third of patients had near complete repigmentation.[26]

Other Conditions

JAK inhibitors have shown promise in treating a variety of additional skin conditions to those detailed in this report. While many of these are the product of small case reports they hint at the excitement and likely potential for many future roles for JAK inhibition in treating previously recalcitrant or orphan skin diseases. Conditions such as dermatomyositis, systemic lupus erythematosus, lichen planus, necrobiosis lipoidica, hypereosinophilic syndrome, cutaneous sarcoidosis and mastocytosis are just some of the disorders where responses to JAK inhibition have been reported. [13,19] Extremely recalcitrant genetic conditions such as hidradenitis suppurativa, Darier's disease, and Hailey-Hailey disease have all been reported to respond to JAK inhibitors (J.A. Dyer, MD personal observation).[1]

Adverse Effects

Despite the enthusiasm around the enormous potential exhibited by JAK inhibitors, these novel drugs carry the potential for side effects. Ruxolitinib and tofacitinib carry black box warnings for increased risk of malignancy, infections, and thrombosis.[13,27] In post marketing surveillance tofacitinib showed increased risk

of deep vein thrombosis, as well as increases in cancer related morbidity and mortality in patients taking 10mg twice daily compared to patients treated with a TNF inhibitor.[21] JAK inhibition can impair the immune surveillance that detects and destroys malignant cells.[13] The long-term risks of suppression of that immunosurveillance are unknown and will require close monitoring of these agents over time. With increased risk of deep vein thrombosis and arterial thrombosis comes increased risk of pulmonary embolism. These thrombotic risks are not well understood and will require more studies to characterize.[13] Other possible adverse effects involve infections, including reactivation of hepatitis, tuberculosis, herpes simplex, and varicella zoster.[2] Lab monitoring of JAK inhibitors is recommended due to reports of pancytopenia and transaminitis.[2,28]

Conclusions

The rapid explosion in the discovery, development, approval, and use of JAK inhibitors has revolutionized the field of dermatology. These incredibly exciting agents appear to provide effective treatments for a number of formerly recalcitrant and difficult to treat cutaneous diseases, including genetic conditions which had few previous therapeutic options. Their therapeutic promise seems vast. However, these agents impact a broad range of immunologic systems and carry the potential for a number of short- and long-term side effects. Now, more than ever, there is need for close and measured ongoing study of these new agents to ensure that these new weapons in our therapeutic arsenal are used safely and appropriately. Such studies must include pediatric populations whenever possible, to ensure we fully understand their impacts in these most vulnerable patients.

References

1. Chapman S, Kwa M, Gold LS, Lim HW. Janus kinase inhibitors in dermatology: Part I. A comprehensive review. J Am Acad Dermatol. 2022;86(2):406-413.
2. Klein B, Treudler R, Simon JC. JAK-inhibitors in dermatology – small molecules, big impact? Overview of the mechanism of action, previous study results and potential adverse effects. JDDG J Dtsch Dermatol Ges. 2022;20(1):19-24.
3. Chuprin J, McCormack L, Richmond JM, et al. Evaluating the use of JAK inhibitors in inflammatory connective tissue diseases in pediatric patients: an update. Expert Rev Clin Immunol. 2022 Mar;18(3):263-272.
4. Furumoto Y, Gadina M. The arrival of JAK inhibitors: advancing the treatment of immune and hematologic disorders. BioDrugs Clin Immunother Biopharm Gene Ther. 2013;27(5):431-438.
5. Schwartz DM, Bonelli M, Gadina M, O'Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. Nat Rev Rheumatol. 2016;12(1):25-36.
6. Mackay-Wiggan J, Jabbari A, Nguyen N, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight. 2016;1(15).
7. Labib a, Yosipovitch G, Olivry T. What can we learn from treating atopic itch in dogs? J Allergy Clin Immunol 2022;150:284-6.
8. Traidl S, Freimooser S, Werfel T. Janus kinase inhibitors for the therapy of atopic dermatitis. Allergol Sel. 2021;5(01):293-304.
9. Traynor K. FDA approves tofacitinib for rheumatoid arthritis. Am J Health Syst Pharm. 2012;69(24):2120.
10. Mascarenhas J, Hoffman R. Ruxolitinib: The First FDA Approved Therapy for the Treatment of Myelofibrosis. Clin Cancer Res. 2012;18(11):3008-3014.
11. Narla S, and Silverberg JI. The suitability of treating atopic dermatitis with Janus kinase inhibitors. Expert Rev Clin Immunol. 2022 May;18(5):439-459.
12. RINVOQ® (upadacitinib) Receives U.S. FDA Approval for Active Psoriatic Arthritis _ AbbVie News Center.pdf.
13. Shalabi MMK, Garcia B, Coleman K, Jr S, Miller A, Tyring SK. Janus Kinase and Tyrosine Kinase Inhibitors in Dermatology: A Review of Their Utilization, Safety Profile and Future Applications. Skin Therapy Lett. 2022 Jan;27(1):4-910.
14. Silverberg JI, Simpson EL. Associations of childhood eczema severity: A US population-based study. Dermat Contact Atopic Occup Drug. 2014;25(3):107-114.
15. Silverberg JI, Chiesa Fuxench ZC, Gelfand JM, et al. Content and construct validity, predictors, and distribution of self-reported atopic dermatitis severity in US adults. Ann Allergy Asthma Immunol. 2018;121(6):729-734.
16. Tameez Ud Din A, Malik I, Arshad D, Tameez Ud Din A. Dupilumab for Atopic Dermatitis: The Silver Bullet We Have Been Searching for? Cureus. Published online April 6, 2020.
17. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2)*. Br J Dermatol. 2021;184(3):437-449.
18. Silverberg JI, Hong HC ho, Thyssen JP, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysis. Dermatol Ther. 2022;12(5):1181-1196.
19 Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol. 2016 Jun;174(6):1266-76.
20. Presentation #D3T01.1F) presented at the European Academy of Dermatology and Venereology (EADV) Congress, taking place September 7-10, 2022; taken from https://news.bms.com/news/corporate-financial/2022/Bristol-Myers-Squibb-Announces-New-Sotyktu-deucravacitinib-Long-Term-Data-Showing-Clinical-Efficacy-Maintained-for-Up-to-Two-Years-with-Continuous-Treatment-in-Moderate-to-Severe-Plaque-Psoriasis/default.aspx
21. Chapman S, Gold LS, Lim HW. Janus kinase inhibitors in dermatology: Part II. A comprehensive review. J Am Acad Dermatol. 2022;86(2):414-422.
22. Craiglow BG, and King BA. Killing two birds with one stone: oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis. J Invest Dermatol. 2014 Dec;134(12):2988-2990
23. Liu LY, King BA, Craiglow BG. Alopecia areata is associated with impaired health-related quality of life: A survey of affected adults and children and their families. J Am Acad Dermatol. 2018 Sep;79(3):556-558.
24. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. J Am Acad Dermatol. 2017;77(4):675-682.e1.
25. Rosmarin D, Pandya AG, Lebwohl, M. et a. Ruxolitinib cream for treatment of vitiligo: a randomized, controlled, phase 2 trial. Lancet 2020; 396(10244):110-120
26. Session #S026 – Late-Breaking Research: Clinical Trials) at the 2022 American Academy of Dermatology (AAD) Annual Meeting, held from March 25-29 in Boston.
27. Damsky W, King BA. JAK inhibitors in dermatology: The promise of a new drug class. J Am Acad Dermatol. 2017;76(4):736-744.
28. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(4):234-243.

Disclosure

None reported. **MM**

Infantile Hemangiomas: A Review and Future Opportunities

by Kimberly A. Eisenstein, MD

School of Medicine
University of Missouri

Despite increased dissemination of knowledge and better treatment modalities for IHs, there are still many poor outcomes, particularly in areas without IH specialists.



Kimberly A. Eisenstein, MD, is Assistant Professor of Clinical Pediatric Dermatology and Child Health in the Department of Dermatology at the University of Missouri-Columbia, Columbia, Missouri.

Abstract

Infantile hemangiomas (IHs) are identified in about 5-12% of infants, making them the most common benign tumor of childhood (Figure 1). IHs are vascular growths characterized by an abnormal proliferation of endothelial cells and aberrant blood vessel architecture.[1] IHs commonly involute after proliferation, traditionally leading to a non-interventional or "wait and see" management approach. However, a large subset of these growths can become problematic causing morbidities such as ulceration and scarring, disfigurement, or functional impairment. Another subset of these cutaneous hemangiomas may also be markers for visceral involvement or other underlying abnormalities. Historically, treatment options were often rife with unwanted side effects and modest results. However, with newer established treatments which are both safe and effective, there is a time-sensitive need for early identification of high-risk hemangiomas to ensure prompt delivery of treatment for best outcomes. Despite a more recent dissemination of awareness of IHs and these newer treatments, there remains a large subset of infants who still experience a delay in care and poor outcomes which are likely avoidable. There may be some avenues in Missouri to help mitigate these delays.

Introduction

The pathogenesis of IHs has yet to be fully defined. A leading hypothesis is that circulating endothelial progenitor cells migrate to locations in which conditions (eg, hypoxia and developmental field disturbances) are favorable for growth.[2] IHs grow in a relatively expected trajectory, with 80% of growth in the first five months of life, and growth which is typically complete by nine months.[3] In 2019 the American Academy of Pediatrics put forth the first Clinical Practice Guidelines for the Management of Infantile Hemangiomas. The guideline helps to stratify infantile hemangiomas which may be more problematic, prompting increased vigilance in monitoring or referral for early treatment. The ability to identify IHs which are more likely to cause morbidity or unfavorable outcomes allows primary care practitioners to decide whether IHs should be characterized as "High Risk" or

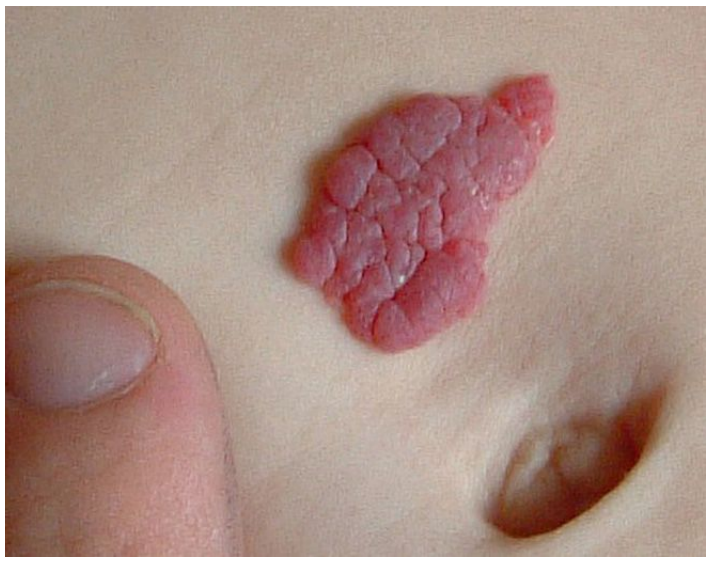




Figure 1. Infantile hemangiomas (IHs) are identified in about 5-12% of infants, making them the most common benign tumor of childhood.

"Low Risk." Making this distinction as "High Risk" then allows for increased monitoring in the primary care setting and/or early referral to an IH specialist for assessment and treatment.

Classification of Hemangiomas: "High Risk" or "Low Risk"

Clinicians should classify an IH as "High Risk" if there is evidence of or potential for the following: 1) life-threatening complications; 2) functional impairment; 3) ulceration; 4) associated structural anomalies (eg, in PHACE syndrome or SACRAL syndrome); or 5) permanent disfigurement, [2] as outlined in Figure 2.

Life threatening complications include IHs of the airway, which most commonly occur in the subglottis, already the narrowest part of the pediatric airway, and present with biphasic stridor. Hepatic hemangiomas, when occurring in a multifocal or diffuse pattern, can in rare circumstances lead to hepatomegaly, hypothyroidism and cardiac failure.[4]

Functional impairment may occur from IHs located around the eyes or mouth. IHs around the eyes, particularly > 1cm, may cause mechanical distortion which ultimately may lead to amblyopia.[5] IHs around the mouth, particularly those which also ulcerate, may leading to feeding difficulties.

Ulceration of the skin or mucosal surfaces, which occurs up to 21% of the time, leads to pain, bleeding, often secondary infection, and always scarring.[6] Ulceration typically occurs by four months of age, and during the proliferative phase of IHs. Certain types of IHs are at higher risk, including superficial, mixed types, segmental IHs, and those involving the scalp, neck, and perioral, perineal, perianal, and intertriginous sites.

In rare circumstances, some infants may have associated structural anomalies with their segmental IHs. PHACE syndrome may be considered in an infant with a large (>5cm) segmental IH on the face, scalp or neck. Cerebrovascular anomalies, present in more than 90% of patients with PHACE syndrome, are the most common extracutaneous feature of the syndrome, followed by cardiac anomalies (67%) and structural brain anomalies (52%).[2] The risk of PHACE syndrome in an infant presenting with a large segmental IH of the head or neck is approximately 30%. LUMBAR syndrome, which should be considered for large segmental IHs of

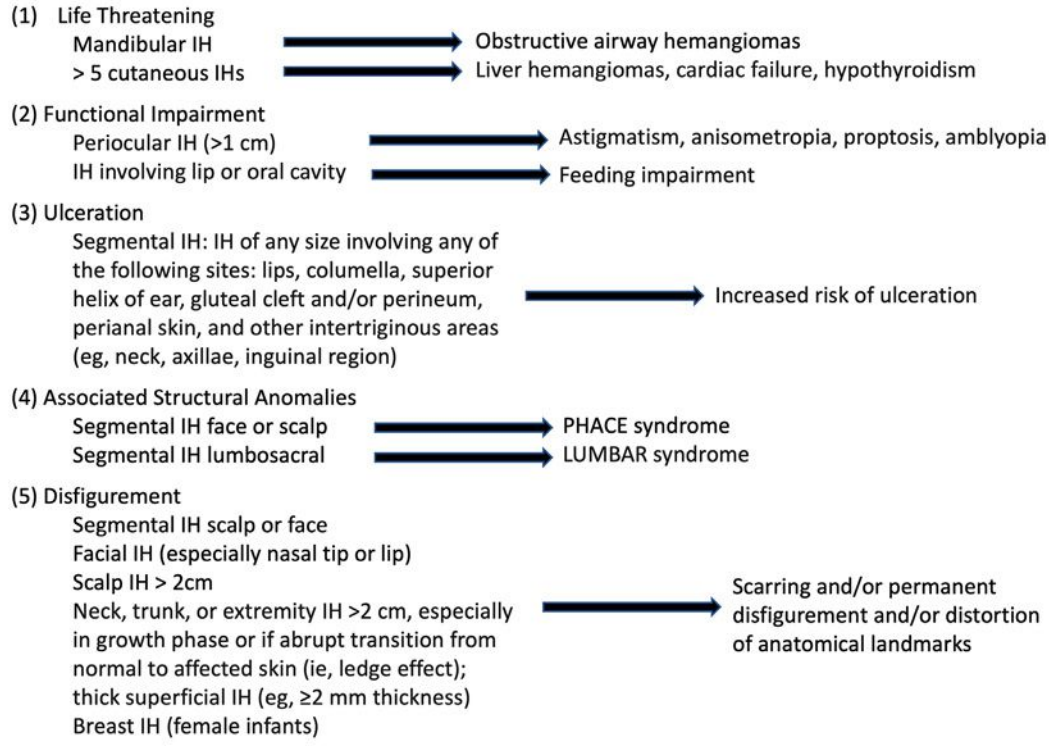


Figure 2.

IH Clinical Findings and Possible Risks

the lumbosacral or perineal areas which extend onto a leg, present with myelopathy as the most common anomaly.

The risk of IHs causing permanent disfigurement is more likely than life threatening or functional problems. This can be caused via scarring or distortion of anatomical landmarks. The shift to treating IHs to prevent future skin changes stems from the development of more effective and safer treatment modalities. This is more often considered in anatomical areas which are not covered by clothing (like the face) or in emotionally sensitive areas (like the breasts).[7]

Treatment Types and Initiation of Treatment

There is good evidence that almost all high risk IHs should be treated first line with systemic beta blocker therapy, typically propranolol solution.[8] Propranolol is a nonselective antagonist of both β-1 and β-2 adrenergic receptors. The precise mechanisms of action of propranolol on IHs are still unclear. Propranolol dose should start between 2 and 3 mg/kg per day unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg, sleep disturbance) that necessitate a lower dose.[2] Treatment should continue until 12-15 months of age to reduce the instance of rebound growth, which commonly occurs, particularly when stopped under nine months of age.[9] Propranolol should be administered with or after feeding, and doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia. Potential adverse effects of propranolol include sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension. It is no longer necessary to screen all infants with EKG prior to initiation of propranolol therapy, except infants with specific comorbidities or family histories.

Providers may prescribe topical timolol maleate as a therapy for thin and/or superficial IHs.[2] There are few risks or adverse side effects related to therapy, and this may be preferred as a possible treatment for patients of parents who have safety concerns regarding the use of oral propranolol in their young infant. Timolol is not typically used on ulcerated IHs.

Difficulties, Systemic Pitfalls in Healthcare… and Opportunities

There is a finite window within the natural history of IHs where intervention is effective. Less commonly is treatment initiated at six months of age or later given the lower likelihood of success, although in some cases with potential significant morbidity, it may be worthwhile to trial systemic medication. Additionally, there are occasionally parental concerns regarding the safety of propranolol given its typical use as a blood pressure medication, and parents may opt to monitor instead.

Given the finite window to treat IHs and thus improve outcomes, one reoccurring pitfall is the time to see an IH specialist. For instance, pediatric dermatologists view infantile hemangioma referrals as more urgent appointments and will try to accommodate patients to be seen within one week or sooner, if needed. When referrals are made, it is of particular importance that medical offices (either PCPs or other specialists) feel comfortable following up referrals with emails, messages, or phone calls to the clinic stating urgency. These appointments should not wait the standard "next available," and the urgency may not be known to all scheduling staff.

One possibility to reduce delays in care could be the establishment of an on-call type of hotline in Missouri, potentially aptly named the "Hemangioma Hotline," where primary care or other providers can call for more immediate triage help regarding the timing for scheduling appointments, finding an IH specialist, or instruction regarding the starting of medication prior to being seen by a specialist. Having this support and establishing this open communication may be an excellent start to decreasing the morbidity that still surrounds high risk IHs. Other possibilities include an ECHO via the MO Telehealth Network or in coordination with MOAAP that would further educate providers regarding the urgency of these tumors and help to guide through initial assessment. Ideas regarding funding or comments regarding general interest level would be welcome.

Conclusion

Despite increased dissemination of knowledge and better treatment modalities for IHs, there are still many poor outcomes, particularly in areas without IH specialists. Education regarding delineation of high risk vs. low risk IHs help to determine the urgency of referral and whether treatment should be initiated. A statewide "Hemangioma Hotline" or other educational tools may help to improve the gap in outcomes.

References

1. Darrow DH, Greene AK, Mancini AJ, Nopper AJ; SECTION ON DERMATOLOGY, SECTION ON OTOLARYNGOLOGY–HEAD AND NECK SURGERY, and SECTION ON PLASTIC SURGERY. Diagnosis and Management of Infantile Hemangioma. Pediatrics. 2015;136(4):e1060-e1104. doi:10.1542/peds.2015-2485.
2. Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics. 2019;143(1):e20183475. doi:10.1542/peds.2018-3475.
3. O'Brien KF, Shah SD, Pope E, et al. Late growth of infantile hemangiomas in children >3 years of age: A retrospective study. J Am Acad Dermatol. 2019;80(2):493-499. doi:10.1016/j.jaad.2018.07.061.
4. Gnarra M, Behr G, Kitajewski A, et al. History of the infantile hepatic hemangioma: From imaging to generating a differential diagnosis. World J Clin Pediatr. 2016;5(3):273-280. Published 2016 Aug 8. doi:10.5409/wjcp.v5.i3.273.
5. Frank RC, Cowan BJ, Harrop AR, Astle WF, McPhalen DF. Visual development in infants: visual complications of periocular haemangiomas. J Plast Reconstr Aesthet Surg. 2010;63(1):1-8. doi:10.1016/j.bjps.2008.08.045.
6. Chamlin SL, Haggstrom AN, Drolet BA, et al. Multicenter prospective study of ulcerated hemangiomas [published correction appears in J Pediatr. 2008 Apr;152(4):597]. J Pediatr. 2007;151(6):684-689.e1. doi:10.1016/j.jpeds.2007.04.055.
7. Tanner JL, Dechert MP, Frieden IJ. Growing up with a facial hemangioma: parent and child coping and adaptation. Pediatrics. 1998;101(3 Pt 1):446-452. doi:10.1542/peds.101.3.446.
8. Léaute-Labrèze C, Boccara O, Degrugillier-Chopinet C, et al. Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: A Systematic Review. Pediatrics. 2016;138(4):e20160353. doi:10.1542/peds.2016-0353.
9. Shah SD, Baselga E, McCuaig C, et al. Rebound Growth of Infantile Hemangiomas After Propranolol Therapy. Pediatrics. 2016;137(4):e20151754. doi:10.1542/peds.2015-1754.

Disclosure

None reported. **MM**

Updates in Cutaneous Oncology

by Jesse Hirner, MD

School of Medicine
University of Missouri

Skin cancer diagnosis is now aided by expanding dermoscopic knowledge, total body photography, and emerging machine-learning technologies.



Jesse Hirner, MD, is the Director of Cutaneous Oncology and Assistant Professor, Department of Dermatology, University of Missouri-Columbia School of Medicine, Columbia, Missouri.

Abstract

Cutaneous oncology is currently a rapidly evolving field. Dermoscopy, total body photography, biomarkers, and artificial intelligence are affecting the way skin cancers, especially melanoma, are diagnosed and monitored. The medical management of locally advanced and metastatic skin cancer is also changing. In this article, we will discuss recent developments in cutaneous oncology with a particular focus on treatment of advanced cancers.

Epidemiology

Melanoma incidence had been rising for decades in the United States,[1] although mortality is falling due to earlier detection and improved treatment options for locoregional and metastatic melanoma. In recent years incidence has stabilized and been falling by approximately 1% annually for people under 50-years old.[1] A similar pattern has occurred for cutaneous squamous cell carcinoma, with incidence increasing in the 2000s and mid-2010s in the US but stabilizing in recent years.[2,3] These changes may be related to changes in occupational and recreational sun exposure, tanning bed use, sun-protection behaviors, and skin cancer detection.

Diagnosis and Biomarkers

Dermoscopy has become a widespread and important tool for dermatologic diagnosis. Dermoscopy, also called epiluminescent microscopy or dermatoscopy, uses magnification with or without light polarization to enhance visualization of subcorneal skin structures. In experienced hands, dermoscopy in combination with traditional exam can improve sensitivity for diagnosing melanoma.[4] Photography with sequential tracking of dermoscopic images may be particularly useful for early detection of melanoma, since early melanomas may lack typical dermoscopic features and the most concerning feature is often longitudinal change.[5–7]

Total body photography (TBP) is gaining traction, mostly at academic centers, to longitudinally track patient's skin exams. TBP images nearly the entire skin surface to allow detection of new lesions or changes in existing lesions. Data suggests that it may facilitate earlier detection of melanoma and reduce the number of benign lesions biopsied.[8,9] Some total body photography systems incorporate convolutional neural networks (CNNs) to identify lesions that may warrant close inspection by the clinician. The best CNNs have shown

Table 1. Biomarkers for Monitoring Merkel Cell Carcinoma Patients

Biomarker	Utility	Specimen	Availability	Turnaround Time	Comment
MCC small-T antigen oncoprotein antibody (AMERK)	Primarily used to monitor for recurrence	Blood	Send-out test to the University of Washington	3-4 weeks	Antibody titers correlate with tumor volume. They fall in response to treatment and rise with recurrence. High predictive value. Only positive in 41-48% of MCC patients. Must obtain at baseline. Often done at each follow up visit. Detects recurrence before radiology in some patients.
Tumor-informed circulating cell-free tumor DNA (ctDNA)	Primarily used for monitoring for recurrence	1st test: FFPE and blood All subsequent tests: Blood	Available via Natera and Gaurdant360	1st test: 2-3 weeks. Subsequent tests: 5-7 days.	ctDNA levels correlate with tumor volume. Used similarly to AMERK, but useable in all MCC patients. Newer and less established in MCC management than AMERK.

AMERK – anti-merkel cell antibody, ctDNA – circulating cell-free tumor DNA, FFPE – formalin-fixed paraffin-embedded tissue.

accuracy similar to board-certified dermatologists for differentiating benign from malignant lesions.[10] However, there is variability between CNNs and they have been particularly weak in skin of color,[10] perhaps due to a relative lack of skin of color images in training sets. Oversensitivity is a common problem with the CNNs used with TBP, but criteria to call out a lesion can be adjusted by the user. Use of TBP will initially require time of both staff and the physician. As familiarity with the software grows, it may expedite exams of high-risk patients. Clinic staff will have to be trained on how to use the system, and some basic equipment, such as photography backgrounds and lighting, are often used. Outside of TBP, CNNs are not yet used in routine practice, but they are receiving growing interest for skin cancer diagnosis.

Biomarkers are becoming increasingly utilized in cutaneous oncology as predictors of treatment response and for surveillance (Table 1). The most well established is $BRAF^{V600}$ mutation testing, which determines eligibility for treatment with combination BRAF and MEK inhibitors for locoregional or metastatic melanoma. Merkel cell polyomavirus (MCPyV) small T oncoprotein antibodies have become well established as powerful tools for monitoring for recurrence in Merkel cell carcinoma (MCC) patients, and are now included in the NCCN guidelines and used at the University of Missouri.[11] These antibodies are sensitive markers of recurrence and provide positive predictive values as high as 97% and negative predictive values as high as 99%.[12,13] Their major limitation is that they are only present in 41-48% of MCC patients.[13–16] Tumor-informed circulating cell-free tumor DNA (ctDNA) has emerged as a biomarker performing largely the same role as MCPyV oncoprotein antibodies, but can be used in all MCC patients and is growing in popularity. It is also being used in some centers for melanoma.

Treatment

Gene expression profiling (GEP) is seeing use for diagnosis, prognosis, and testing for $BRAF^{V600}$ mutations in melanoma. GEP quantifies mRNA levels and uses artificial intelligence (AI) to predict outcomes for melanocytic tumors. However, clinicopathologic risk stratification in melanoma is relatively accurate,

Table 2. Medical Therapies for Advanced Skin Cancers

Cancer	Treatment	Comments
Melanoma	Nivolumab Pembrolizumab	Immunotherapy should generally be first-line over targeted therapy in *BRAF*^{V600}-mutant melanoma
	Nivolumab with relatlimab	Higher PFS than nivolumab monotherapy. Lower rate of adverse events than nivolumab with ipilimumab
	Nivolumab with ipilimumab	
	Vemurafenib with cobimetinib	Vemurafenib may cause photosensitivity. BRAF inhibitors may cause benign and malignant cutaneous squamous tumors.
	Dabrafenib with trametinib	Dabrafenib may cause febrile episodes
	Encorafenib with binimetinib	Encorafenib may cause hepatotoxicity
	Atezolizumab with vemurafenib and cobimetinib	Uncommonly used
	Talimogene laherparepvec	Later-line therapy
Squamous cell carcinoma	Cemiplimab	
	Pembrolizumab	Less frequent infusions than cemiplimab – every 3 weeks rather than every 2 weeks
	Cetuximab	Approved for head and neck squamous cell carcinoma
	Chemotherapy	Includes cisplatin ± 5-FU, carboplatin ± paclitaxel, may be used with radiotherapy
Basal cell carcinoma	Vismodegib	
	Sonidegib	Not approved for metastatic BCC, only locally advanced disease, due to poor ORR in metastatic BCC in the BOLT trial
	Cemiplimab	Approved for BCC previously treated with a hedgehog inhibitor

PFS – progression-free survival, ORR – overall response rate

creating a high bar for GEP to clear. GEP AI tools were trained on old data samples that are not consistent with prognoses in the era of targeted and immune therapies. Some clinicians find continuous GEP results difficult to interpret and communicate to the patient. Dichotomous results are provided to solve this problem, but dichotomization attenuates predictive ability. Inaccuracy is a major limiting factor. Marchetti et al. performed a meta-analysis of seven studies on GEP used to predict recurrence for stage I and II melanoma. DecisionDx-Melanoma correctly predicted only 29% of recurrences in stage I melanoma – a 71% false negative rate.[17] For stage II disease it had a 56% false-positive rate.[17] MelaGenix had a 68% false-negative rate for stage I disease and 57% false-positive rate for stage II disease.[17]

Medical management of locoregional and metastatic skin cancers remains dynamic. The LAG-3 inhibitor relatlimab was approved with nivolumab in March 2022 for patients 12-years-old and older with unresectable or metastatic melanoma. The RELATIVITY-047 trial of relatlimab with nivolumab vs. nivolumab monotherapy showed a median progression-free survival (PFS) of 10.1 months for the combination and 4.6 months for nivolumab monotherapy (p=0.006).[18] PFS at 12 months was 47.7% for relatlimab with nivolumab and 36.0% for nivolumab.[18] Treatment-related adverse events occurred in 81.1% of relatlimab with nivolumab patients and 69.9% of nivolumab patients.[18] CTCAE Grade 3-4 adverse events occurred in 18.9% of relatlimab with nivolumab patients and 9.7% of nivolumab patients.[18] Head-to-head data is lacking, but PFS is comparable between relatlimab-nivolumab and nivolumab-ipilimumab.[19] However, relatlimab-nivolumab may be safer than nivolumab-ipilimumab. As noted, 18.9% of patients receiving relatlimab-nivolumab suffer severe adverse events.[18] In contrast 55.0% of nivolumab-ipilimumab patients suffer severe adverse events,[19] a 2.9-fold increase. We are still waiting on important data, since RELATIVITY-047 excluded patients with untreated brain metastases. The immunotherapy doublet is being evaluated in patients with active brain metastases in a study at

MD Anderson Cancer Center. Overall survival (OS) data for relatlimab-nivolumab is not yet published, but the regimen is likely to find a prominent place in treatment of metastatic melanoma.

Recently, we received FDA approval for pembrolizumab for stage IIB and IIC melanoma based on improved recurrence-free survival (RFS) in KEYNOTE-716.[20] Multiple immunotherapies and dabrafenib-trametinib had received approvals for adjuvant treatment for stage IIIA and higher melanoma, but it is known that stage IIC disease has worse RFS and OS compared to IIIA disease.[21] 26.5% of stage IIC melanoma patients will be recurrence-free at five years, compared to 44.8% of stage IIIA patients.[21] Similarly, stage IIC melanoma has a 71.0% 5-year OS, compared to 81.0% for stage IIIA.[21] In the KEYNOTE-716 trial of adjuvant pembrolizumab vs. placebo for stage IIB or IIC melanoma, RFS at 20.9 months of follow up was 85% in the pembrolizumab group and 76% in the placebo group.[20] OS data from KEYNOTE-716 are not yet reported. Risk prediction tools can be helpful when considering adjuvant therapy. AJCC-8 staging is useful but is limited by including only tumor-level data and excluding factors such as mitotic index and prior treatment. Melanomarisk.org.au and melanomaprognosis.net are two risk calculators to help inform patient discussions and treatment decisions (Table 2).

For $BRAF^{V600}$-mutant metastatic melanoma it was unclear for years whether first-line targeted therapy or immunotherapy performed better. Preliminary results of the DREAMseq trial were presented at the American Society of Clinical Oncology meeting in November 2021 and first-line nivolumab-ipilimumab demonstrated superior two-year OS compared to first-line dabrafenib-trametinib in stage III-IV disease.[22] Two-year OS for patients receiving first-line nivolumab-ipilimumab was 72% compared to 52% for patients receiving first-line dabrafenib-trametinib.[22] The OS difference caused the data safety and monitoring committee to recommend halting enrollment early and offer patients on first-line targeted therapy a switch to immunotherapy. Median duration-of-response was not reached in the immunotherapy arm but was 12.7 months in the targeted therapy arm – another favorable finding for first-line nivolumab-ipilimumab. Dabrafenib-trametinib had a higher PFS until six6 months and higher OS until 10-months, but longer-term outcomes favored immunotherapy. Patients were able to switch to the second regiment if they progressed on first-line treatment, and dabrafenib-trametinib performed equally well in the first and second lines. In contrast, 46% of patients on first-line nivolumab-ipilimumab responded, but only 30% responded to second-line immunotherapy. The major limitation of DREAMseq is that first-line immunotherapy is more commonly PD-1 monotherapy rather than doublet nivolumab-ipilimumab, and a monotherapy arm did not exist in this trial. Van Breeschoten et al. used the Dutch Melanoma Treatment Registry to examine first-line PD-1 inhibitor monotherapy against BRAF-MEK targeted therapy in a propensity-score matched cohort of 584 $BRAF^{V600}$-mutant melanoma patients.[23] Patients receiving first-line PD-1 inhibition had median OS of 42.3 months and 2-year OS of 65.4%.[23] First-line BRAF-MEK inhibition had a median OS of 19.8 months and two-year OS of 41.7%.[23] Both the Dutch registry study and DREAMseq trial suggest that first-line immunotherapy is generally preferred over targeted therapy in BRAF-mutant melanoma. Exceptions include patients with contraindications to immunotherapy and when a rapid response is needed and pseudoprogression may be dangerous, such as with symptomatic brain metastases.

For years completion lymph node dissection was standard management of melanoma with sentinel lymph node positivity or clinically detectable locoregional disease. However, two large trials evaluating completion lymph node dissection against observation found no improvement in overall survival or disease-specific survival.[24,25] One did find the three-year disease-free survival to be 5% higher in the dissection group (68% v. 63%, p=0.05).[24] In recent years, multiple studies have shown overall survival and recurrence-free survival benefit from adjuvant immunotherapy and targeted therapy regimens, and this has led to adjuvant treatment usurping completion lymph node dissection for management of locoregional melanoma in many centers.[26–31] A trial comparing ipilimumab against placebo in resected stage IIIA-C melanoma with a tumor deposit of at least 1 mm found five-year OS in the ipilimumab group was 65.4% and in the placebo group was 54.4%

(p=0.001). The five-year RFS was 40.8% and 30.3%, respectively (p<0.001). However, 54.1% of patients in the ipilimumab group experienced grade three to four adverse events, so the risk-benefit ratio must be carefully considered. Two trials of adjuvant nivolumab vs. ipilimumab in stage III or IV melanoma found superior RFS with nivolumab, with markedly lower risk of immune-related adverse events.[28,29] One found a comparable, although slightly higher, four-year OS with nivolumab compared to ipilimumab that was not statistically significant (77.9% vs. 76.6% p=0.31). In a trial of adjuvant nivolumab with ipilimumab vs. nivolumab vs. placebo for resected stage IV melanoma with no evidence of disease, one-year RFS in the nivolumab with ipilimumab group was 75%, in the nivolumab group it was 52% and in the placebo group it was 32%. Treatment-related grade three to four adverse events occurred in 71% of the doublet immunotherapy group and 27% of the nivolumab group. Adjuvant dabrafenib with trametinib vs. placebo in stage III melanoma with tumor deposits > 1 mm demonstrated superior three-year OS (86% vs. 77% p=0.006) and RFS (58% vs. 39%, p<0.001).[31] These data clearly favor adjuvant medical management over completion lymph node dissection for improved OS and disease-free survival. Risk of immune-related adverse events must be considered and discussed with the patient and contrasted with the risk of lymphedema and surgical complications from completion dissection. Lymphedema occurs in approximately 24% of melanoma patients after completion lymph node dissection.[24] Multiple studies excluding stage IIIA patients with nodal tumor deposits < 1 mm in diameter weakens support for adjuvant treatment in this lower-risk population. In some of these patients, completion dissection will increase their stage from IIIA to IIID, since completion dissection does provide more complete staging information compared to sentinel-lymph node biopsy.

There is interest in adjuvant and neoadjuvant cemiplimab for high-risk cutaneous squamous cell carcinoma, and there are ongoing trials for both. There is also interest in neoadjuvant immunotherapy and targeted therapy for melanoma. Neoadjuvant therapy may allow for reduced extent of surgery. It also allows for pathologic assessment of immunotherapy response and pathologic complete or partial response is a predictor of improved RFS.[32] Neoadjuvant therapy can often be given without delaying surgery,[33] but severe immune-related adverse events can delay surgery if they occur. The clinical context must be considered.

In 2021 the FDA approved cemiplimab for locally advanced and metastatic basal cell carcinoma (BCC) in patients previously treated with a hedgehog inhibitor. The approval was based on response rate in locally advanced BCC patients who had previously progressed on or not tolerated a hedgehog inhibitor. Objective response rate was 26%, with 6% achieving a complete response and 25% a partial response.[34] Prior to this approval, the hedgehog inhibitors vismodegib and sonidegib were the only agents approved for locally advanced or metastatic BCC. Many patients are unable to tolerate hedgehog pathway inhibition due to muscle spasms, dysgeusia, alopecia, and weight loss, so having a third agent available is important for these rare but challenging cancers. Grade 3-4 adverse events were documented in 48% of patients, with the most common side effects being fatigue, musculoskeletal pain, diarrhea, rash, and pruritus. Cemiplimab was approved for locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC) in 2018. In 2020 pembrolizumab was approved for recurrent or metastatic cSCC or cSCC not curable by surgery or radiation. Given the complexity of management of these patients, a multidisciplinary cutaneous oncology tumor board is a valuable tool that we are fortunate to have at the University of Missouri.

Conclusion

Cutaneous oncology is a rapidly changing field. Skin cancer diagnosis is now aided by expanding dermoscopic knowledge, total body photography, and emerging machine-learning technologies. Biomarkers are increasingly prevalent and are most useful currently for guiding treatment (as with $BRAF^{V600}$ mutation testing) and surveillance. As GEP and other biomarkers develop, they may develop a larger niche in diagnosis and risk stratification. LAG-3 inhibitors recently entered the market with relatlimab's approval for melanoma, adding an effective regiment for these patients. Adjuvant immunotherapy replacing completion lymph node dissection for locoregional melanoma is improving survival in these patients.

Nonmelanoma skin cancer is also seeing new developments with the approval of PD-1 inhibitors in BCC and cSCC. We are excited to be offering these advances to our patients via our cutaneous oncology program at the University of Missouri and can expect the field to remain dynamic in coming years.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. doi:10.3322/caac.21708
2. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the U.S. Population, 2012. JAMA Dermatol. 2015;151(10):1081-1086. doi:10.1001/jamadermatol.2015.1187
3. Stang A, Khil L, Kajüter H, et al. Incidence and mortality for cutaneous squamous cell carcinoma: comparison across three continents. J Eur Acad Dermatol Venereol. 2019;33(S8):6-10. doi:10.1111/jdv.15967
4. Dinnes J, Deeks JJ, Chuchu N, et al. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. Cochrane Database Syst Rev. 2018;2018(12). doi:10.1002/14651858.CD011902.pub2
5. Menzies SW, Gutenev A, Avramidis M, Batrac A, McCarthy WH. Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. Arch Dermatol. 2001;137(12):1583-1589. doi:10.1001/archderm.137.12.1583
6. Skvara H, Teban L, Fiebiger M, Binder M, Kittler H. Limitations of dermoscopy in the recognition of melanoma. Arch Dermatol. 2005;141(2):155-160. doi:10.1001/archderm.141.2.155
7. Kittler H, Guitera P, Riedl E, et al. Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. Arch Dermatol. 2006;142(9):1113-1119. doi:10.1001/archderm.142.9.1113
8. Ji-Xu A, Dinnes J, Matin R n. Total body photography for the diagnosis of cutaneous melanoma in adults: a systematic review and meta-analysis*. Br J Dermatol. 2021;185(2):302-312. doi:10.1111/bjd.19759
9. Drugge ED, Sarac RM, Elston DM, Drugge RJ. Correlation of total body photography frequency and invasive melanoma depth. J Am Acad Dermatol. 2020;82(3):768-769. doi:10.1016/j.jaad.2019.11.003
10. Fried L, Tan A, Bajaj S, Liebman TN, Polsky D, Stein JA. Technological advances for the detection of melanoma. J Am Acad Dermatol. 2020;83(4):983-992. doi:10.1016/j.jaad.2020.03.121
11. Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel Cell Carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(6):742-774. doi:10.6004/jnccn.2018.0055
12. Paulson KG, Lewis CW, Redman MW, et al. Viral oncoprotein antibodies as a marker for recurrence of Merkel cell carcinoma: A prospective validation study. Cancer. 2017;123(8):1464-1474. doi:10.1002/cncr.30475
13. Lachance K, Akaike T, Cahill K, et al. 590 Detecting Merkel cell carcinoma recurrence using a blood test: Outcomes from 774 patients. J Invest Dermatol. 2019;139(5):S101. doi:10.1016/j.jid.2019.03.666
14. Paulson KG, Lewis CW, Redman MW, et al. Viral oncoprotein antibodies as a marker for recurrence of Merkel cell carcinoma: A prospective validation study: Viral Oncoprotein Antibodies in MCC. Cancer. 2017;123(8):1464-1474. doi:10.1002/cncr.30475
15. Paulson KG, Carter JJ, Johnson LG, et al. Antibodies to Merkel Cell Polyomavirus T Antigen Oncoproteins Reflect Tumor Burden in Merkel Cell Carcinoma Patients. Cancer Res. 2010;70(21):8388-8397. doi:10.1158/0008-5472.CAN-10-2128
16. Samimi M, Molet L, Fleury M, et al. Prognostic value of antibodies to Merkel cell polyomavirus T antigens and VP1 protein in patients with Merkel cell carcinoma. Br J Dermatol. 2016;174(4):813-822. doi:10.1111/bjd.14313
17. Marchetti MA, Coit DG, Dusza SW, et al. Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma: A Systematic Review and Meta-analysis. JAMA Dermatol. 2020;156(9):953-962. doi:10.1001/jamadermatol.2020.1731
18. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022;386(1):24-34. doi:10.1056/NEJMoa2109970
19. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23-34. doi:10.1056/NEJMoa1504030
20. Luke JJ. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. 2022;399:12.
21. Bajaj S, Donnelly D, Call M, et al. Melanoma Prognosis: Accuracy of the American Joint Committee on Cancer Staging Manual Eighth Edition. JNCI J Natl Cancer Inst. 2020;112(9):921-928. doi:10.1093/jnci/djaa008
22. Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134. J Clin Oncol. 2021;39(36_suppl):356154-356154. doi:10.1200/JCO.2021.39.36_suppl.356154
23. van Breeschoten J, Wouters MWJM, Hilarius DL, et al. First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAFV600-mutant advanced melanoma patients: a propensity-matched survival analysis. Br J Cancer. 2021;124(7):1222-1230. doi:10.1038/s41416-020-01229-1
24. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med. 2017;376(23):2211-2222. doi:10.1056/NEJMoa1613210
25. Leiter U, Stadler R, Mauch C, et al. Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node. J Clin Oncol Off J Am Soc Clin Oncol. 2019;37(32):3000-3008. doi:10.1200/JCO.18.02306
26. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med. 2016;375(19):1845-1855. doi:10.1056/NEJMoa1611299
27. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018;378(19):1789-1801. doi:10.1056/NEJMoa1802357
28. Ascierto PA, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2020;21(11):1465-1477. doi:10.1016/S1470-2045(20)30494-0
29. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017;377(19):1824-1835. doi:10.1056/NEJMoa1709030
30. Zimmer L, Livingstone E, Hassel JC, et al. Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Lond Engl. 2020;395(10236):1558-1568. doi:10.1016/S0140-6736(20)30417-7
31. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF -Mutated Melanoma. N Engl J Med. 2017;377(19):1813-1823. doi:10.1056/NEJMoa1708539
32. Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2021;27(2):301-309. doi:10.1038/s41591-020-01188-3
33. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655-1661. doi:10.1038/s41591-018-0198-0
34. Stratigos AJ, Sekulic A, Peris K, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):848-857. doi:10.1016/S1470-2045(21)00126-1

Disclosure

None reported.

MM

Bugs, Bumps, and Bacteria: The Role of Virtual Collaborative Learning Network in Pediatric Dermatology

by Kathleen Long, MD, Madison Ortega, Robert Pierce, MD, Paula Arinze, MS, Mimi Propst, MD, Lisa Pierce, MD &, Mirna Becevic, PhD

School of Medicine
University of Missouri

Dermatology ECHO is an "all teach, all learn" platform which serves as a trusted, local dermatology specialist hub that supports PCPs in providing care to patients with cutaneous diseases.



Kathleen Long, MD, is in the Department of Dermatology, University of Missouri-Columbia School of Medicine. Madison Ortega is at the University of Missouri-Columbia. Robert Pierce, MD, and Lisa Pierce, MD are in the Department of Family and Community Medicine, University of Missouri-Columbia. Paula Arinze, MS, MHA, is with the Missouri Telehealth Network, University of Missouri-Columbia. Mimi Propst, MD, is with CoxHealth Skin Care, Springfield, Missouri. Mirna Becevic, PhD, (above), is Assistant Professor and Lead Project Evaluate for the Show-Me ECHO project, University of Missouri - Columbia School of Medicine, Columbia, Missouri.

Abstract

Patients in rural and underserved areas face significant barriers in accessing specialty care due to unavailability of services, geographic isolation, travel burden, and other cultural and socioeconomic factors.[1] Pediatric dermatology is among the top three subspecialties that provides routine care for pediatric patients, however, shortage and maldistribution of pediatric dermatologists have remained a major hurdle for those living in remote and isolated areas.[2] Pediatric dermatologists cluster in urban areas with high-patient volume and estimated wait times for new patients that often exceed 13 weeks, making access one of the major drivers of inequity for rural patients.[2–4]

Show-Me ECHO for Dermatology Extension

Complete inaccessibility of healthcare providers, physical and financial barriers, and insurance coverage are some of the reasons patients delay, miss, or postpone specialty medical appointments.[3] Instead, rurally-located patients rely on community primary care providers (PCPs) to provide pediatric dermatologic care.[4,5] More than 65 percent of patients with dermatological problems seek initial care with their PCP and an estimated 10 to 30 percent of all pediatric outpatient visits in primary care settings include evaluation of one or more skin diseases.[2,6]

Skin conditions, however, can be challenging to diagnose, which often leads to misdiagnosis and incorrect treatment resulting in poor health outcomes and increased costs for patients and healthcare systems.[7] PCPs report lack of training, knowledge, and experience with skin diseases, especially in pediatric patients.[8] Previous studies recommended solutions such as increased mentorship, training, and supervision of advanced non-dermatologist providers to improve access and alleviate some of the issues caused by maldistribution of general and pediatric dermatologists.[9]

The University of Missouri School of Medicine's Department of Dermatology and the Missouri Telehealth Network implemented Dermatology Extension for Community Healthcare Outcomes (ECHO) project in 2015 with the aim of providing telementoring

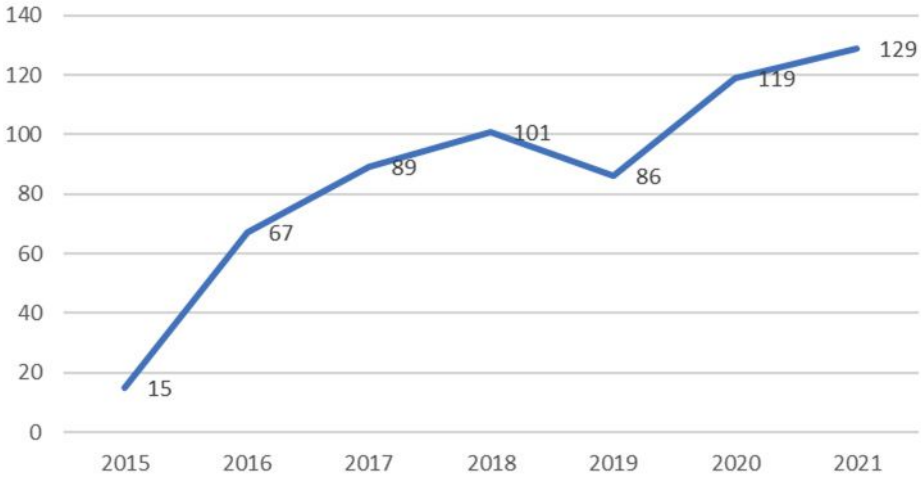


Figure 1: Unique attendees by year

Table 1: Dermatology ECHO pediatric case presentation categories

Diagnostic Categories	Example Diagnoses	Number of Case Presentations
inflammatory/rashes	atopic dermatitis, hypersensitivity reaction, acne vulgaris, granuloma annulare	42
infectious/infestation	scabies, ezcema herpeticum, flat warts	13
neoplastic/lesion	infantile hemangioma, congenital nevus, angiofibroma	27
other	vitiligo, cutis aplasia/nevus, suture reaction	15
Total		97

and education to PCPs across the state. The goal of Dermatology ECHO is to increase the capacity of community providers to diagnose, treat, and manage patients with complex skin conditions.[10] Each ECHO session consists of an expert didactic lecture and one or more real-life de-identified patient cases presented by participating PCPs requiring guidance and mentoring from the Dermatologists ECHO hub team.

A total of 160 ECHO sessions were held from project inception in 2015 until June 18, 2021 with 550 cases reviewed and discussed. Dermatology ECHO has seen a steady increase in participation (Figure 1) and case presentations. A slight decrease in attendance was observed in 2019, when session frequency changed from weekly to bi-weekly in February 2019. As new attendees continue to join, participation increased in 2020 and 2021.

In this case series report we included four pediatric dermatology cases presented by PCPs between November 2015 and June 2021. A total of 97 pediatric

dermatology cases were discussed during this time in four broad categories: inflammation/rashes (n=42), infectious diseases/infestations (n=13), neoplasms/lesions (n=27), and other (n=15) (Table 1).

All Dermatology ECHO cases are de-identified prior to submission for presentation in ECHO session. Data was collected from de-identified case forms submitted by PCPs and recommendation forms submitted by Dermatology ECHO hub team. Video recordings of ECHO sessions were also viewed to verify data quality and completeness.

The aim of this report is to describe characteristics, images and outcomes among pediatric dermatology patients presented in Dermatology ECHO. We will also highlight selected cases and review diagnoses and management strategies as recommended by the ECHO hub team dermatologists.

Case 1: STARI Disease vs. Anthropoid Bite

Erythema migrans (EM), an erythematous annular plaque, is the most common cutaneous feature of Lyme disease, a tickborne infection caused by the spirochete Borrelia burgdorferi.[11] Patients from the southeast and south-central United States may also develop EM-like lesions after tick bites, but testing for B. burgdorferi is negative[12]. These patients are considered to have southern tick-associated rash illness (STARI) or Masters disease, originally described in Missouri.[12] The etiology has not been identified, although the vector is the lone star tick (Amblyomma americanum). STARI presents with a circular erythematous plaque with central clearing. Illness (with symptoms including fever, headache, arthralgias and/or myalgias) tends to be milder with STARI compared to Lyme disease.[12] Treatment with antibiotics (generally doxycycline or amoxicillin) is recommended, which usually results in prompt improvement in symptoms.[13] While Lyme disease is not endemic to Missouri, it is important to consider STARI in a patient who presents with a targetoid rash and possible systemic symptoms, particularly if there is a history of a tick bite. The differential diagnosis of an acute annular plaque includes hypersensitivity reactions to other arthropod bites, which are more likely to have associated pruritus and less likely to exhibit expanding erythema[13]

In 2016, a 7-year-old male presented to his PCP in a rural Missouri county with a one-day history of an eruption on his left forearm (Figure 2). The child did not recall a specific incidence of a bite or sting but the family lives in the country and commonly encounters ticks. The rash was not particularly itchy or tender. In clinic, the child was afebrile and was not in any apparent distress. Examination revealed an approximately 5 cm by 7 cm erythematous patch with a zone of pallor and central punctum. No other lesions were noted by physical exam. The child was started on amoxicillin, 40mg/kg/day to cover for possible STARI. The PCP was a regular participant in Dermatology ECHO and presented this case with the main question for the specialist hub team regarding correct diagnosis.



Figure 2. Erythematous patch with a zone of pallor and central punctum on left arm of a 7-year-old-male.

The Dermatology hub team reviewed the photograph and discussed a differential diagnosis of an urticarial hypersensitivity reaction to an arthropod bite, versus STARI. The hub team specialists agreed that in this case, STARI would be more likely if the erythema expanded over the next several days; however, the presence of a punctum or crust was more suggestive of a hypersensitivity reaction. In addition to continuing the prescribed treatment, they recommended adding symptomatic treatment such as antihistamines for itching, cold packs, anti-inflammatories or topical steroids if needed, and continued monitoring. The child's rash resolved and the patient required no further treatment.

Case 2: Pitted Keratolysis

Pitted keratolysis is a common bacterial skin infection of the stratum corneum most often due to Gram-positive Kytococcus sedentarius, Corynebacterium species, Actinomyces species, or Dermatophilus congolensis.[14,15] It presents with



Figure 3. Pitted keratolysis on the plantar surface of both feet on a 17-year old male high school football player.

discrete, superficial erosions or pits on the plantar feet with associated malodor; maceration and hyperhidrosis are commonly present. Bacterial proteases dissolve the stratum corneum, creating the pits, and produce sulfur-containing compounds, causing the foul smell.[14,15] Risk factors include hyperhidrosis, prolonged wearing of occlusive footwear, humid climates, poor foot hygiene, and immunodeficiency.[14–16] Young adults and adolescents are most often affected, with a male predominance.[14,15] The condition is also more common in athletes.[16]

In 2017, a 17-year-old male high school football player presented to his PCP in a rural Missouri county with a history of foul-smelling pitting on the bottom of his bilateral feet. The patient had used topical antifungals without improvement. On presentation, the physician noted thickened, stippled, malodorous skin over the sole of the foot, with minimal scale and no redness. KOH scraping was negative. A differential diagnosis was considered, including dyshidrosis and pitted keratolysis.

The PCP presented the case to Dermatology ECHO hub team with the main question regarding the correct diagnosis and treatment recommendations. The Dermatology hub team reviewed the photos and history and agreed with the diagnosis of pitted keratolysis (Figure 3). Treatment includes topical antibiotics such as clindamycin, erythromycin or mupirocin one to two times daily. Topical benzoyl peroxide is also an effective treatment, although patients should be warned that it may bleach clothing or linens. Oral antibiotics may be useful in treating recalcitrant disease. It is important to continue treatment until the infection has resolved, which may take several weeks. Continued use of benzoyl peroxide wash can be helpful as a preventive strategy in patients prone to recurrence. In patients with hyperhidrosis, measures such as absorbent socks (changed frequently when damp) and topical aluminum chloride should also be recommended. Patients should also be instructed to wash feet with soap and water at least daily.

The patient was treated with topical erythromycin and benzoyl peroxide, and dryness measures were recommended. Patient required no further treatment.



Figure 4. Scabies erythematous papules on a 12-month-old male.

Case 3: Scabies

Scabies is a highly contagious infestation by the mite Sarcoptes scabiei var hominis, which generally presents with an intensely pruritic rash.[17] Although the worldwide prevalence is estimated to affect 200 to 300 million individuals annually, only 5-10% of these cases are thought to occur in children.[18] The manifestation of scabies in the pediatric population can differ from adults, which can make it difficult to diagnose.[17,19]

In 2020, a 12-month-old male presented to his PCP with a persistent rash on his feet, legs, abdomen, back, arms, and hands that had started eight months prior. The PCP made a provisional diagnosis of atopic dermatitis or arthropod bites. Initial treatment included two doses of prednisolone with temporary improvement, and triamcinolone ointment with partial improvement.

Mother breastfed the child and noted that she developed a similar rash on her abdomen. The father and brother had also experienced a similar intermittent rash. Primary care provider preformed viral and bacterial cultures which were negative. The patient was seen three times by the PCP over the course of eight months without any improvement in the condition.

PCP presented the case to Dermatology ECHO for recommendations regarding diagnosis and treatment. With the aid of images, the Dermatology ECHO hub team diagnosed the child with scabies (Figure 4). In infants and toddlers, scabies will often present on the plantar foot, instep, and the diaper region with erythematous papules and yellow-brown crust. The axillae and diaper region may also have pustular and nodular lesions. In adults, lesions are common in the interdigital spaces, axillae, areolae, flexor wrists, and genitals. To diagnose scabies, it is recommended to perform a mineral oil preparation to look for the scabies mite, ova, or scybala (feces) under the microscope. To achieve a better yield, sample should



Figure 5. Eczema herpeticum cutaneous vesicular eruption on a 4-year-old female.

be obtained from the entire stretch of a linear papule (burrow), often found on the hands or feet.

Treatment with topical permethrin 5% cream was recommended for the entire household, including any asymptomatic members. This should be applied to all regions from the ear lobe down to the toes, including intertriginous areas; it should remain on the skin overnight and then washed off in the morning. Breastfeeding mothers must treat the areolas. One week following, this process should be repeated, for a total of two applications. All household members should be treated on the same night to eradicate all mites. In addition to permethrin treatment, a deep cleaning of the environment, including blankets, pillows, and stuffed animals should occur. It is important to note that the rash may remain for up to four to six weeks after the completion of treatment. Topical steroids and oral antihistamines may be used to treat symptoms.

The child was treated as recommended, and the condition resolved without the need for further care.

Case 4: Eczema Herpeticum

Eczema herpeticum is a disseminated cutaneous infection that presents with eruption of monomorphic, dome-shaped papulovesicles that form punched-out ulcers over previously existing eczematous areas.[20,21] This infection is due to herpes simplex virus, and children with atopic dermatitis have a higher risk of developing eczema herpeticum.[20,21].Early recognition is crucial, as the infection can progress to viremia and secondary septicemia.[3]

In 2019, a 4-year-old female was presented by her PCP to Dermatology hub team with questions regarding diagnosis and management. The patient was seen three times over 12 months by her PCP for a rash located on her arm, face, leg, and trunk region. She was diagnosed with eczema, which had recently started flaring. She was taking cetirizine and hydroxyzine and applying Aquaphor® and triamcinolone 0.1% cream as needed with minimal improvement.

Images submitted for hub team review revealed several monomorphic "punched-out" ulcerations on the child's forearm (Figure 5). The Dermatology ECHO hub team diagnosed the child with eczema herpeticum caused by herpes simplex virus. They recommended swabbing the erosions to confirm the diagnosis and initiating treatment with acyclovir while awaiting results.

Household members of children with atopic dermatitis should be educated to recognize signs and symptoms of eczema herpeticum, including associated fevers or pain with eczema flares, and promptly notify their provider, as this can progress to a life-threatening condition.

The physician returned to the Dermatology hub team three weeks later to report that the child was treated with acyclovir and the rash resolved.

Conclusion

This series highlights the impact clinicians' participation in ECHO can make on their patients' lives. We presented four cases that had considerable impact on patients, as their suffering continued over many months or even years, and included multiple visits and treatments. One child suffered with undiagnosed scabies for several months, an infestation which can cause intense pruritus, disrupt sleep, and spread to other family members. Early identification, aggressive and rapid treatment of scabies provide

relief to patients and help infection control. Eczema herpeticum is an infection which requires timely diagnosis with prompt initiation of antiviral therapy, as it can lead to serious complications and even mortality if left untreated, particularly in infants. The malodor associated with pitted keratolysis has been shown to have significant adverse impact on quality of life, so clinical recognition and appropriate treatment of the condition is key, particularly since effective cures are available.[15] While Lyme disease is unlikely in Missouri, STARI should be considered in patients who present with an erythema migrans-like annular skin lesion, particularly with prior tick exposure and systemic symptoms.

It is estimated that over 40 percent of U.S. population lives in areas without access to dermatology expertise.[22] Dermatologists are not able to meet patient demand due to workforce shortages and can only see one-third of all patients with skin conditions.[22] This means that community PCPs now face increasing responsibilities of diagnosing and treating patients with complex and costly skin conditions. Telehealth technologies have become ubiquitous, and expanded from one-to-one patient care to many-to-many ECHO and ECHO-like models that benefit multiple providers and multiple patients at the same time. Dermatology ECHO is an "all teach, all learn" platform which serves as a trusted, local dermatology specialist hub that supports PCPs in providing care to patients with cutaneous diseases. Mentoring and guidance regarding cases presented in Dermatology ECHO does not only support presenting clinicians and their patients, but all other clinicians in attendance who care for patients with same conditions.

We invite you to consider joining Dermatology ECHO, or an ECHO in an area of interest. We hope that you will gain expertise that will benefit yourself and your patients. Virtual learning networks, such as ECHO, foster knowledge-sharing between specialists and PCPs with the aim of improving patient outcomes.

References

1. Douthit N, Kiv S, Dwolatzky T, Biswas S. Exposing some important barriers to health care access in the rural USA. Public Health. 2015;129(6):611-620. doi:10.1016/j.puhe.2015.04.001
2. Update on the Pediatric Dermatology Workforce Shortage. Accessed April 29, 2022. https://www.mdedge.com/dermatology/article/248300/pediatrics/update-pediatric-dermatology-workforce-shortage
3. N. B, J. N, C. C, J. S, K. P, L.A S. Breaking the Barriers to Specialty Care: Practical Ideas to Improve Health Equity and Reduce Cost. FSG and Bristol-Myers Squibb Foundation.2016 http://www.fsg.org/publications/breaking-barriers-specialty-care.
4. Cyr ME, Etchin AG, Guthrie BJ, Benneyan JC. Access to specialty healthcare in urban versus rural US populations: a systematic literature review. BMC Health Serv Res. 2019;19(1):974. doi:10.1186/s12913-019-4815-5
5. Research Update: Health Care in Rural and Urban America. Center For Children and Families. Published October 20, 2017. Accessed May 3, 2022. https://ccf.georgetown.edu/2017/10/20/research-update-health-care-in-rural-and-urban-america/
6. Rübsam ML, Esch M, Baum E, Bösner S. Diagnosing skin disease in primary care: a qualitative study of GPs' approaches. Fam Pract. 2015;32(5):591-595. doi:10.1093/fampra/cmv056
7. Armstrong K. Common skin problems in the community and primary care. Br J Community Nurs. 2014;19(10):482-488. doi:10.12968/bjcn.2014.19.10.482
8. Le Roux E, Powell K, Banks JP, Ridd MJ. GPs' experiences of diagnosing and managing childhood eczema: A qualitative study in primary care. Br J Gen Pract. 2018;68(667):e73-e80. doi:10.3399/bjgp18X694529
9. Prindaville B, Horii KA, Siegfried EC, Brandling-Bennett H. Pediatric dermatology workforce in the United States. Pediatr Dermatol. 2019;36(1):166-168. doi:10.1111/pde.13684
10. Dermatology ECHO - an innovative solution to address limited access to dermatology expertise. doi:10.3316/informit.138946085298849
11. Cardenas-de la Garza JA, De la Cruz-Valadez E, Ocampo-Candiani J, Welsh O. Clinical spectrum of Lyme disease. Eur J Clin Microbiol Infect Dis. 2019;38(2):201-208. doi:10.1007/s10096-018-3417-1
12. Feder HM, Hoss DM, Zemel L, Telford SR, Dias F, Wormser GP. Southern Tick-Associated Rash Illness (STARI) in the North: STARI following a tick bite in Long Island, New York. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011;53(10):e142-146. doi:10.1093/cid/cir553
13. Masters EJ, Grigery CN, Masters RW. STARI, or Masters disease: Lone Star tick-vectored Lyme-like illness. Infect Dis Clin North Am. 2008;22(2):361-376, viii. doi:10.1016/j.idc.2007.12.010
14. Leung AKC, Barankin B. Pitted Keratolysis. J Pediatr. 2015;167(5):1165. doi:10.1016/j.jpeds.2015.07.056
15. Bunyaratavej S, Leeyaphan C, Chanyachailert P, Pattanaprichakul P, Ongsri P, Kulthanan K. Clinical manifestations, risk factors and quality of life in patients with pitted keratolysis: a cross-sectional study in cadets. Br J Dermatol. 2018;179(5):1220-1221. doi:10.1111/bjd.16923
16. Bristow IR, Lee YLH. Pitted keratolysis: a clinical review. J Am Podiatr Med Assoc. 2014;104(2):177-182. doi:10.7547/0003-0538-104.2.177
17. Thompson R, Westbury S, Slape D. Paediatrics: how to manage scabies. Drugs Context. 2021;10:2020-12-13. doi:10.7573/dic.2020-12-3
18. Leung AKC, Lam JM, Leong KF. Scabies: A Neglected Global Disease. Curr Pediatr Rev. 2020;16(1):33-42. doi:10.2174/1573396315666190717114131
19. Karthikeyan K. Scabies in children. Arch Dis Child Educ Pract Ed. 2007;92(3):ep65-69. doi:10.1136/adc.2005.073825
20..Xiao A, Tsuchiya A. Eczema Herpeticum. In: StatPearls. StatPearls Publishing; 2022. Accessed May 3, 2022. http://www.ncbi.nlm.nih.gov/books/NBK560781/
21. Liaw FY, Huang CF, Hsueh JT, Chiang CP. Eczema herpeticum: a medical emergency. Can Fam Physician Med Fam Can. 2012;58(12):1358-1361.
22. http://fyra.io. Primary Care Providers as Allies in Dermatology. Practical Dermatology. Accessed March 30, 2021. https://practicaldermatology.com/articles/2015-sep/primary-care-providers-as-allies-in-dermatology

Disclosure

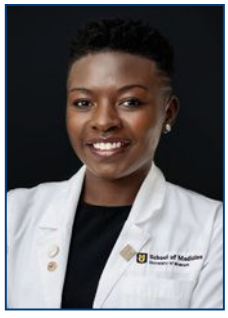
None reported. **MM**

Diversity, Equity, and Inclusion Efforts at MU SOM and the Department of Dermatology

by Lydiah Fridah Mpyisi, MS, Kathleen Ann Long, MD & Nkanyezi Ferguson, MD

School of Medicine
University of Missouri

More diverse healthcare teams have been associated with reduced racial health disparities, improved patient outcomes and satisfaction, and better team communication, risk assessment, and clinical decision-making.



Lydiah Fridah Mpyisi, MS, (above), is a medical student at the University of Missouri-Columbia School of Medicine. Kathleen Ann Long, MD, and Nkanyezi Ferguson, MD, are in the Department of Dermatology, University of Missouri-Columbia School of Medicine, Columbia, Missouri.

Introduction

To address health care inequities and improve patient outcomes, especially in populations that are underrepresented in medicine, intentional and simultaneous efforts are needed by the medical community at the individual, local, regional, and national level. Reevaluating and innovating our strategies toward medical education and patient care is essential to produce impactful and sustainable results. Targeted efforts to integrate diversity, equity, and inclusion (DEI) initiatives are important in order to ensure comprehensive medical education and patient access to high quality equitable healthcare. This can be done through addressing cultural bias in medicine, diversifying the healthcare workforce, mentorship, incorporating diverse patient populations in medical education and creating awareness of microaggression, implicit bias and social determinants of health.

A lack of diversity, equity, and inclusion in medicine poses a major hurdle to delivering equitable healthcare services, especially to underrepresented communities. This is underscored by the fact that when compared to whites, racial and ethnic minority groups consistently experience higher rates of morbidity and mortality across most medical specialties, even when accounting for factors that contribute to health disparities.[1] In dermatology, Hispanic and Black patients are less likely to receive outpatient dermatologic care compared to non-Hispanic white patients, as are less-educated, lower-income, publicly insured and uninsured Americans.[2] Although the U.S. population continues to grow more diverse, Black and Hispanic dermatologists are significantly underrepresented; Black and Hispanic dermatologists make up only 3% and 4.2% of all dermatologists respectively, compared with 12.8% Black and 16.3% Hispanic in the general U.S. population.[3] Subsequently, dermatology is recognized as the second least diverse medical specialty which underscores the critical need for DEI efforts in dermatology. Dermatologic organizations have been working nationally to prioritize workforce diversification, DEI education, mentorship, and research efforts to improve access and quality of dermatologic care.[4]

In healthcare education, studies have shown that students educated in diverse learning environments demonstrate broadened perspectives of race, religion, ethnicity, and cultural diversity; they also report improved learning outcomes including active thinking, empathy, intellectual engagement, and motivation.[5] In addition, prioritizing diversity and inclusion has been shown to result in improved communication, decision-making, adherence to care plans, and problem-solving for complex medical issues.[6,7] More diverse healthcare teams have been associated with reduced racial health disparities, improved patient outcomes and satisfaction, and better team communication, risk assessment, and clinical decision-making.[8] With a vision to become "the premier and transformational academic health system for Missouri," the University of Missouri School of Medicine (MU SOM) strives to save and improve lives through exemplary education, research, and patient care. Working toward this goal, the academic health system has incorporated diversity, equity, and inclusion as one of its core values. In this article, we highlight system-wide initiatives to help improve diversity, equity, and inclusion at MU SOM and in the Department of Dermatology.

DEI Efforts Underway at MU SOM

MU SOM is committed to fostering a diverse and inclusive environment. Each department has a Diversity Ambassador to build a culture of collaboration and help ensure the success of each unit's efforts. The Diversity Ambassadors are encouraged to exchange ideas and share initiatives among departments to reproduce and collaborate on effective strategies.

The Addressing and Reducing Cultural Bias in Medicine curriculum is offered to faculty with the goal to develop a more capable faculty workforce with the ability to manage discussions surrounding race and discrimination, including their role in healthcare. Topics include the historical context of race, cultural self-awareness, privilege, implicit bias, microaggressions, and intersectionality.

Amongst the student body, third- and fourth-year medical students who have demonstrated commitment to advancing diversity, equity, and inclusion are selected to become Student Diversity Ambassadors. They work under the guidance of the Office of Diversity and Inclusion, serving as liaisons between the student body and assisting with centralizing student organization DEI efforts.

The MU SOM Visiting Student Diversity Program provides an opportunity for fourth-year medical students from other institutions to complete an elective rotation with the University of Missouri School of Medicine. The Department of Dermatology and eleven other participating departments highly encourage students in groups underrepresented in medicine to apply for this program, which includes a housing stipend to support the student during their time participating in clinical and educational activities, conferences, and mentorship opportunities. There are several other pipeline programs developed for students underrepresented in medicine, first generation college students, socio-economically disadvantaged students, nontraditional students and those from rural areas, including Med Prep Series, Pathways to Success Pre-Admission Program, Bryant Scholars, Medical Explorations, Excellence in Learning, and the Summer Research Internship.

The Office of Admissions established the Inclusivity Symposium to highlight the school's commitment to improving inclusion, diversity, and equity. These symposia are held during the interview season for interviewees to directly experience the culture and community of inclusive excellence. Students often enthusiastically volunteer to partake in such activities and are encouraged to give suggestions on how DEI initiatives can be improved.

As a health system, MU SOM was chosen as one of 11 schools to participate in the Anti-Racist Transformation in Medical Education project, a three-year program that develops an institution's capacity to implement the multi-phased change management strategy of Icahn SOM Mt. Sinai. Goals include building the capacity of institutions to dismantle systemic racism and bias in work and learning environments and promoting shared learning on how to dismantle racism in medical schools.[9]

Among many other initiatives, the Dean for Diversity and Inclusion offers lectures and workshops on microaggression, implicit bias, and social determinants of health. During such lectures,

students are encouraged to participate in small group activities to engage in respectful discussions and nurture enthusiasm for improving diversity, equity, and inclusion.

DEI Efforts Underway in the Department of Dermatology

Missouri is an incredibly diverse state, and as the Department of Dermatology of the University of Missouri, our program is committed to training Dermatologists who can care for all Missourians. The department and its training programs have long prioritized improving dermatologic care for underserved Missourians. This necessitates training a diverse group of young physicians from a variety of backgrounds utilizing the broad patient population who accesses our health system. For a number of years we have implemented a holistic review of residency applications, considering all aspects of the applicant including academic evaluations, attributes, and experiences and how they align with the mission of the department and SOM. This approach helps to reduce systemic bias, with the goal of selecting an exceptional and well-rounded group of future dermatologists who will contribute to learning, teaching, and the practice of medicine.[9,10]

Representatives from the department usually attend regional and national meetings organized by the Student National Medical Association (SNMA) - an independent, student-run organization focused on the needs and concerns of underrepresented in medicine (URiM) medical students in the United States. These meetings serve as opportunities to create awareness about the dermatology program at MU SOM and recruit top talents from diverse backgrounds to apply to our program.

To ensure comprehensive dermatological education of trainees, dermatology faculty have increased the representation of cutaneous pathology in the skin of color in all lectures to show the diverse presentations of cutaneous manifestations of different diseases. The J. Otto Lottes Health Sciences Library strives to offer books like Taylor and Kelly's *Dermatology for Skin of Color* to familiarize students with the presentation of various dermatologic disorders in different skin colors. The Deparment of Dermatology also offers grand rounds and department didactics on a variety of topics related to DEI. Dermatology faculty participate in mentorship and shadowing programs, including the MU SOM Pathways to Success Pre-Admission Program for undergraduate students and the National Medical Association Dermatology Mentorship program for medical students interested in dermatology. Dermatology residents and faculty help organize and staff a monthly specialty night at MedZou Community Health Clinic, which provides free medical services to uninsured residents of central Missouri. This helps reduce disparities and increase access to dermatologic care for diagnosis and treatment of cutaneous conditions in underserved populations. Within the Dermatology Department, a new skin of color clinic has been created as of October 2022 with the goal of offering specialized services for patients of color (defined as skin types IV-VI in the Fitzpatrick Skin Type Classification) to further address medical, surgical, and cosmetic concerns unique to this patient demographic.

DEI Efforts Underway in Dermatology Nationally

At the national level, there are increasing efforts by U.S. dermatologic societies to partake in DEI initiatives with a goal to create a healthcare landscape that is reflective of the population of patients needing dermatologic care. Dermatologic organizations have been working to prioritize DEI education, mentorship, and research efforts such as the Annual Skin of Color Society Scientific Symposium, Diversity Champion Workshop, numerous mentorship programs, and lecture series and curriculum modules with emphasis on skin of color, healthcare disparities, and implicit bias.[4] The American Academy of Dermatology (AAD) has a well-established AAD Diversity Committee, which created a three-year (2021 – 2023) DEI plan, to help foster diversity in dermatology and increase the availability of dermatological services to under-served populations.[11]

To affirm its commitment to eliminating health inequities and increasing access to dermatological care, in 2021 the AAD published a formal "Position Statement on Dermatology Workforce Diversity and Health Disparities."[12] In this position statement, the AAD acknowledges the need to increase awareness of health disparities and social determinants of

health among physicians. The statement further affirms the following: 1) supporting policies that allow Fellows of the American Academy of Dermatology (FAAD) to deliver care to all patients with dermatologic conditions that need care; 2) developing and increasing research of dermatologic conditions that occur disproportionately in racially and ethnically diverse groups; 3) supporting the promotion of leadership and faculty development of dermatologists from ethnic and racial groups that are underrepresented among physicians in dermatology; and 4) supporting policies that address systemic and institutional inequities outside of health care that lead to poor health outcomes.[12]

Effective collaboration is a key feature of inclusive leadership.[13] In recognition for the need of effective collaboration to enhance DEI initiatives, the AAD established an Intersociety Diversity Task Force (IDTF) to "support the goals and facilitate awareness, communication, and implementation of the AAD DEI initiatives." The IDTF includes the dermatologic societies AAD, Association of Professors of Dermatology, Skin of Color Society, Society of Investigative Dermatology, Women's Dermatology Society, National Medical Association Dermatology Section, and American Society of Dermatologic Surgeons. The IDTF has also collaborated with the National Hispanic Association, and the program, Nth Dimensions—a pipeline program for women and minorities seeking to match in competitive medical specialties. The program hosts BioSkills workshops at Historically Black Colleges and Universities in an "effort to offer URiM students early exposure opportunities to learn basic dermatologic procedures."[14]

Conclusion

MU SOM and the Department of Dermatology are committed to leading the efforts to improve patient health and quality of care by promoting diversity, equity, and inclusion in the medical school and residency program. The DEI initiatives implemented thus far range from small group discussions in classes, to department-wide efforts, and to recruitment and retention of top talent across the academic health system. With dermatology being the second least diverse medical specialty after orthopedic surgery,[15] we hope that the efforts of the Department of Dermatology at MU SOM will help bridge this gap in order to provide quality, compassionate and comprehensive care to all patients.

References

1. Institute of Medicine (US) Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care, Smedley BD, Stith AY, Nelson AR, eds. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington (DC): National Academies Press (US); 2003.
2. Tripathi R, Knusel KD, Ezaldein HH, Scott JF, Bordeaux JS. Association of Demographic and Socioeconomic Characteristics With Differences in Use of Outpatient Dermatology Services in the United States. JAMA Dermatol. 2018;154(11):1286-1291. doi:10.1001/jamadermatol.2018.3114
3. Pandya AG, Alexis AF, Berger TG, Wintroub BU. Increasing racial and ethnic diversity in dermatology: A call to action. J Am Acad Dermatol. 2016;74(3):584-587. doi:10.1016/j.jaad.2015.10.044
4. Desai SR, Khanna R, Glass D, et al. Embracing diversity in dermatology: Creation of a culture of equity and inclusion in dermatology. Int J Womens Dermatol. 2021;7(4):378-382. Published 2021 Aug 5. doi:10.1016/j.ijwd.2021.08.002
5. Gurin P, Dey EL, et al. Diversity and higher education: theory and impact on educational outcomes. Harvard Educ Rev. 2002;72:330–336.
6. Simms C. Voice: the importance of diversity in healthcare. Int J Clin Pract. 2013;67:394–396.
7. Rosenkranz KM, Arora TK, Termuhlen PM, et al. Diversity, Equity and Inclusion in Medicine: Why It Matters and How do We Achieve It?. J Surg Educ. 2021;78(4):1058-1065. doi:10.1016/j.jsurg.2020.11.013
8. Gomez LE, Bernet P. Diversity improves performance and outcomes. J Natl Med Assoc. 2019;111(4):383-392. doi:10.1016/j.jnma.2019.01.006
9. Luke J, Cornelius L, Lim HW. Dermatology resident selection: Shifting toward holistic review?. J Am Acad Dermatol. 2021;84(4):1208-1209. doi:10.1016/j.jaad.2020.11.025
10. Chen A, Shinkai K. Rethinking How We Select Dermatology Applicants-Turning the Tide. JAMA Dermatol. 2017;153(3):259-260. doi:10.1001/jamadermatol.2016.4683
11. Stategic Plan. American Academy of Dermatology. Accessed October 11, 2022. https://www.aad.org/member/membership/governance/strategic
12. Position Statement on Dermatology Workforce Diversity and Health Disparities. American Academy of Dermatology Association. November 6, 2021
13. Bourke J, Espedido A. 2019. Why inclusive leaders are good for organizations, and how to become one. Harvard Business Review, 29 (2019). Accessed October 11th, 2022. https://hbr.org/2019/03/why-inclusive-leaders-are-good-for-organizations-and-how-to-become-one
14. Munjal A, Ferguson NN. Diversity, Equity, and Inclusion Initiatives in Dermatology Organizations.
15. Akhiyat S, Cardwell L, Sokumbi O. Why dermatology is the second least diverse specialty in medicine: How did we get here? Clin Dermatol. 2020 May-Jun;38(3):310-315. doi: 10.1016/j.clindermatol.2020.02.005. Epub 2020 Feb 19. PMID: 32563342.

Disclosure

None reported. **MM**

Complementary and Alternative Medicine Approaches in Alzheimer Disease and Other Neurocognitive Disorders

by David Q. Beversdorf, MD, Haley W. Crosby & Joel I. Shenker, MD, PhD

School of Medicine
University of Missouri

A discussion of complementary and alternative treatments regarding dementia should emphasize that there is likely a vastly greater preventative role rather than a way to treat extant neurocognitive impairment.



David Q. Beversdorf, MD, (above), is in the Departments of Neurology, Radiology, and Psychological Sciences, and is the William and Nancy Thompson Endowed Chair in Radiology. **Haley W. Crosby** is a fourth-year medical student at the School of Medicine. **Joel I. Shenker, MD, PhD,** is in the Department of Neurology. All are at University of Missouri-Columbia School of Medicine, Columbia, Missouri.

Abstract

As our population ages, there is interest in delaying or intervening in cognitive decline. While newer agents are under development, agents in mainstream use do not impact the course of diseases that cause cognitive decline. This increases interest in alternative strategies. Even as we welcome possible new disease-modifying agents, they are likely to remain costly. Herein, we review the evidence behind other complementary and alternative strategies for cognitive enhancement and prevention of cognitive decline.

Background

Dementia from Alzheimer disease (AD) and other causes has a major impact on patients and their families, resulting in a loss of quality of life for the patient, and at times devastating the lives of families and others that care for patients. Current approved therapies offer limited help, such as AD treatments, cholinesterase inhibitors, and NMDA antagonists. These agents have some impact on functional ability, but do not impact disease trajectory. Newer approaches target pathogenesis of diseases such as AD, but decades of work along these lines have struggled to yield definitive clinical results for any agent. Therefore, families, desperate for other options, often ask about complementary and alternative treatment approaches. Herein, we review evidence for such approaches.

Alternative Approaches for Treatment

Any discussion of this type should consider prevention. Substantial evidence supports strategies that might prevent dementia. A recent report by the Lancet Commission,[1] identified a 12 factor life-course model for modifiable factors that may affect dementia outcomes. In this study, less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, infrequent social contact, excessive alcohol consumption, head injury, and air pollution exposure collectively contributed about 40% risk for dementia. Referring to ways to promote good cognitive outcomes, an extensive review of "successful aging" strategies[2] supported regular physical activity, treatment of cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, obesity, metabolic syndrome), cognitively stimulating activities, social engagement,

a heart healthy diet, smoking cessation, managing stress and depression, getting adequate sleep, avoiding anticholinergics, assessing sensory deficits, limiting alcohol use, and avoiding physical and toxin-related brain damage. A very recent study also showed that greater adherence to Healthy Lifestyle Factors (no current smoking, moderate alcohol consumption, regular physical activity, healthy diet, adequate sleep, less sedentary behavior, and frequent social contact) is associated with decreased incidence of dementia in patients with type 2 diabetes.[3] However, in the case of AD dementia, when it is already in place, the most consistent data argue that outcomes are most affected by a more narrow set of risk factors, including malnutrition, genetic variants, altered gene regulation, baseline cognitive level, neuropsychiatric symptoms, and extrapyramidal signs.[4] Therefore, a discussion of complementary and alternative treatments regarding dementia should emphasize that there is likely a vastly greater preventative role rather than a way to treat extant neurocognitive impairment.

Dietary Interventions

One of the most consistent findings in complementary and alternative approaches to dementia has been decreased risk of Alzheimer disease dementia or neurocognitive decline more generally in people who follow a "Mediterranean diet."[5-8] This type of diet consists of high intake of vegetables, legumes, fruits, nuts, cereals, and unsaturated fatty acids (mostly olive oil), moderate to high fish intake, low to moderate intake of dairy, low intake of meat and saturated fatty acids, and regular but limited alcohol use.[8] The Mediterranean diet has been found to be associated with less accumulation of cerebral beta-amyloid, an AD biomarker, in the Australian Imaging, Biomarkers, and Lifestyle Study of Ageing[9] and in a study based at New York University School of Medicine/Weill Cornell Medical College,[10] and mitigated decreases in total brain volume over three years from age 73 to 76 in a Scottish cohort.[11] When the Mediterranean is blended with the "DASH" (Dietary Approaches to Stop Hypertension) diet, the resultant catchy-named MIND (Mediterranean – DASH Intervention for Neurodegenerative Delay) diet is associated with less emergence of dementia.[12-13] The MIND diet modifies the Mediterranean diet by allocating separate categories for green leafy vegetables and berries, fruit is not included, and fish consumption is reduced from daily to two to three times a week.[14] One study suggested similar future cognitive benefits from either MIND or Mediterranean diets,[15] while a more recent study suggested the 12-year risk of cognitive decline was better for the MIND diet than the Mediterranean diet.[14] Trials of the Mediterranean diet with additional olive oil or nuts had better cognitive results in patients with cardiovascular risk.[16] Clear evidence of the benefits of dietary interventions in patients with existing cognitive decline is lacking: whereas one pilot study found a beneficial effect of a coconut oil enriched Mediterranean diet on cognitive performance in people already diagnosed with AD,[17] a large Swedish population-based study did not find a protective effect from a Mediterranean diet.[18] As for other dietary regimens, a decreased risk of incident dementia has been found to correlate with a greater adherence to a Japanese diet.[19] Elsewhere, adherence to a healthy diet as assessed by a modified version of the Alternative Healthy Eating Index was associated with a decreased risk of a three or more point decline in the Mini-Mental State Examination Score.[20] Further, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study found that among 1,260 healthy older adults there was a significantly positive association between adherence to a healthy diet on global cognition and executive function.[21]

One dietary intervention with intriguing recent support is a ketogenic diet. This diet allows the brain to use ketones to switch away from obligatory processing of glucose. One small study showed AD patients had improvement in daily function and quality of life with a ketogenic diet.[22] Another study, using randomized assignments of a ketogenic drink, found that improved brain energy was associated with cognitive improvements in patients with mild cognitive impairment (MCI) from AD.[23] Yet another study suggested benefit for memory from a modified Atkins diet for early AD dementia and MCI patients.[24] A medium-chain triglyceride-based ketogenic formula was also found to be beneficial for cognition in patients with mild-to-moderate AD.[25]

Finally, diets emphasizing specific types of food have received attention. Consumption of green leafy vegetables has been associated with decreased cognitive decline with aging in the Memory and Aging Project[26] and also a decreased risk of developing all-cause MCI was found in the China Longitudinal Aging Study.[27]

Diets rich in fruits and vegetables also resulted in better cognitive performance in older adults in a large European study,[28] as well as in a study in the United States,[29] further supported by a meta-analysis,[30] and for subjective cognition as well.[31] Diets rich in citrus have also been associated with decreased risk of all-cause dementia in a Japanese cohort study.[32] Diets including a specific fibre supplementation targeting the microbiome has also been associated with improved cognitive performance in healthy adults.[33]

Specific Dietary Components

Numerous lines of evidence have argued that docosahexaenoic acid (DHA) and omega-3 fatty acids have a protective effect for dementia.[34] Red blood cell DHA was associated with decreased risk of both AD dementia and all-cause dementia in the Framingham offspring study.[35] A trial of polyunsaturated fatty acids in patients with AD showed a better profile of neurodegenerative markers (neurofilament light (NfL) and chitinase-2-like protein 1 (YKE-40)) in the treated group as compared to the untreated group.[36] The combination of omega-3 fatty acid and alpha lipoic acid was found to slow functional decline in AD in a small randomized trial.[37] Additionally, DHA intake was associated with decreased structural changes on brain imaging in cognitively unimpaired individuals with two copies of the high AD risk APOE ε4 allele[38]. The protective effect of omega-3 fatty acids against development of AD dementia among those at greatest genetic risk is further supported by protection of memory function and lowered amyloid burden among the high risk APOE ε4 carriers,[39] and decreased risk of cognitive decline in multiple domains was found with one meal per week of seafood and long chain n-3 fatty acids in APOE ε4 carriers.[40] A measure of "fluid intelligence" was found to be associated with greater alpha-linolenic acid, stearidonic acid, and eicosatrienoic acid among omega-3 fatty acids in a population of healthy aging individuals,[41] and higher alpha-linolenic acid intake was associated with slower cognitive decline in global cognition and memory in middle and older age individuals in the Doetinchem Cohort Study.[42] However, in a clinical trial in diagnostically diverse sample of non-demented patients who already had memory complaints, neither omega-3 fatty acids nor a multidomain intervention, nor their combination, impacted cognitive function followed over a three-year epoch.[43] Additionally, an earlier randomized, placebo-controlled trial of high dose omega-3 fatty acids including DHA did not show benefit in patients with Alzheimer disease[44]. Despite the negative studies in trials of patients with active cognitive decline, reviews suggest that supplementation in APOE ε4 carriers might be promising for prevention.[45] Other 'healthier' fatty acids also have suggested benefits that may be relevant for dementia. Higher olive oil intake has also been associated with decreased risk of death associated with neurodegenerative diseases in the Nurses Health Study,[46] and in a randomized prospective trial with MCI patients, high phenolic early harvest extra virgin olive oil resulted in better cognitive outcomes than seen with other dietary interventions.[47] Virgin olive oil has also been shown to benefit cognition in a randomized trial in healthy older adults in primary care centers at the University of Navarra.[48]

Increased consumption of dietary flavonoids have also been associated with decreased risk of cognitive decline[49] as well as subjective cognitive decline in the Nurses Health Study,[50] and is associated with a decreased risk of AD in the Rush Memory and Aging Project[51] as well as the Framingham Offspring Cohort[52] and the French Three-City (3C) Study cohort.[53] Consumption of cocoa-based flavanols was associated with better performance on hippocampal-dependent list-learning in a trail of healthy aging adults.[54] Consumption of blueberries in individuals with subjective cognitive impairment in midlife has been associated with an increased lexical access and decreased memory interference as well as decreased self-reported encoding difficulties in daily activities.[55] Blueberry intake was also found to alter circulating phenolic compounds and improve aspects of cognition on healthy older adults.[56-57] Increased neuronal activation was also observed with blueberries in MCI patients.[58] Such improvement with blueberries is supported in systematic reviews, but a conclusion was limited by methodological heterogeneity.[59] Consumption of cranberries for 12 weeks was also found to improve episodic memory and regional perfusion in the brain.[60] Concord grape juice was also found to improve memory in MCI patients.[61] Montmorency tart cherry juice was found to improve memory in a randomized controlled trial of older adults with normal cognitive function.[62] One postmortem study of a large population suggested that strawberry and pelargonidin intake was associated with fewer phosphorylated tau tangles.[63] A meta-analysis of the cognitive benefits for polyphenols, though, supported only a tentative positive effect, a finding also

limited by methodological heterogeneity.[64] Citrus consumption has also been associated with decreased risk of developing all-cause dementia in the Ohsaki Cohort Study.[32]

Coffee and tea might also have neuroprotective effects. Higher coffee consumption was found to be associated with slower cognitive decline and decreased amyloid beta accumulation in a population of healthy older adults in Australia.[65] A significant decrease in risk for dementia was also observed among those consuming two to three cups of coffee or two to three cups of tea in the UK Biobank cohort study.[66] Another meta-analysis argued that the risk of cognitive disorders was lowest with the daily consumption of one to two cups of coffee daily, compared to no coffee drinking or more than three cups a day.[67] Data from the Women's Health Initiative Memory Study showed that caffeine intake was associated with a lower risk of cognitive impairment.[68] Regular tea consumption was also found to be associated with decreased risk of neurocognitive disorders among Chinese elderly in the Singapore Longitudinal Aging Study.[69] Tea consumption was also associated with better performance in attention and psychomotor speed in the Newcastle 85+ longitudinal study.[70] Green tea consumption has also been associated with significantly decreased risk of all-cause dementia in the Ohsaki Cohort Study,[71] and associated with decreased AD biomarkers in healthy older adults in the Chinese Alzheimer's Biomarker and LifestylE (CABLE) study.[72] Chocolate has also been associated with better overall cognitive function in a community based sample in the Maine-Syracuse Longitudinal Study.[73] Decreased risk of developing all-cause MCI has also been associated with greater consumption of mushrooms,[74] and a decreased risk of developing all-cause dementia has also been associated with mushroom consumption.[75] An 18-month double-blind, placebo-controlled trial of curcumin was found to result in improved memory and attention as well as decreased amyloid and tau accumulation on PET in non-demented adults.[76] A large study of community-dwelling elders in Korea found that lifetime consumption of ginseng was associated with better cognitive function.[77]

Additionally, avoiding ultraprocessed foods appears to be protective against risk of all-cause dementia,[78] and greater consumption of ultraprocessed foods is associated with greater cognitive decline in a large community sample from six Brazilian cities.[79] A higher dietary inflammatory index was also found to be associated with MRI markers of brain aging in the Framingham Heart Study Offspring Cohort.[80]

Potential Impact of Individual Agents

Dietary interventions involve a large number of individual nutrients. Additionally, individual food items also involve a large number of individual nutrients. Therefore, dietary advice may involve synergistic effects of individual nutrients. Nonetheless, there is evidence specific to individual nutrients as well. Resveratrol was found to preserve hippocampal volume, improve hippocampal connectivity, but without differential effects on memory, in a randomized controlled trial in MCI patients,[81] and improved memory performance, hippocampal connectivity, and glucose metabolism in healthy older adults.[82] Oroxylum indicum extract, a traditional Ayurvedic medicine, was found to increase episodic memory among older adults with cognitive complaints in a double-blind, placebo-controlled, randomized trial.[83] Decreased zinc levels have also been associated with greater amyloid PET deposition in cognitively normal older adults in study in Korea.[84] Animal model evidence also suggests potential dementia-associated neuroprotection for some specific nutrients: astaxanthins, derived from marine mircoorganisms;[85] centella asiatica, an herb used in Ayurvedic and traditional Chinese medicine;[86] epigallocatechin-gallate (EGCG), a polyphenol found in green tea;[87-88] quercetin, a bioflavonoid common in fruits and vegetables;[89] yokukansan, a traditional Japanese herbal medicine;[90] N-acetylcysteine, a widely used antioxidant;[91] berberine, a protoberberine alkaloid used in Chinese medicine;[92] dietary supplementation with walnuts[93]; β-lactolin, a whey-derived lacto-tetrapeptide;[94] royal jelly, a secretion of honeybee hypopharyngeal and mandibular glands;[95] and boldine, an alkaloid derived from the bark and leaves of the Chilean tree Peumus boldus.[96] There is also growing evidence in support of curcumin, also known as turmeric, a spice also used as a remedy in India and China.[97] Electroacupuncture was also found to impact cognition by regulating tau phosphorylation in an AD mouse model.[98] Intermittent fasting has been shown to alleviate the increase of lipoprotein lipase in the brains of an AD model of mice.[99] Resveratrol, the polyphenol found in red wine and other fruit sources, was found to reverse cognitive disturbances induced by a high fat diet in aged mice,[100] and also reverses the effects of cholesterol and isoprenoid-mediated amyloidogenic

processing in AD mouse models.[101]

A study using data from the National Health and Nutrition Examination Surveys exploring the effects of serum antioxidants and carotenoids found that incidence all-cause dementia was inversely associated with serum lutein+zeaxanthin and β-cryptoxanthin levels.[102] Examination of this dataset also demonstrated better cognitive performance with higher dietary intake of B_9 and B_{12}.[103] A randomized controlled trial of B vitamins to lower homocysteine was found to slow the rate of brain atrophy in MCI patient in a recent study.[104] Others have reported that elevated homocysteine levels are associated with an increased incidence of all-cause dementia[105], and in the Czech Brain Aging Study are also associated with worsened memory performance in older adults with subjective cognitive decline or amnestic MCI.[106] In yet another study of Korean patients with and without cognitive impairment, a putative protective effect of folate was found.[107] A meta-analysis also has concluded that B vitamin supplementation may play a preventative role in cognitive decline in older adults,[108] and similarly for homocysteine and folic acid.[109] Greater vitamin C levels have been associated with better cognitive function,[110] with similar findings in the Boston Puerto Rican Health Study for vitamin B-6.[111] A meta-analysis has continued to support the association between vitamin E levels and risk of developing dementia,[112] but long double-blind randomized clinical trials did not show benefit for prevention of AD from vitamin E,[113] while others did report benefit over two years.[114] Additionally, serum 25-hydroxyvitamin D concentrations were inversely associated with risk of dementia among individuals with type 2 diabetes in the UK Biobank[115] as well as in the Washington Heights-Inwood Columbia Aging Project.[116] Serum vitamin D levels were also associated with cognitive function in a community sample of older adults in the Cooper Center Longitudinal Study.[117] Genetically decreased vitamin D has also been associated with AD risk.[118] Furthermore one study did suggest better cognition and Alzheimer biomarker profile among AD patients in a randomized double-blind placebo-controlled trial of vitamin D.[119] However, one 18-year follow-up study in community living older males in Sweden found no association with vitamin D levels and incident dementia or cognitive impairment.[120] In a randomized single-blinded placebo controlled trial of patients with symptomatic AD, cognitive outcomes were better in individuals who got folic acid and vitamin B12.[121] One study suggested improvement in cognition and blood-based amyloid-beta related biomarkers with folate in a randomized controlled trial using MCI patients.[122] The Cochrane Database of Systematic Reviews, though, concluded that evidence in support of vitamin or mineral supplementation was insufficient to conclude a meaningful effect for preventing decline[123] or for intervening once people have MCI.[124] Better outcomes were reported for Salvia officinalis extract, derived from sage, in double blind placebo controlled trials in mild to moderate AD patients.[125-126]

Non-Nutrient Approaches

In addition to nutrient- based approaches, research has addressed other nonpharmacological interventions. Acupuncture was associated with decreased risk of dementia in migraine patients in a population study in Taiwan.[127] An overview of systematic reviews suggested that support for the idea that acupuncture may be helpful in AD has been limited by the low quality of studies available.[128] Yoga decreased gray matter atrophy in women at risk for AD in a randomized controlled trial.[129] Tai chi was associated with improved memory as well as hippocampal structure and function in a cross sectional study of the elderly,[130] and a trial of tai chi suggested benefits on cognition and activities of daily living in community dwelling MCI patients.[131] Musical literacy was associated with a lower incidence of all-cause dementia in a Brazilian population.[132] An 18-month meditation intervention study in healthy older adults revealed better performance on attention regulation but no effect on brain volume or perfusion in target areas.[133] Postponing retirement was associated with decreased risk of dementia in a large population in the U.S. Health and Retirement Study.[134] Cognitively engaging activity was associated with greater cortical and subcortical volumes in older adults,[135] and playing analog games was associated with better cognitive performance with aging in a large study of community-dwelling individuals in Scotland.[136] Integrated cognitive and physical fitness training, implemented by using a closed-loop, motion-capture video game, also improves attentional abilities in healthy older adults.[137] A recent review and meta-analysis showed that leisure activities involving physical, social, and cognitive activity were associated with a decreased risk of dementia.[138] One recent study also showed that greater physical activity was associated with decreased progression plasma neurofilament light chain in an

observational study of patients who are carriers for autosomal dominant frontotemporal dementia.[139] Additionally, one population study in Finland found that greater use of sauna bathing was associated with a lower risk of dementia[140] and also in the Kuopio Ischaemic Heart Disease cohort study.[141] 'Positive age beliefs,' or positive perceptions about various aspects of old age, were associated with decreased risk of dementia in patients at high risk for AD due to presence of the APOE ε4 allele, possibly because these beliefs helped reduce stress.[142] Neighborhood greenness was associated with decreased risk of dementia in a large population of U.S. Medicare Beneficiaries.[143] Neighborhood socioeconomic status, along with cardiovascular risk factors, are associated with higher dementia risk in the U.S. Health and Retirement study,[144] and neighborhood level disadvantage was associated with Alzheimer pathology in a population study in Wisconsin and California.[145] In the Rush Memory and Aging Project, people with early life cognitive enrichment had a lower risk of dementia.[146]

Turning to patients with memory impairment established, mindfulness-based training did not improve outcomes in one randomized controlled trial of MCI patients,[147] but another small study of MCI patients did show cognition benefits with mindfulness-based stress reduction.[148] One meta-analysis did find benefit for cognitive function from muscle resistance training among older adults with cognitive impairment as well as those that were cognitively healthy.[149] A meta-analysis of MCI plus dementia patients showed modest benefit from music participation[150] and similarly for acupuncture.[151] One randomized study of a multi-component cognitive training intervention found that in AD MCI patients memory improved and in AD with mild to moderate dementia activities of daily living were improved.[152] Acupuncture therapy resulted in better cognition in a randomized trial of AD patients in a small study in China,[153] and Kundalini yoga produced better cognition in a randomized trial of MCI patients in a small study at UCLA.[154]

Conclusion

Current literature is replete with data addressing putative complementary and alternative approaches in AD and other causes of dementia and cognitive impairment. However, what we can state with certainty remains rather limited. The topic remains one of an emerging science. In general, the evidence for potential preventative roles is stronger than for intervention after cognitive impairment already exists. A very recent study further supports this, finding no effects of six months of a randomized clinical trial of mindfulness training and exercise on episodic memory or executive function in older adults with subjective cognitive complaints.[155] Among specific diets, the evidence is strongest for preventative roles of the Mediterranean diet and MIND diet, and similarly, among specific dietary components, the evidence is strongest for a preventive role for omega-3 fatty acids. However, the data for this is also mixed, with no reduced risk of developing all-cause dementia, AD, or vascular dementia observed in 20 years of follow-up associated with adherence to a modified Mediterranean diet in the Swedish population-based Malmö Diet and Cancer Study.[18] Intriguing data exist for interventions such as a ketotic diet, but trials with large populations are needed. Future work must examine interactions between factors that may have synergistic effects. More research is needed about how lifestyle modifications for known cardiovascular factors may also impact cognitive decline as an additional benefit, independent of cardiovascular benefits, and whether this can impact patients with emerging cognitive decline. Also needed is a better understanding of how prevention or interventions may affect cognitive decline generally, as distinguished specifically from that which occurs in particular diseases such as AD, the most common cause of dementia.

References

1. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. Aug 8 2020;396(10248):413-446. doi:10.1016/s0140-6736(20)30367-6
2. Krivanek TJ, Gale SA, McFeeley BM, Nicastri CM, Daffner KR. Promoting Successful Cognitive Aging: A Ten-Year Update. J Alzheimers Dis. 2021;81(3):871-920. doi:10.3233/jad-201462
3. Wang B, Wang N, Sun Y, Tan X, Zhang J, Lu Y. Association of Combined Healthy Lifestyle Factors With Incident Dementia in Patients With Type 2 Diabetes. Neurology. Nov 22 2022;99(21):e2336-e2345. doi:10.1212/wnl.0000000000201231
4. Loeffler DA. Modifiable, Non-Modifiable, and Clinical Factors Associated with Progression of Alzheimer's Disease. J Alzheimers Dis. 2021;80(1):1-27. doi:10.3233/jad-201182
5. Moustafa B, Trifan G, Isasi CR, et al. Association of Mediterranean Diet With Cognitive Decline Among Diverse Hispanic or Latino Adults From the Hispanic Community Health Study/Study of Latinos. JAMA Netw Open. Jul 1 2022;5(7):e2221982. doi:10.1001/jamanetworkopen.2022.21982
6. Ballarini T, Melo van Lent D, Brunner J, et al. Mediterranean Diet, Alzheimer Disease Biomarkers and Brain Atrophy in Old Age. Neurology. May 5 2021;96(24):e2920-32. doi:10.1212/wnl.0000000000012067
7. Andreu-Reinón ME, Chirlaque MD, Gavrila D, et al. Mediterranean Diet and Risk of Dementia and Alzheimer's Disease in the EPIC-Spain Dementia Cohort Study. Nutrients. Feb 22 2021;13(2)doi:10.3390/nu13020700
8. Vassilaki M, Aakre JA, Syrjanen JA, et al. Mediterranean Diet, Its Components, and Amyloid Imaging Biomarkers. J Alzheimers Dis. 2018;64(1):281-290. doi:10.3233/jad-171121
9. Rainey-Smith SR, Gu Y, Gardener SL, et al. Mediterranean diet adherence and rate of cerebral Aβ-amyloid accumulation: Data from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Transl Psychiatry. Oct 30 2018;8(1):238. doi:10.1038/s41398-018-0293-5

10. Berti V, Walters M, Sterling J, et al. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology. May 15 2018;90(20):e1789-e1798. doi:10.1212/wnl.0000000000005527
11. Luciano M, Corley J, Cox SR, et al. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology. Jan 31 2017;88(5):449-455. doi:10.1212/wnl.0000000000003559
12. de Crom TOE, Mooldijk SS, Ikram MK, Ikram MA, Voortman T. MIND diet and the risk of dementia: a population-based study. Alzheimers Res Ther. Jan 12 2022;14(1):8. doi:10.1186/s13195-022-00957-1
13. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement. Sep 2015;11(9):1015-22. doi:10.1016/j.jalz.2015.04.011
14. Hosking DE, Eramudugolla R, Cherbuin N, Anstey KJ. MIND not Mediterranean diet related to 12-year incidence of cognitive impairment in an Australian longitudinal cohort study. Alzheimers Dement. Apr 2019;15(4):581-589. doi:10.1016/j.jalz.2018.12.011
15. McEvoy CT, Guyer H, Langa KM, Yaffe K. Neuroprotective Diets Are Associated with Better Cognitive Function: The Health and Retirement Study. J Am Geriatr Soc. Aug 2017;65(8):1857-1862. doi:10.1111/jgs.14922
16. Martínez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. Dec 2013;84(12):1318-25. doi:10.1136/jnnp-2012-304792
17. de la Rubia Ortí JE, García-Pardo MP, Drehmer E, et al. Improvement of Main Cognitive Functions in Patients with Alzheimer's Disease after Treatment with Coconut Oil Enriched Mediterranean Diet: A Pilot Study. J Alzheimers Dis. 2018;65(2):577-587. doi:10.3233/jad-180184
18. Glans I, Sonestedt E, Nägga K, et al. Association Between Dietary Habits in Midlife With Dementia Incidence Over a 20-Year Period. Neurology 2023;100:e28-e37. doi:10.1212/WNL.0000000000201336
19. Lu Y, Matsuyama S, Sugawara Y, Sone T, Tsuji I. Changes in a specific dietary pattern and incident dementia: A prospective cohort study. Clin Nutr. May 2021;40(5):3495-3502. doi:10.1016/j.clnu.2020.11.036
20. Smyth A, Dehghan M, O'Donnell M, et al. Healthy eating and reduced risk of cognitive decline: A cohort from 40 countries. Neurology. Jun 2 2015;84(22):2258-65. doi:10.1212/wnl.0000000000001638
21. Lehtisalo J, Levälahti E, Lindström J, et al. Dietary changes and cognition over 2 years within a multidomain intervention trial-The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Alzheimers Dement. Mar 2019;15(3):410-417. doi:10.1016/j.jalz.2018.10.001
22. Phillips MCL, Deprez LM, Mortimer GMN, et al. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. Alzheimers Res Ther. Feb 23 2021;13(1):51. doi:10.1186/s13195-021-00783-x
23. Fortier M, Castellano CA, Croteau E, et al. A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment. Alzheimers Dement. May 2019;15(5):625-634. doi:10.1016/j.jalz.2018.12.017
24. Brandt J, Buchholz A, Henry-Barron B, Vizthum D, Avramopoulos D, Cervenka MC. Preliminary Report on the Feasibility and Efficacy of the Modified Atkins Diet for Treatment of Mild Cognitive Impairment and Early Alzheimer's Disease. J Alzheimers Dis. 2019;68(3):969-981. doi:10.3233/jad-180995
25. Ota M, Matsuo J, Ishida I, et al. Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. Neurosci Lett. Jan 18 2019;690:232-236. doi:10.1016/j.neulet.2018.10.048
26. Morris MC, Wang Y, Barnes LL, Bennett DA, Dawson-Hughes B, Booth SL. Nutrients and bioactives in green leafy vegetables and cognitive decline: Prospective study. Neurology. Jan 16 2018;90(3):e214-e222. doi:10.1212/wnl.0000000000004815
27. Li W, Sun L, Yue L, Li G, Xiao S. The Association Between Eating Green Vegetables Every Day And Mild Cognitive Impairment: A Community-Based Cross-Sectional Study In Shanghai. Neuropsychiatr Dis Treat. 2019;15:3213-3218. doi:10.2147/ndt.s221074
28. Gehlich KH, Beller J, Lange-Asschenfeldt B, Köcher W, Meinke MC, Lademann J. Consumption of fruits and vegetables: improved physical health, mental health, physical functioning and cognitive health in older adults from 11 European countries. Aging Ment Health. Apr 2020;24(4):634-641. doi:10.1080/13607863.2019.1571011
29. Mao X, Chen C, Xun P, et al. Intake of Vegetables and Fruits Through Young Adulthood Is Associated with Better Cognitive Function in Midlife in the US General Population. J Nutr. Aug 1 2019;149(8):1424-1433. doi:10.1093/jn/nxz076
30. Jiang X, Huang J, Song D, Deng R, Wei J, Zhang Z. Increased Consumption of Fruit and Vegetables Is Related to a Reduced Risk of Cognitive Impairment and Dementia: Meta-Analysis. Front Aging Neurosci. 2017;9:18. doi:10.3389/fnagi.2017.00018
31. Yuan C, Fondell E, Bhushan A, et al. Long-term intake of vegetables and fruits and subjective cognitive function in US men. Neurology. Jan 1 2019;92(1):e63-e75. doi:10.1212/wnl.0000000000006684
32. Zhang S, Tomata Y, Sugiyama K, Sugawara Y, Tsuji I. Citrus consumption and incident dementia in elderly Japanese: the Ohsaki Cohort 2006 Study. Br J Nutr. Apr 2017;117(8):1174-1180. doi:10.1017/s000711451700109x
33. Berding K, Long-Smith CM, Carbia C, et al. A specific dietary fibre supplementation improves cognitive performance-an exploratory randomised, placebo-controlled, crossover study. Psychopharmacology (Berl). Jan 2021;238(1):149-163. doi:10.1007/s00213-020-05665-y
34. Wood AHR, Chappell HF, Zulyniak MA. Dietary and supplemental long-chain omega-3 fatty acids as moderators of cognitive impairment and Alzheimer's disease. Eur J Nutr. Mar 2022;61(2):589-604. doi:10.1007/s00394-021-02655-4
35. Sala-Vila A, Satizabal CL, Tintle N, et al. Red Blood Cell DHA Is Inversely Associated with Risk of Incident Alzheimer's Disease and All-Cause Dementia: Framingham Offspring Study. Nutrients. Jun 9 2022;14(12)doi:10.3390/nu14122408
36. Tofiq A, Zetterberg H, Blennow K, et al. Effects of Peroral Omega-3 Fatty Acid Supplementation on Cerebrospinal Fluid Biomarkers in Patients with Alzheimer's Disease: A Randomized Controlled Trial-The OmegAD Study. J Alzheimers Dis. 2021;83(3):1291-1301. doi:10.3233/jad-210007
37. Shinto L, Quinn J, Montine T, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. J Alzheimers Dis. 2014;38(1):111-20. doi:10.3233/jad-130722
38. Sala-Vila A, Arenaza-Urquijo EM, Sánchez-Benavides G, et al. DHA intake relates to better cerebrovascular and neurodegeneration neuroimaging phenotypes in middle-aged adults at increased genetic risk of Alzheimer disease. Am J Clin Nutr. Jun 1 2021;113(6):1627-1635. doi:10.1093/ajcn/nqab016
39. Li L, Xu W, Tan CC, et al. A gene-environment interplay between omega-3 supplementation and APOE ε4 provides insights for Alzheimer's disease precise prevention amongst high-genetic-risk population. Eur J Neurol. Feb 2022;29(2):422-431. doi:10.1111/ene.15160
40. van de Rest O, Wang Y, Barnes LL, Tangney C, Bennett DA, Morris MC. APOE ε4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. Neurology. May 31 2016;86(22):2063-70. doi:10.1212/wnl.0000000000002719
41. Zamroziewicz MK, Paul EJ, Zwilling CE, Barbey AK. Determinants of fluid intelligence in healthy aging: Omega-3 polyunsaturated fatty acid status and frontoparietal cortex structure. Nutr Neurosci. Oct 2018;21(8):570-579. doi:10.1080/1028415x.2017.1324357
42. Nooyens ACJ, van Gelder BM, Bueno-de-Mesquita HB, van Boxtel MPJ, Verschuren WMM. Fish consumption, intake of fats and cognitive decline at middle and older age: the Doetinchem Cohort Study. Eur J Nutr. Jun 2018;57(4):1667-1675. doi:10.1007/s00394-017-1453-8
43. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. May 2017;16(5):377-389. doi:10.1016/s1474-4422(17)30040-6
44. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. Jama. Nov 3 2010;304(17):1903-11. doi:10.1001/jama.2010.1510
45. Yassine HN, Braskie MN, Mack WJ, et al. Association of Docosahexaenoic Acid Supplementation With Alzheimer Disease Stage in Apolipoprotein E ε4 Carriers: A Review. JAMA Neurol. Mar 1 2017;74(3):339-347. doi:10.1001/jamaneurol.2016.4899
46. Guasch-Ferré M, Li Y, Willett WC, et al. Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults. J Am Coll Cardiol. Jan 18 2022;79(2):101-112. doi:10.1016/j.jacc.2021.10.041
47. Tsolaki M, Lazarou E, Kozori M, et al. A Randomized Clinical Trial of Greek High Phenolic Early Harvest Extra Virgin Olive Oil in Mild Cognitive Impairment: The MICOIL Pilot Study. J Alzheimers Dis. 2020;78(2):801-817. doi:10.3233/jad-200405
48. Martínez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. J Nutr Health Aging. 2013;17(6):544-52. doi:10.1007/s12603-013-0027-6
49. Devore EE, Kang JH, Breteler MM, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. Ann Neurol. Jul 2012;72(1):135-43. doi:10.1002/ana.23594
50. Yeh TS, Yuan C, Ascherio A, Rosner BA, Willett WC, Blacker D. Long-term Dietary Flavonoid Intake and Subjective Cognitive Decline in US Men and Women. Neurology. Sep 7 2021;97(10):e1041-e1056. doi:10.1212/wnl.0000000000012454
51. Holland TM, Agarwal P, Wang Y, et al. Dietary flavonols and risk of Alzheimer dementia. Neurology. Apr 21 2020;94(16):e1749-e1756. doi:10.1212/wnl.0000000000008981
52. Shishtar E, Rogers GT, Blumberg JB, Au R, Jacques PF. Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring Cohort. Am J Clin Nutr. Aug 1 2020;112(2):343-353. doi:10.1093/ajcn/nqaa079
53. Lefèvre-Arbogast S, Gaudout D, Bensalem J, et al. Pattern of polyphenol intake and the long-term risk of dementia in older persons. Neurology. May 29 2018;90(22):e1979-e1988. doi:10.1212/wnl.0000000000005607
54. Sloan RP, Wall M, Yeung LK, et al. Insights into the role of diet and dietary flavanols in cognitive aging: results of a randomized controlled trial. Sci Rep. Feb 15 2021;11(1):3837. doi:10.1038/s41598-021-83370-2
55. Krikorian R, Skelton MR, Summer SS, Shidler MD, Sullivan PG. Blueberry Supplementation in Midlife for Dementia Risk Reduction. Nutrients. 2022;14(8):1619.
56. Miller MG, Hamilton DA, Joseph JA, Shukitt-Hale B. Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial. Eur J Nutr. Apr 2018;57(3):1169-1180. doi:10.1007/s00394-017-1400-8
57. Rutledge GA, Sandhu AK, Miller MG, Edirisinghe I, Burton-Freeman BB, Shukitt-Hale B. Blueberry phenolics are associated with cognitive enhancement in supplemented healthy older adults. Food Funct. Jan 7 2021;12(1):107-118. doi:10.1039/d0fo02125c
58. Boespflug EL, Eliassen JC, Dudley JA, et al. Enhanced neural activation with blueberry supplementation in mild cognitive impairment. Nutr Neurosci. May 2018;21(4):297-305. doi:10.1080/1028415x.2017.1287833
59. Travica N, D'Cunha NM, Naumovski N, et al. The effect of blueberry interventions on cognitive performance and mood: A systematic review of randomized controlled trials. Brain Behav Immun. Mar 2020;85:96-105. doi:10.1016/j.bbi.2019.04.001

60. Flanagan E, Cameron D, Sobhan R, et al. Chronic Consumption of Cranberries (Vaccinium macrocarpon) for 12 Weeks Improves Episodic Memory and Regional Brain Perfusion in Healthy Older Adults: A Randomised, Placebo-Controlled, Parallel-Groups Feasibility Study. Front Nutr. 2022;9:849902. doi:10.3389/fnut.2022.849902
61. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. Br J Nutr. Mar 2010;103(5):730-4. doi:10.1017/s0007114509992364
62. Chai SC, Jerusik J, Davis K, Wright RS, Zhang Z. Effect of Montmorency tart cherry juice on cognitive performance in older adults: a randomized controlled trial. Food Funct. Jul 17 2019;10(7):4423-4431. doi:10.1039/c9fo00913b
63. Agarwal P, Holland TM, James BD, et al. Pelargonidin and Berry Intake Association with Alzheimer's Disease Neuropathology: A Community-Based Study. J Alzheimers Dis. 2022;88(2):653-661. doi:10.3233/jad-215600
64. Lamport DJ, Williams CM. Polyphenols and Cognition In Humans: An Overview of Current Evidence from Recent Systematic Reviews and Meta-Analyses. Brain Plast. Feb 9 2021;6(2):139-153. doi:10.3233/bpl-200111
65. Gardener SL, Rainey-Smith SR, Villemagne VL, et al. Higher Coffee Consumption Is Associated With Slower Cognitive Decline and Less Cerebral Aβ-Amyloid Accumulation Over 126 Months: Data From the Australian Imaging, Biomarkers, and Lifestyle Study. Front Aging Neurosci. 2021;13:744872. doi:10.3389/fnagi.2021.744872
66. Zhang Y, Yang H, Li S, Li WD, Wang Y. Consumption of coffee and tea and risk of developing stroke, dementia, and poststroke dementia: A cohort study in the UK Biobank. PLoS Med. Nov 2021;18(11):e1003830. doi:10.1371/journal.pmed.1003830
67. Wu L, Sun D, He Y. Coffee intake and the incident risk of cognitive disorders: A dose-response meta-analysis of nine prospective cohort studies. Clin Nutr. Jun 2017;36(3):730-736. doi:10.1016/j.clnu.2016.05.015
68. Driscoll I, Shumaker SA, Snively BM, et al. Relationships Between Caffeine Intake and Risk for Probable Dementia or Global Cognitive Impairment: The Women's Health Initiative Memory Study. J Gerontol A Biol Sci Med Sci. Dec 2016;71(12):1596-1602. doi:10.1093/gerona/glw078
69. Feng L, Chong MS, Lim WS, et al. Tea Consumption Reduces the Incidence of Neurocognitive Disorders: Findings from the Singapore Longitudinal Aging Study. J Nutr Health Aging. 2016;20(10):1002-1009. doi:10.1007/s12603-016-0687-0
70. Okello EJ, Mendonça N, Stephan B, Muniz-Terrera G, Wesnes K, Siervo M. Tea consumption and measures of attention and psychomotor speed in the very old: the Newcastle 85+ longitudinal study. BMC Nutr. 2020;6:57. doi:10.1186/s40795-020-00361-8
71. Tomata Y, Sugiyama K, Kaiho Y, et al. Green Tea Consumption and the Risk of Incident Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study. Am J Geriatr Psychiatry. Oct 2016;24(10):881-9. doi:10.1016/j.jagp.2016.07.009
72. Ma YH, Wu JH, Xu W, et al. Associations of Green Tea Consumption and Cerebrospinal Fluid Biomarkers of Alzheimer's Disease Pathology in Cognitively Intact Older Adults: The CABLE Study. J Alzheimers Dis. 2020;77(1):411-421. doi:10.3233/jad-200410
73. Crichton GE, Elias MF, Alkerwi A. Chocolate intake is associated with better cognitive function: The Maine-Syracuse Longitudinal Study. Appetite. May 1 2016;100:126-32. doi:10.1016/j.appet.2016.02.010
74. Feng L, Cheah IK, Ng MM, et al. The Association between Mushroom Consumption and Mild Cognitive Impairment: A Community-Based Cross-Sectional Study in Singapore. J Alzheimers Dis. 2019;68(1):197-203. doi:10.3233/jad-180959
75. Zhang S, Tomata Y, Sugiyama K, Sugawara Y, Tsuji I. Mushroom Consumption and Incident Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study. J Am Geriatr Soc. Jul 2017;65(7):1462-1469. doi:10.1111/jgs.14812
76. Small GW, Siddarth P, Li Z, et al. Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial. Am J Geriatr Psychiatry. Mar 2018;26(3):266-277. doi:10.1016/j.jagp.2017.10.010
77. Lho SK, Kim TH, Kwak KP, et al. Effects of lifetime cumulative ginseng intake on cognitive function in late life. Alzheimers Res Ther. May 24 2018;10(1):50. doi:10.1186/s13195-018-0380-0
78. Li H, Li S, Yang H, et al. Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort. Neurology. Jul 27 2022;doi:10.1212/wnl.0000000000200871
79. Gomes Gonçalves N, Vidal Ferreira N, Khandpur N, et al. Association Between Consumption of Ultraprocessed Foods and Cognitive Decline. JAMA Neurol. Dec 5 2022;doi:10.1001/jamaneurol.2022.4397
80. Melo Van Lent D, Gokingco H, Short MI, et al. Higher Dietary Inflammatory Index scores are associated with brain MRI markers of brain aging: Results from the Framingham Heart Study Offspring cohort. Alzheimers Dement. May 6 2022;doi:10.1002/alz.12685
81. Köbe T, Witte AV, Schnelle A, et al. Impact of Resveratrol on Glucose Control, Hippocampal Structure and Connectivity, and Memory Performance in Patients with Mild Cognitive Impairment. Front Neurosci. 2017;11:105. doi:10.3389/fnins.2017.00105
82. Witte AV, Kerti L, Margulies DS, Flöel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. J Neurosci. Jun 4 2014;34(23):7862-70. doi:10.1523/jneurosci.0385-14.2014
83. Lopresti AL, Smith SJ, Majeed M, Drummond PD. Effects of an Oroxylum indicum Extract (Sabroxy(®)) on Cognitive Function in Adults With Self-reported Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Study. Front Aging Neurosci. 2021;13:728360. doi:10.3389/fnagi.2021.728360
84. Kim JW, Byun MS, Yi D, et al. Serum zinc levels and in vivo beta-amyloid deposition in the human brain. Alzheimers Res Ther. Nov 19 2021;13(1):190. doi:10.1186/s13195-021-00931-3
85. Galasso C, Orefice I, Pellone P, et al. On the Neuroprotective Role of Astaxanthin: New Perspectives? Mar Drugs. Jul 24 2018;16(8)doi:10.3390/md16080247
86. Speers AB, García-Jaramillo M, Feryn A, et al. Centella asiatica Alters Metabolic Pathways Associated With Alzheimer's Disease in the 5xFAD Mouse Model of ß-Amyloid Accumulation. Front Pharmacol. 2021;12:788312. doi:10.3389/fphar.2021.788312
87. Mori T, Koyama N, Tan J, Segawa T, Maeda M, Town T. Combined treatment with the phenolics (-)-epigallocatechin-3-gallate and ferulic acid improves cognition and reduces Alzheimer-like pathology in mice. J Biol Chem. Feb 22 2019;294(8):2714-2731. doi:10.1074/jbc.RA118.004280
88. Fernandes L, Cardim-Pires TR, Foguel D, Palhano FL. Green Tea Polyphenol Epigallocatechin-Gallate in Amyloid Aggregation and Neurodegenerative Diseases. Front Neurosci. 2021;15:718188. doi:10.3389/fnins.2021.718188
89. Benameur T, Soleti R, Porro C. The Potential Neuroprotective Role of Free and Encapsulated Quercetin Mediated by miRNA against Neurological Diseases. Nutrients. Apr 16 2021;13(4)doi:10.3390/nu13041318
90. Kaushik R, Morkovin E, Schneeberg J, et al. Traditional Japanese Herbal Medicine Yokukansan Targets Distinct but Overlapping Mechanisms in Aged Mice and in the 5xFAD Mouse Model of Alzheimer's Disease. Front Aging Neurosci. 2018;10:411. doi:10.3389/fnagi.2018.00411
91. More J, Galusso N, Veloso P, et al. N-Acetylcysteine Prevents the Spatial Memory Deficits and the Redox-Dependent RyR2 Decrease Displayed by an Alzheimer's Disease Rat Model. Front Aging Neurosci. 2018;10:399. doi:10.3389/fnagi.2018.00399
92. Cai Z, Wang C, Yang W. Role of berberine in Alzheimer's disease. Neuropsychiatr Dis Treat. 2016;12:2509-2520. doi:10.2147/ndt.s114846
93. Muthaiyah B, Essa MM, Lee M, Chauhan V, Kaur K, Chauhan A. Dietary supplementation of walnuts improves memory deficits and learning skills in transgenic mouse model of Alzheimer's disease. J Alzheimers Dis. 2014;42(4):1397-405. doi:10.3233/jad-140675
94. Ano Y, Ohya R, Takaichi Y, et al. β-Lactolin, a Whey-Derived Lacto-Tetrapeptide, Prevents Alzheimer's Disease Pathologies and Cognitive Decline. J Alzheimers Dis. 2020;73(4):1331-1342. doi:10.3233/jad-190997
95. You M, Pan Y, Liu Y, et al. Royal Jelly Alleviates Cognitive Deficits and β-Amyloid Accumulation in APP/PS1 Mouse Model Via Activation of the cAMP/PKA/CREB/BDNF Pathway and Inhibition of Neuronal Apoptosis. Front Aging Neurosci. 2018;10:428. doi:10.3389/fnagi.2018.00428
96. Toledo JP, Fernández-Pérez EJ, Ferreira IL, et al. Boldine Attenuates Synaptic Failure and Mitochondrial Deregulation in Cellular Models of Alzheimer's Disease. Front Neurosci. 2021;15:617821. doi:10.3389/fnins.2021.617821
97. Voulgaropoulou SD, van Amelsvoort T, Prickaerts J, Vingerhoets C. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. Brain Res. Dec 15 2019;1725:146476. doi:10.1016/j.brainres.2019.146476
98. Xu A, Zeng Q, Tang Y, et al. Electroacupuncture Protects Cognition by Regulating Tau Phosphorylation and Glucose Metabolism via the AKT/GSK3β Signaling Pathway in Alzheimer's Disease Model Mice. Front Neurosci. 2020;14:585476. doi:10.3389/fnins.2020.585476
99. Zhang J, Li X, Ren Y, et al. Intermittent Fasting Alleviates the Increase of Lipoprotein Lipase Expression in Brain of a Mouse Model of Alzheimer's Disease: Possibly Mediated by β-hydroxybutyrate. Front Cell Neurosci. 2018;12:1. doi:10.3389/fncel.2018.00001
100. Palomera-Ávalos V, Griñán-Ferré C, Izquierdo V, Camins A, Sanfeliu C, Pallàs M. Metabolic Stress Induces Cognitive Disturbances and Inflammation in Aged Mice: Protective Role of Resveratrol. Rejuvenation Res. Jun 2017;20(3):202-217. doi:10.1089/rej.2016.1885
101. Sathya M, Moorthi P, Premkumar P, Kandasamy M, Jayachandran KS, Anusuyadevi M. Resveratrol Intervenes Cholesterol- and Isoprenoid-Mediated Amyloidogenic Processing of AβPP in Familial Alzheimer's Disease. J Alzheimers Dis. 2017;60(s1):S3-s23. doi:10.3233/jad-161034
102. Beydoun MA, Beydoun HA, Fanelli-Kuczmarski MT, et al. Association of Serum Antioxidant Vitamins and Carotenoids With Incident Alzheimer Disease and All-Cause Dementia Among US Adults. Neurology. May 24 2022;98(21):e2150-e2162. doi:10.1212/wnl.0000000000200289
103. Xu H, Wang S, Gao F, Li C. Vitamin B(6), B(9), and B(12) Intakes and Cognitive Performance in Elders: National Health and Nutrition Examination Survey, 2011-2014. Neuropsychiatr Dis Treat. 2022;18:537-553. doi:10.2147/ndt.s337617
104. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. Sep 8 2010;5(9):e12244. doi:10.1371/journal.pone.0012244
105. Lauriola M, D'Onofrio G, Ciccone F, et al. Relationship of Homocysteine Plasma Levels with Mild Cognitive Impairment, Alzheimer's Disease, Vascular Dementia, Psychobehavioral, and Functional Complications. J Alzheimers Dis. 2021;82(1):235-248. doi:10.3233/jad-210166
106. Nelson ME, Andel R, Nedelska Z, et al. The Association Between Homocysteine and Memory in Older Adults. J Alzheimers Dis. 2021;81(1):413-426. doi:10.3233/jad-201558
107. Kim S, Choi BY, Nam JH, Kim MK, Oh DH, Yang YJ. Cognitive impairment is associated with elevated serum homocysteine levels among older adults. Eur J Nutr. Feb 2019;58(1):399-408. doi:10.1007/s00394-017-1604-y
108. Li S, Guo Y, Men J, Fu H, Xu T. The preventive efficacy of vitamin B supplements on the cognitive decline of elderly adults: a systematic review and meta-analysis. BMC Geriatr. Jun 16 2021;21(1):367. doi:10.1186/s12877-021-02253-3
109. Wang Q, Zhao J, Chang H, Liu X, Zhu R. Homocysteine and Folic Acid: Risk

Factors for Alzheimer's Disease-An Updated Meta-Analysis. Front Aging Neurosci. 2021;13:665114. doi:10.3389/fnagi.2021.665114
110. Travica N, Ried K, Sali A, Hudson I, Scholey A, Pipingas A. Plasma Vitamin C Concentrations and Cognitive Function: A Cross-Sectional Study. Front Aging Neurosci. 2019;11:72. doi:10.3389/fnagi.2019.00072
111. Palacios N, Scott T, Sahasrabudhe N, Gao X, Tucker KL. Lower Plasma Vitamin B-6 is Associated with 2-Year Cognitive Decline in the Boston Puerto Rican Health Study. The Journal of Nutrition. 2019;149(4):635-641. doi:10.1093/jn/nxy268
112. Dong Y, Chen X, Liu Y, et al. Do low-serum vitamin E levels increase the risk of Alzheimer disease in older people? Evidence from a meta-analysis of case-control studies. Int J Geriatr Psychiatry. Feb 2018;33(2):e257-e263. doi:10.1002/gps.4780
113. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). JAMA Neurol. May 1 2017;74(5):567-573. doi:10.1001/jamaneurol.2016.5778
114. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. Jama. Jan 1 2014;311(1):33-44. doi:10.1001/jama.2013.282834
115. Geng T, Lu Q, Wan Z, et al. Association of serum 25-hydroxyvitamin D concentrations with risk of dementia among individuals with type 2 diabetes: A cohort study in the UK Biobank. PLoS Med. Jan 2022;19(1):e1003906. doi:10.1371/journal.pmed.1003906
116. Zhao C, Tsapanou A, Manly J, Schupf N, Brickman AM, Gu Y. Vitamin D intake is associated with dementia risk in the Washington Heights-Inwood Columbia Aging Project (WHICAP). Alzheimers Dement. Oct 2020;16(10):1393-1401. doi:10.1002/alz.12096
117. Pavlovic A, Abel K, Barlow CE, Farrell SW, Weiner M, DeFina LF. The association between serum vitamin d level and cognitive function in older adults: Cooper Center Longitudinal Study. Prev Med. Aug 2018;113:57-61. doi:10.1016/j.ypmed.2018.05.010
118. Mokry LE, Ross S, Morris JA, Manousaki D, Forgetta V, Richards JB. Genetically decreased vitamin D and risk of Alzheimer disease. Neurology. Dec 13 2016;87(24):2567-2574. doi:10.1212/wnl.0000000000003430
119. Jia J, Hu J, Huo X, Miao R, Zhang Y, Ma F. Effects of vitamin D supplementation on cognitive function and blood Aβ-related biomarkers in older adults with Alzheimer's disease: a randomised, double-blind, placebo-controlled trial. J Neurol Neurosurg Psychiatry. Dec 2019;90(12):1347-1352. doi:10.1136/jnnp-2018-320199
120. Olsson E, Byberg L, Karlström B, et al. Vitamin D is not associated with incident dementia or cognitive impairment: an 18-y follow-up study in community-living old men. Am J Clin Nutr. Apr 2017;105(4):936-943. doi:10.3945/ajcn.116.141531
121. Chen H, Liu S, Ge B, et al. Effects of Folic Acid and Vitamin B12 Supplementation on Cognitive Impairment and Inflammation in Patients with Alzheimer's Disease: A Randomized, Single-Blinded, Placebo-Controlled Trial. J Prev Alzheimers Dis. 2021;8(3):249-256. doi:10.14283/jpad.2021.22
122. Ma F, Li Q, Zhou X, et al. Effects of folic acid supplementation on cognitive function and Aβ-related biomarkers in mild cognitive impairment: a randomized controlled trial. Eur J Nutr. Feb 2019;58(1):345-356. doi:10.1007/s00394-017-1598-5
123. Rutjes AW, Denton DA, Di Nisio M, et al. Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life. Cochrane Database Syst Rev. Dec 17 2018;12(12):Cd011906. doi:10.1002/14651858.CD011906.pub2
124. McCleery J, Abraham RP, Denton DA, et al. Vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild cognitive impairment. Cochrane Database Syst Rev. Nov 1 2018;11(11):Cd011905. doi:10.1002/14651858.CD011905.pub2
125. Lopresti AL. Salvia (Sage): A Review of its Potential Cognitive-Enhancing and Protective Effects. Drugs R D. Mar 2017;17(1):53-64. doi:10.1007/s40268-016-0157-5
126. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther. Feb 2003;28(1):53-9. doi:10.1046/j.1365-2710.2003.00463.x
127. Huang CH, Lin MC, Chou IC, Hsieh CL. Acupuncture Treatment is Associated with Reduced Dementia Risk in Patients with Migraine: A Propensity-Score-Matched Cohort Study of Real-World Data. Neuropsychiatr Dis Treat. 2022;18:1895-1906. doi:10.2147/ndt.s372076
128. Huang J, Shen M, Qin X, Wu M, Liang S, Huang Y. Acupuncture for the Treatment of Alzheimer's Disease: An Overview of Systematic Reviews. Front Aging Neurosci. 2020;12:574023. doi:10.3389/fnagi.2020.574023
129. Krause-Sorio B, Siddarth P, Kilpatrick L, et al. Yoga Prevents Gray Matter Atrophy in Women at Risk for Alzheimer's Disease: A Randomized Controlled Trial. J Alzheimers Dis. 2022;87(2):569-581. doi:10.3233/jad-215563
130. Yue C, Yu Q, Zhang Y, et al. Regular Tai Chi Practice Is Associated With Improved Memory as Well as Structural and Functional Alterations of the Hippocampus in the Elderly. Front Aging Neurosci. 2020;12:586770. doi:10.3389/fnagi.2020.586770
131. Siu MY, Lee DTF. Effects of tai chi on cognition and instrumental activities of daily living in community dwelling older people with mild cognitive impairment. BMC Geriatr. Feb 2 2018;18(1):37. doi:10.1186/s12877-018-0720-8
132. Capuano AW, Wilson RS, Leurgans SE, et al. Relation of Literacy and Music Literacy to Dementia in Older Black and White Brazilians. J Alzheimers Dis. 2021;84(2):737-744. doi:10.3233/jad-210601
133. Chételat G, Lutz A, Klimecki O, et al. Effect of an 18-Month Meditation Training on Regional Brain Volume and Perfusion in Older Adults: The Age-Well Randomized Clinical Trial. JAMA Neurol. Nov 1 2022;79(11):1165-1174. doi:10.1001/jamaneurol.2022.3185
134. Hale JM, Bijlsma MJ, Lorenti A. Does postponing retirement affect cognitive function? A counterfactual experiment to disentangle life course risk factors. SSM Popul Health. Sep 2021;15:100855. doi:10.1016/j.ssmph.2021.100855
135. Seider TR, Fieo RA, O'Shea A, Porges EC, Woods AJ, Cohen RA. Cognitively Engaging Activity Is Associated with Greater Cortical and Subcortical Volumes. Front Aging Neurosci. 2016;8:94. doi:10.3389/fnagi.2016.00094
136. Altschul DM, Deary IJ. Playing Analog Games Is Associated With Reduced Declines in Cognitive Function: A 68-Year Longitudinal Cohort Study. J Gerontol B Psychol Sci Soc Sci. Feb 14 2020;75(3):474-482. doi:10.1093/geronb/gbz149
137. Anguera JA, Volponi JJ, Simon AJ, et al. Integrated cognitive and physical fitness training enhances attention abilities in older adults. NPJ Aging. Aug 30 2022;8(1):12. doi:10.1038/s41514-022-00093-y
138. Su S, Shi L, Zheng Y, et al. Leisure Activities and the Risk of Dementia: A Systematic Review and Meta-Analysis. Neurology. Aug 10 2022;99(15):e1651-63. doi:10.1212/wnl.0000000000200929
139. Casaletto KB, Kornack J, Paolillo EW, et al. Association of Physical Activity With Neurofilament Light Chain Trajectories in Autosomal Dominant Frontotemporal Lobar Degeneration Variant Carriers. JAMA Neurol. Nov 14 2022;doi:10.1001/jamaneurol.2022.4178
140. Knekt P, Järvinen R, Rissanen H, Heliövaara M, Aromaa A. Does sauna bathing protect against dementia? Prev Med Rep. Dec 2020;20:101221. doi:10.1016/j.pmedr.2020.101221
141. Laukkanen T, Kunutsor S, Kauhanen J, Laukkanen JA. Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men. Age Ageing. Mar 1 2017;46(2):245-249. doi:10.1093/ageing/afw212
142. Levy BR, Slade MD, Pietrzak RH, Ferrucci L. Positive age beliefs protect against dementia even among elders with high-risk gene. PLoS One. 2018;13(2):e0191004. doi:10.1371/journal.pone.0191004
143. Aitken WW, Lombard J, Wang K, et al. Relationship of Neighborhood Greenness to Alzheimer's Disease and Non-Alzheimer's Dementia Among 249,405 U.S. Medicare Beneficiaries. J Alzheimers Dis. 2021;81(2):597-606. doi:10.3233/jad-201179
144. Kuchibhatla M, Hunter JC, Plassman BL, et al. The association between neighborhood socioeconomic status, cardiovascular and cerebrovascular risk factors, and cognitive decline in the Health and Retirement Study (HRS). Aging Ment Health. Sep 2020;24(9):1479-1486. doi:10.1080/13607863.2019.1594169
145. Powell WR, Buckingham WR, Larson JL, et al. Association of Neighborhood-Level Disadvantage With Alzheimer Disease Neuropathology. JAMA Netw Open. Jun 1 2020;3(6):e207559. doi:10.1001/jamanetworkopen.2020.7559
146. Oveisgharan S, Wilson RS, Yu L, Schneider JA, Bennett DA. Association of Early-Life Cognitive Enrichment With Alzheimer Disease Pathological Changes and Cognitive Decline. JAMA Neurol. Oct 1 2020;77(10):1217-1224. doi:10.1001/jamaneurol.2020.1941
147. Doshi K, Henderson SL, Fan Q, Wong KF, Lim J. Mindfulness-Based Training Does Not Improve Neuropsychological Outcomes in Mild Cognitive Impairment More Than Spontaneous Reversion Rates: A Randomized Controlled Trial. J Alzheimers Dis. 2021;84(1):449-458. doi:10.3233/jad-215035
148. Marciniak R, Šumec R, Vyhnálek M, et al. The Effect of Mindfulness-Based Stress Reduction (MBSR) on Depression, Cognition, and Immunity in Mild Cognitive Impairment: A Pilot Feasibility Study. Clin Interv Aging. 2020;15:1365-1381. doi:10.2147/cia.s249196
149. Coelho-Junior H, Marzetti E, Calvani R, Picca A, Arai H, Uchida M. Resistance training improves cognitive function in older adults with different cognitive status: a systematic review and Meta-analysis. Aging Ment Health. Feb 2022;26(2):213-224. doi:10.1080/13607863.2020.1857691
150. Dorris JL, Neely S, Terhorst L, VonVille HM, Rodakowski J. Effects of music participation for mild cognitive impairment and dementia: A systematic review and meta-analysis. J Am Geriatr Soc. Sep 2021;69(9):2659-2667. doi:10.1111/jgs.17208
151. He W, Li M, Han X, Zhang W. Acupuncture for Mild Cognitive Impairment and Dementia: An Overview of Systematic Reviews. Front Aging Neurosci. 2021;13:647629. doi:10.3389/fnagi.2021.647629
152. Giuli C, Papa R, Lattanzio F, Postacchini D. The Effects of Cognitive Training for Elderly: Results from My Mind Project. Rejuvenation Res. Dec 2016;19(6):485-494. doi:10.1089/rej.2015.1791
153. Peng J, Chen X, Wang A-p, Luo L, Zhou B, Zhang H-y. Efficacy evaluation on electroacupuncture for Alzheimer's disease. Journal of Acupuncture and Tuina Science. 2017;15(4):296-299. doi:10.1007/s11726-017-1017-8
154. Eyre HA, Siddarth P, Acevedo B, et al. A randomized controlled trial of Kundalini yoga in mild cognitive impairment. Int Psychogeriatr. Apr 2017;29(4):557-567. doi:10.1017/s1041610216002155
155. Lenze EJ, Voegtle M, Miller JP, et al. Effects of Mindfulness Training and Exercise on Cognitive Function in Older Adults: A Randomized Clinical Trial. JAMA 2022;328(22):2218-2229. doi:10.1001/jama.2022.21680

Disclosure

DQB has received consultancy fees and/or honoararia for Biogen, YAMO Pharmaceuticals, Stalicla Biosciences, Scioto Biosciences, Impel Pharmaceuticals, Quadrant Bisociences, MA Pharmaceuticals, and Human Bioscience. **MM**

Bridging the Gap: Innovative 'Center for Precision Oncology' in Missouri

by Beth Gustafson, PharmD, Lindsey Douglass, PharmD, Timothy Pluard, MD & Janakiraman Subramanian, MD

Saint Luke's CANCER INSTITUTE

There is a need to bring together people with different skillsets such as medical oncologists, molecular pathologists, pharmacists, genetic counselors, and nurse coordinators to establish the molecular tumor board.



Beth Gustafson PharmD, BCOP, Lindsey Douglass,PharmD, BCPS, BCOP, and Timothy Pluard, MD are with the Saint Luke's Cancer Institute, and Dr. Pluard is also with the University of Missouri - Kansas City, Kansas City, Missouri. Janakiraman Subramanian, MD, MPH, (above), is Co-Director of Thoracic Oncology, Inova Schar Cancer Institute, Fairfax, Virginia.

Abstract

Background

Next generation sequencing (NGS) has become standard practice for identification and treatment of targetable driver mutations in advanced cancer. However, NGS interpretation of clinical applicability can be challenging to clinician, with potential impact on patient's outcome. Specialized precision medicine services are poised to bridge this gap by creating collaborative frameworks to formulate and deliver genomic patient care plans.

Methods

Saint Luke's Cancer Institute in Kansas City, Missouri, (SLCI) instituted the Center for Precision Oncology (CPO) in 2017. The program accepts patient referrals for a multidisciplinary molecular tumor board and offers CPO clinic visits. An Institutional Review Board-approved molecular registry was initiated. It catalogues genomic files along with patient demographics, treatment and outcomes. CPO patient volumes, recommendation acceptance, clinical trial matriculation and funding for drug procurement were closely tracked.

Results

In 2020 there were 93 referrals to the CPO with 29 patient clinic visits. 20 patients matriculated to CPO-recommended therapies. Two patients were successfully enrolled in Expanded Access Programs (EAPs). CPO successfully procured eight off-label treatments. Treatments initiated per CPO recommendations totaled over $1 million in drug costs.

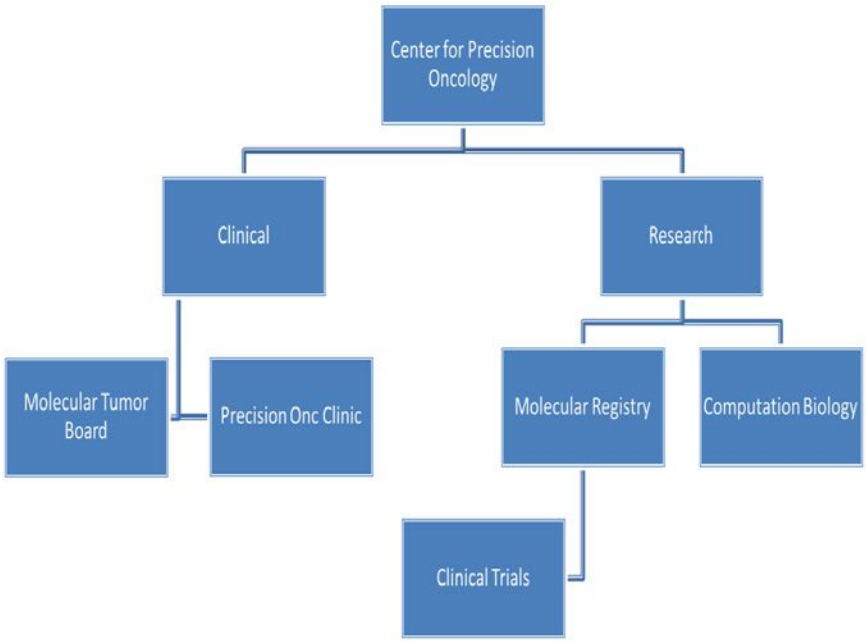
Conclusion

Precision medicine services are essential tool for oncology clinicians. In addition to expert NGS analysis interpretation, precision medicine programs provide crucial multidisciplinary support for patients to understand the implications of their genomic report and pursue targeted treatment as indicated. Molecular registries associated with these services offer valuable opportunities for research.

Introduction

Two decades of technological progress have resulted in significant advances in the science and speed of genomic sequencing.[1] Early genome sequencing technologies were prohibitively expensive and time consuming. With next

Figure 1. CPO combines aspects of both research and clinical patient care.



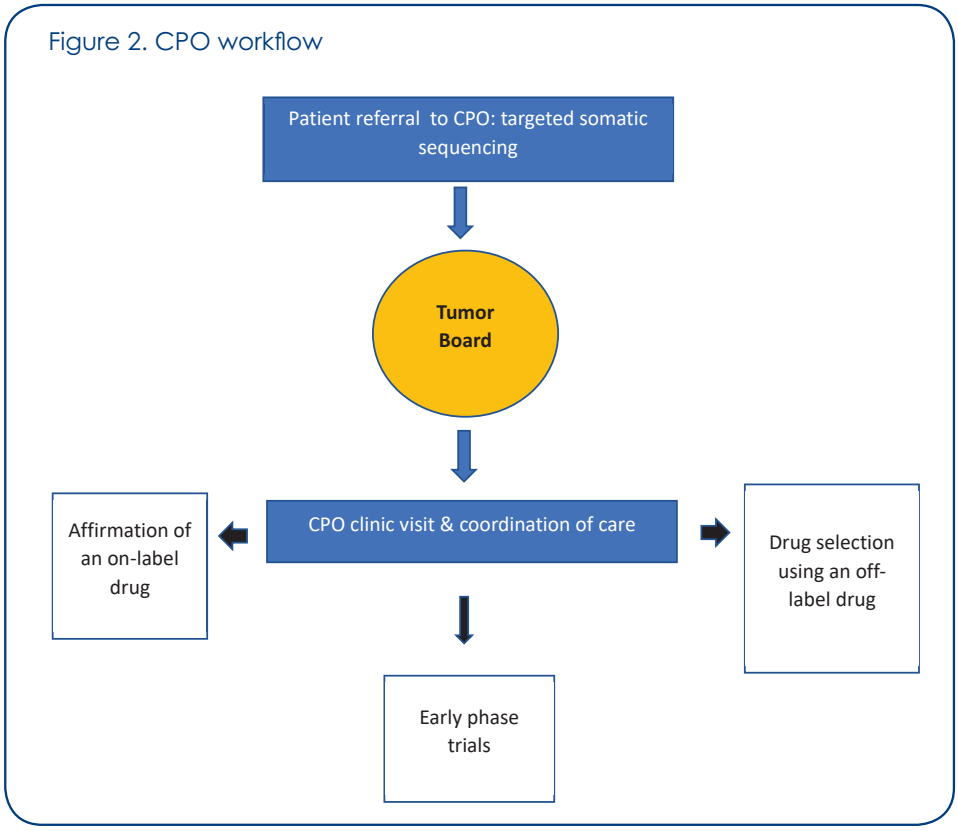
generation sequencing (NGS), it is now possible to sequence a patient's genome at a fraction of the time and cost.[1] This has allowed NGS to become part of routine clinical testing in care of patients with cancer.[2] The power of NGS to individualize patient care is profoundly apparent in oncology practice.

NGS may lead to identification of oncogenic driver mutations which respond to targeted therapies or resistance mutations that can help select the appropriate standard treatments.[2] Despite its advantages, analysis of genomic data is rarely straightforward. Interpreting whether a molecular alteration is actionable can be challenging to the clinician and these decisions can have significant impact on patient outcomes.[2] Molecular tumor boards which combine genomic and clinical expertise are a potent tool to bridge the growing gap between clinician education and genomic potential.[3]

In 2017, Saint Luke's Cancer Institute (SLCI) in Kansas City, Missouri, opened the Center for Precision Oncology (CPO). The program was modeled after the Indiana University Precision Genomics Program.[4] Similar programs have been implemented in institutions across the country.[5-9] CPO has both research and clinical components (Figure 1). The CPO core group consists of medical oncologists, clinical pharmacists, molecular pathologist, and nurse navigator. After being referred to the program, the navigator notifies the pharmacist who collects pertinent clinical information, genomic results, therapy options (including clinical trial and on- and off-label therapies), compiles the data. The case is then discussed in the weekly molecular tumor board by a multidisciplinary team, including oncologists, molecular pathologists, and genetic counselors. A tailored treatment plan guided by the molecular testing is created for the patient and shared with the referring provider. The patient meets with the medical oncologist and pharmacist in the CPO clinic to discuss genomic findings and treatment options (Figure 2). The pharmacist plays the key role of educating the patient on the genomic test results. Further, they coordinate with the research department to identify clinical trial options. At times they also work with insurance and pharmaceuticals to obtain approval for recommended treatments.

CPO tracks recommendations and gathers annual metrics. In 2020, 93 patients were discussed in CPO molecular tumor boards. Of these, 29 completed a dedicated CPO clinic visit

Figure 2. CPO workflow



to discuss targeted therapies. During this period, 20 patients were initiated on targeted therapies based on the recommendations made in CPO. For eight patients the CPO pharmacy team successfully appealed to the pharmaceutical companies and/or insurance payors to obtain approval for the molecular testing result guided treatment. Together, treatments initiated per CPO recommendations totaled over $1 million in drug costs. Overall recommendation acceptance rate of CPO treatments in 2020 was 21% (20/93). While this number seems low, it is imperative to understand that many patients brought to CPO were refractory to multiple lines of therapy. In such patients, enrollment and travel to clinical trials or initiation of new therapies is complicated by their performance status and social situation. Many of our patients find it difficult to travel to distant sites to participate in clinical trials. This highlights the major unmet need of better patient access to clinical trials in the Kansas City area.

Research

CPO has a substantial research component. Since 2017, an Institutional Review Board-approved Molecular Registry Study has accrued over 500 patients. This database is linked to genomic data files and tracks CPO patient characteristics, lines of therapy, and treatment response. Several multi-institution studies are currently in progress with data from the Molecular Registry. In addition to the database, clinical trial accrual is key research component of CPO. Early phase genomic-based clinical trial enrollment and Expanded Access Program (EAP) initiation broaden CPO patients' therapy options. The database allows the precision team to identify areas of need which guides our selection and opening of clinical trials and expanded access programs at Saint Luke's Cancer Institute. In 2020, expanded access to Amgen 510 (sotorasib) was successfully implemented by CPO for two patients with KRAS G12C mutations. In addition, CPO is in the process of entering a molecularly-based clinical trial network with rapid opening capabilities for patients with qualifying mutations. In 2020 it was estimated that 50 patients would have preliminarily qualified for these trials.

Education

CPO was instrumental to the creation of the Midwest Precision Oncology Consortium (MWPOC), founded in 2019. This multi-

institution tumor board currently includes nine institutions, bringing together oncologists throughout the region each month to discuss challenging cases and provide treatment recommendations based on the tumor molecular test results. In addition to providing genomic expertise and fostering collaboration among providers, the conference offers continuing education for medical professionals who participate. To date, 50 cases have been discussed at MWPOC.

Conclusion

As our ability to analyze tumor molecular landscape continues to grow by leaps and bounds, it has become increasingly challenging for the clinician to keep pace with the information deluge. There is a need to bring together people with different skillsets such as medical oncologists, molecular pathologists, pharmacists, genetic counselors, and nurse coordinators to establish the molecular tumor board. At Saint Luke's Cancer Institute, the nurse coordinator and pharmacist are the key program coordinators who ensure the smooth functioning of the CPO. The CPO along with the MWPOC serve an important need in the clinical management of patients with advanced cancer in the Kansas City area. The CPO is engaged in cutting edge research in the field of molecular oncology and is involved in the education of oncology health care providers in this area. Even more importantly it highlights the need for expanding clinical trial access for our patients in the Kansas City area. To ensure that the Kansas City area patients with cancer receive excellent care, a concerted effort is needed from physicians, cancer center administrators, and policy makers to realize precision medicine's full potential.

To further highlight how molecular tumor boards can assist cancer patients and to emphasize the need to deliver better treatments including clinical trials of novel cancer therapies, we will be presenting in future issues of *Missouri Medicine* a series of cases discussed in the MWPOC. Cases will include patients with complex molecular and clinical characteristics and showcase the role of precision oncology collaboration in their care.

References

1. Freedman A, Klabunde C, Wiant K, et al. Use of next-generation sequencing tests to guide cancer treatment: results from a nationally representative survey of oncologists in the united states. JCO Precision Oncology. 2018 Nov 13; (2): 1-13. https://doi.org/10.1200/PO.18.00169
2. Schwaederle M, Zhao M, Lee J et al. Impact of precision medicine in diverse cancer: a meta-analysis of phase II clinical trials. Journal of Clinical Oncology. 2015 Aug 24; 33(32), 3817-3825. https://doi.org/10.1200/JCO.2015.61.5997
3. Kato S, Kim K.H, Lim H.J, et al. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. Nat Commun 2020, Oct 2; (11) 4965. https://doi.org/10.1038/s41467-020-18613-3
4. Indiana University Health: Precision Genomics Clinic. https://iuhealth.org/find-medical-services/precision-genomics (accessed 4 March 2022)
5. Levit L.A., Kim E.S, McAneny B.L., et al. Implementing precision Medicine in Community-Based Oncology Programs: Three Models. J. Oncol Pract. 2019 June 1; (15), 325–329. https://doi.org/10.1200/JOP.18.00661
6. IU Health Precision Genomics Program. Available online: https://iuhealth.org/find-medical-services/precision-genomics (accessed on 3 March 2021)
7. Meric-Bernstam F, Farhangfar C, Mendelsohn, J, et al. Building a personalized medicine infrastructure at a major cancer center. J Clin Oncol. 2013 May 20; 31 (15): 1849–1857. https://doi.org 10.1200/JCO.2012.45.3043
8. Knepper TC, Gillian BC, Hicks JK, et al. Key lessons learned from Moffit's molecular tumor board: the clinical genomics action committee experience. The Oncologist. 2017 Feb 8; (22);144-151. http://doi: 10.1634/theoncologist.2016-0195
9. Precision Medicine Clinic (PMC) for Research. University of Kentucky Markey Cancer Center. Available online: https://ukhealthcare.uky.edu/markey-cancer-center/research/pmc (accessed on 4 March, 2022)

Disclosure

JS has received honorarium from stra-Zeneca, Boehringer-Ingelheim, Jazz Pharma, G1 therapeutics, Jannsen and stra-Zeneca, Blueprint, Boehringer-Ingelheim, Eli Lilly, Jazz Pharma, G1 therapeutics, Jannsen, Novartis, Oncocyte, Pfizer, Takeda. **MM**

Relationship Between Weight and Severity of Fibromyalgia

by Karla Núñez-Nevárez, MsC, Alicia López-Betancourt, PhD, Vicente Cisneros-Pérez, PhD, Cinthya Nallely Rodríguez-Márquez, Graciela Zambrano Galván, PhD, Abelardo Camacho-Luis, PhD & Martha-Angelica Quintanar-Escorza, PhD

There is a positive correlation between the severity of fibromyalgia symptoms and higher than ideal BMI. Efforts to reduce obesity among fibromyalgia patients is an important component of treatment.



Karla Núñez-Nevárez, MsC and Cinthya Nallely Rodríguez-Márquez, Biochemistry Research Laboratory; Alicia López-Betancourt, PhD, Faculty of Exact Sciences, Juárez University, Durango, México. Vicente Cisneros-Pérez, PhD, Graciela Zambrano Galvan, PhD, Abelardo Camacho Luis, PhD, and Martha Angélica Quintanar Escorza, PhD, (above), are all in the Faculty of Medicine and Nutrition, Juárez University, Durango, México.

Abstract

Fibromyalgia is a chronic pain syndrome with diffuse pain, muscle weakness, and other symptoms. A relationship between the severity of symptoms and obesity has been observed.

Objective

To determine the relationship between weight and the severity of fibromyalgia.

Material and Methods

42 patients with fibromyalgia were studied. BMI and fibromyalgia severity are classified weight by FIQR. Results: The mean age was 47.3 ± 9.4 years, 78% presented severe and extreme fibromyalgia, and 88% were overweight or obese. There was a positive correlation between the severity of the symptoms and the BMI (r = 0. 309). The reliability test for FIQR presented a Cronbach's α of 0.94.

Conclusion

About 80% of the participants do not show controlled symptoms, and their prevalence of obesity is high, observing a positive correlation between both.

Introduction

Fibromyalgia was recognized in 1990 by the American College of Rheumatology (ACR)[1] and in 1992 by the World Health Organization (WHO).[2] In 1990, the ACR created the Diagnostic Criteria for Fibromyalgia,[3,4] which was last updated in 2016.[5] It is conceptualized as a chronic pain syndrome with diffuse pain, accompanied by muscle weakness and various symptoms such as chronic fatigue, sleep disorders, morning stiffness, headache, cognitive disturbances, anxiety, depression, irritable bowel syndrome, and others.[1,4,6-8]

The worldwide prevalence of fibromyalgia is 2 to 4%,[9] and in Mexico, 0.7%.[10] It affects women with a 9:1 ratio compared to men, and the ages of most significant impact are between 25 and 50 years of age.[3,7] Numerous factors increase the propensity to suffer it, such as infections, trauma, autoimmune diseases, and psychological stress.[6,11]

Within the pathophysiology of fibromyalgia, there is evidence of central and peripheral sensitization, with alterations at the cerebral level, in sleep hours, presence of small fiber neuropathy, muscle and skin alterations, decreased serum levels of serotonin and melatonin and increased pro-

inflammatory cytokines, increased oxidants and decreased antioxidants and polymorphisms in genes related to serotonin, dopamine, and substance P.[1, 3, 7-9, 11-19]

The WHO recognized obesity in 1997 as a pathological entity of its own.[20] Suarez defines it as an abnormal or excessive accumulation of fat that can be detrimental to health. Pasca and Montero also gave a complete definition: "Chronic systemic, multi-organ, metabolic and inflammatory disease, multidetermined by the interrelationship between the genomic and the environmental, phenotypically expressed by an excess of body fat (about the sufficiency of the organism to accommodate it), which carries an increased risk of morbidity and mortality."[21]

The WHO refers to a prevalence of overweight and obesity in adults of 52% globally,[20] the Panamerican Health Organization (PAHO) of 58% in Latin America and the Caribbean, and the National Institute of Public Health (INSP) 72.5% in Mexico.[22,23] The WHO considers that the fundamental cause of obesity is an energy imbalance between calories consumed and calories expended due to an increase in the intake of high-calorie foods rich in fat and a decrease in physical activity.[20]

Obesity can be peripheral and central; in the former, hyperplasia of the adipocytes remains functional, with an accumulation of peripheral subcutaneous fat. In the second, there is hypertrophy of the adipocytes, with translocation of fatty acids to the liver, heart, muscle, pancreas, and brain and release of pro-inflammatory factors, such as IL-6 and TNF-α, and insulin resistance.[21]

Other authors have found a significant relationship between increased pain and obesity (p=0.016) and symptom severity and obesity (p=0.017). Likewise, a low positive correlation was found between pain and seriousness to obesity (r=0.277, p=0.002; r=0.292, p=0.001).[24]

Due to those mentioned above, this study was conducted to determine the relationship between weight and fibromyalgia severity, using the Revised Fibromyalgia Impact Questionnaire (FIQR), since there are no studies on this subject Mexican population, nor studies on obesity in fibromyalgia using the FIQR.

Table 1. Sociodemographic characteristics of the participants.
Source: Author's elaboration

Variable		n	%
Sex	Women	37	88
	Men	5	12
Marital status	Single	10	24
	Married	24	57
	Free Union	3	7
	Divorced	5	12
Education	Middle school	5	12
	High school	9	21
	Bachelor's degree	18	43
	Master´s degree / PhD	10	24
Occupation Employee	Employee	17	41
	Businessman	4	9
	Trader	2	5
	Housekeeper	5	12
	Retired	4	9
	Disability pensioner	1	3
	Unemployed	4	9
	Other	5	12

Material and Methods

A descriptive, correlational and retrospective study was conducted, of 42 participants with a diagnosis of fibromyalgia, contacted in the rheumatology and pain clinic of physicians in Durango, Mexico, as well as in the associations "Por el Derecho a Existir con Fibromialgia y EM/SFC" and "CreSer Fibromialgia Bajío"; during the years 2019

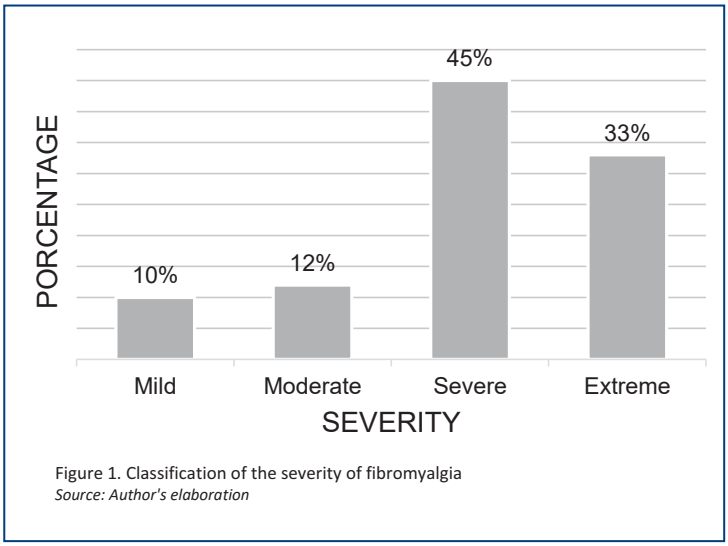


Figure 1. Classification of the severity of fibromyalgia
Source: Author's elaboration

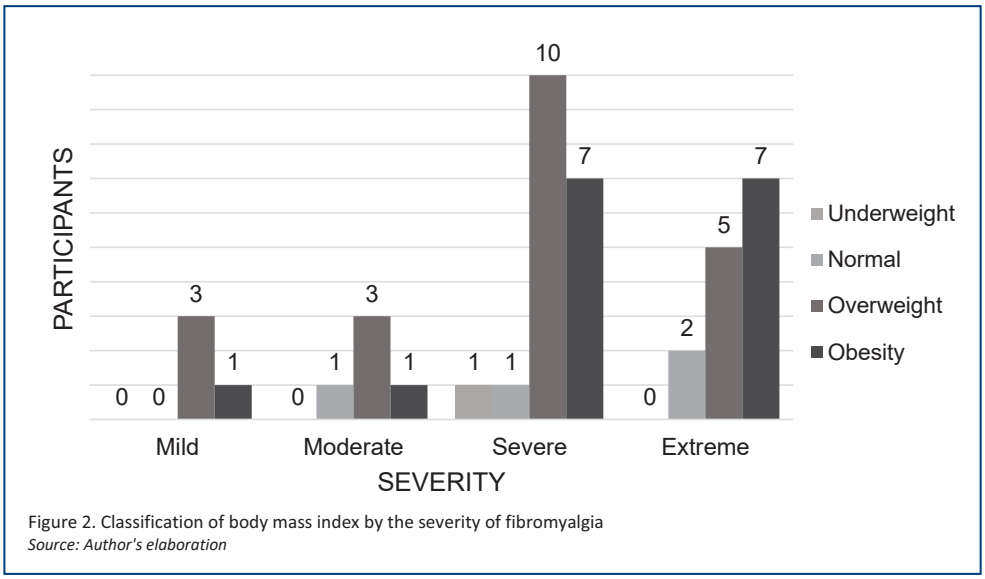


Figure 2. Classification of body mass index by the severity of fibromyalgia
Source: Author's elaboration

and 2020. The inclusion criteria were aged 30 to 70 years and who met the 2016 Fibromyalgia Diagnostic Criteria from the ACR. The exclusion criteria were pregnant or postpartum women, as well as cancer.

Sociodemographic data were collected through a structured questionnaire. To classify the severity of fibromyalgia, the FIQR was used, which is an author-reported Likert-type scale containing 21 items divided into three components (function, widespread impact, and severity of symptoms)[25] and which considers a maximum of 100 points, classifying it as mild (0-42 points), moderate (43-59 points), severe (60-74 points) and extreme (75-100 points). Its Spanish version was validated by Salgueiro et al. with a Cronbach's α coefficient of 0.95.[26]

For the anthropometric measurement, the body mass index (BMI) was taken into account, which classifies weight as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), and obese (≥30).[20]

The information was analyzed with the IBM SPSS Statistics 21 statistical program, looking for measures of central tendency, graphs, normality tests, chi-square, Pearson correlation, and reliability tests.

The research had the approval of the Academic Committee of the Master's Degree in Health Sciences of FAMEN-UJED and the Research Committee and Research Ethics Committee of Hospital General 450 (folio #166). It complied with the Regulations of the General Health Law on Health Research and the International Ethical Guidelines for Biomedical Research on Human Subjects, and all participants signed an informed consent form.

Results

The were 49 participants who agreed to participate in this study: 42 fulfilling the inclusion criteria. The mean age was 47.3 ±9.4 (30-64) years. Table 1 shows their sociodemographic characteristics.

Thirty-one percent of the participants mentioned having one or more family members with fibromyalgia, and only six participants reported not suffering from any other pathology besides fibromyalgia. They presented a fibromyalgia evolution time of 16.7 ±13.2 (3-52) years, with a delay of 9.6 years between the onset of symptoms and their diagnosis. Regarding fibromyalgia severity, a mean of 70.3 ±16.9 (27-98) points on the FIQR was obtained. Seventy-eight percent were found to have severe to extreme fibromyalgia (Figure 1).

Within the anthropometric measurements, a mean weight of 77.2 ±13.5 (49.0-107.2) kg, height

Table 2. Chi-square for the severity of fibromyalgia and BMI.

		BMI				Total
		Underweight	Normal	Overweight	Obesity	
Severity	Mild	0	0	3	1	4
	Moderate	0	1	3	1	5
	Severe	1	1	10	7	19
	Extreme	0	2	5	7	14
Total		1	4	21	16	42

Source: Author's elaboration
(p=0.817)
BMI: body mass index

Table 3. Pearson's correlation between BMI and FIQR score, including its three components.

Variable	Correlation	*p*
Fibromyalgia severity	0.127	0.424
Function (FIQR1)	-0.007	0.963
Overall Impact (FIQR2)	-0.080	0.614
Symptoms (FIQR3)	0.309*	0.046

Source: Author's elaboration
**statistically significant.*
BMI: body mass index
FIQR: Revised Fibromyalgia Impact Questionnaire

of 1.63 ±0.07 (1.45-1.80) m and BMI of 29.0 ±4.6 (18.0-41. 9) kg/m2, observing that 88 % of the participants were located between overweight and obesity, with 48 % of those overweight being concentrated in severe fibromyalgia and 88% of those obese being equally distributed between severe and extreme fibromyalgia (Figure 2).

Shapiro-Wilk goodness-of-fit tests were performed for the severity and BMI variables, finding a normal distribution of the data (p=0.081 and p=0.100, respectively). Chi-square tests were performed, which were not significant (p=0.817). However, it was observed that 89.4 % of those with severe fibromyalgia and 85.7 % of those with extreme fibromyalgia were overweight or obese (Table 2).

The three components of the FIQR were analyzed (Table 3), finding significant data in the third component (symptoms), with a positive correlation between this and BMI (r=0.309). The correlations with the first (function) and second (overall impact) components and the FIQR as a whole were not statistically significant. A reliability test was performed for the FIQR, finding a Cronbach's α of 0.94.

Discussion

Fibromyalgia is chronic and has very diverse symptomatology. It has a worldwide prevalence of 2 to 4% and 0.7% in Mexico; however, due to the little knowledge about it and the difficulty of its diagnosis, these data could underestimate the true prevalence. The mean age found, 46.6 ±9.93 years, agrees with the ages of the most significant impact of 25 to 50 years that have been recorded,[3] falling within the range of the economically active population. Although 67% have professional or higher education, only 55% are gainfully employed,

which could be because the severity of the symptoms does not allow them to maintain a job.

Of the six participants who reported having no comorbidities, only two were not overweight or obese, so the prevalence of comorbidities was higher than in Spanish patients (84 %).[27] A delay of 9.6 years was found between the onset of symptoms and diagnosis, confirming the difficulty in diagnosis. Even though 93% take medication to control their symptoms, only four participants present mild fibromyalgia, finding 78% between severe and extreme, with a mean of 70.3 ±16.9 points on the FIQR, similar to what was found when the instrument was validated in its Spanish version.[26]

The mean BMI was 29.0 ±4.6 kg/m^2, very similar to that of other Mexican and Turkish patients.[28, 29] A large number of overweight participants present severe fibromyalgia (48%) and most of those with obesity present severe to extreme fibromyalgia (88%); these anthropometric alterations could be caused by the sedentary lifestyle of most of the patients, mostly generated by the multiple uncontrolled symptoms of the disease, which in turn causes an increase in these symptoms, and consequently a cycle that deteriorates the quality of life.[24,30,31]

When studying the three components of the FIQR separately, it was found that the third (severity of symptoms) presents a positive correlation with BMI (r=0.309). Despite the sample size, the above resembles other investigations using scales different from the FIQR, with samples of more than 100 patients. A reliability test of the FIQR was performed to assess whether the instrument was adequate, finding a Cronbach's α of 0.94, similar to that presented by Salgueiro when validating his Spanish version[26], which is essential since it is a more updated instrument to assess the severity of fibromyalgia specifically.

One limitation of this study is the small number of participants, due to the underdiagnosis of the disease and the health crisis caused by the SARS-CoV-2 pandemic, which led to the suspension of many specialty medical consultations and preventive health measures, including social isolation. Another limitation was the lack of information on the level of exercise of the participants. Nevertheless, we consider that the data obtained during this investigation reflect the magnitude of the effects of weight concerning the severity of fibromyalgia. It would be important to conduct a longitudinal study to observe whether the weight decrease would lead to the decrease in fibromyalgia severity.

Conclusion

Most of the participants present at least one pathology in addition to fibromyalgia. We observed that about 80% of the participants do not show controlled symptomatology, and their prevalence of obesity is high; this, added to the fact that it was observed that there is a positive correlation between the severity of symptoms and BMI. This leads us to conclude that it would be of great importance to conduct a study with a larger sample, where the leading causes of obesity in these patients are also investigated, to find better treatments to reduce the symptomatology and improve the quality of life. We found that the Spanish version of the FIQR is a reliable instrument for the population studied, so it can continue to be used in the Mexican people for subsequent studies.

References

1. Fitzcharles, M. A., Ste-Marie, P. A., Goldenberg, D. L., Pereira, J. X., Abbey, S., Choinière, M., . . . Shir, Y. (2012). Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome. Oshawa (ON): Canadian Pain Society (CPS), 1-44. Retrieved from http://rheum.ca/en/publications/cra_fm_guidelines.
2. WHO Scientific Group on Rheumatic Diseases & World Health Organization. (1992). Enfermedades reumáticas : informe de un grupo científico de la OMS [se reunió en Ginebra del 26 al 30 de junio de 1989]. Organización Mundial de la Salud. ISSN 0509-2507. https://apps.who.int/iris/handle/10665/39682
3. Berrocal Kasay, A. (2014). Fibromialgia: Un diagnóstico que debe ser oportuno. Revista Médica Herediana, 25, 93-97. ISSN 1729-214X.
4. Moyano, S., Kilstein, J. G., & Alegre de Miguel, C. (2014). Nuevos criterios diagnósticos de fibromialgia: ¿vinieron para quedarse? Reumatología Clínica. doi:10.1016/j.reuma.2014.07.008
5. Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. L., Mease, P.J., Russell, A.S, Russell, I.J., & Walitt, B. (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Seminars in Arthritis and Rheumatism, 46, 319-329. doi:10.1016/j.semarthrit.2016.08.012
6. Clauw, D. J. (2014). Fibromyalgia: A Clinical Review. JAMA, 311, 1547-1555. doi:10.1001/jama.2014.3266
7. Covarrubias Gómez, A., & Carrillo Torres, O. (2016). Actualidades conceptuales sobre fibromialgia. Revista Mexicana de Anestesiología, 39, 58-63. Retrieved from http://www.medigraphic.com/rma

8. Sánchez Domínguez, B., Bullón, P., Román Malo, L., Marín Aguilar, F., Alcocer Gómez, E., Carrión, A. M., Sánchez Alcazar, J.A., & Cordero, M. D. (2015). Oxidative stress, mitochondrial dysfunction and, inflammation common events in skin of patients with Fibromyalgia. Mitochondrion, 21, 69-75. doi:10.1016/j.mito.2015.01.010
9. Fatima, G., Das, S. K., & Mahdi, A. A. (2015). Some oxidative and antioxidative parameters and their relationship with clinical symptoms in women with fibromyalgia syndrome. International Journal of Rheumatic Diseases, 39-45. doi:10.1111/1756-185X.12550
10. Peláez Ballestas, I., Sanin, L. H., Moreno Montoya, J., Alvarez Nemegyei, J., Burgos Vargas, R., Garza Elizondo, M., Rodríguez Amado, J., Goycochea Robles, M.V,, Madariaga, M., Zamudio, J., Santana, N., & Cardiel, M. (2011). Epidemiology of the rheumatic diseases in Mexico. A study of 5 regions based on the COPCORD methodology. The Journal of Rheumatology Supplement, 86, 3-8. doi.org/10.3899/jrheum.100951.
11. Häuser, W., Ablin, J., Fitzcharles, M.-A., Littlejohn, G., Luciano, J. V., Usui, C., & Walitt, B. (2015). Fibromyalgia. Nature reviews Disease primers, 1(1), 1-16. doi:10.1038/nrdp.2015.22
12. Barrera Villalpando, M. I., Cortés Sotres, J. F., Mendieta Cabrera, D., & Guerrero León, D. (2015). Disminución del influjo parasimpático en fibromialgia: Su relación con la Psiquiatría en un centro especializado de referencia nacional. Salud Mental, 38, 123-128. ISSN 0185-3325.
13. Cordero, M. D., Alcocer-Gómez, E., Cano-García, F. J., De Miguel, M., Carrión, A. M., Navas, P., & Alcázar, J. A. S. (2011). Clinical symptoms in fibromyalgia are better associated to lipid peroxidation levels in blood mononuclear cells rather than in plasma. PLoS One, 6(10). doi:https://doi.org/10.1371/journal.pone.0026915
14. Doppler, K., Rittner, H. L., Deckart, M., & Sommer, C. (2015). Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia. Pain, 156(11), 2319-2325. doi:http://dx.doi.org/10.1097/j.pain.0000000000000285
15. Fayed, N., García Martí, G., Sanz Requena, R., Marti Bonmatí, L., & Garcia Campayo, J. (2017). Diferencias en el volumen cerebral regional entre pacientes de fibromialgia y meditadores de larga duración. Actas Españolas de Psiquiatría, 45, 268-276. ISSN 1139-9287.
16. La Rubia, M., Rus, A., Molina, F., & del Moral, M. L. (2013). Is fibromyalgia-related oxidative stress implicated in the decline of physical and mental health status? Clin Exp Rheumatol, 31, 121-127. PMID: 24373370.
17. Limas Santos, N. I., & Contreras Sánchez, J. (2019). Asociación de neuropatía de fibras pequeñas y fibromialgia en el Hospital Central Militar. Revista de Sanidad Militar, 73(3-4), 201-205. doi:https//dx.doi.org/10.35366/SM193_4B
18. Mendieta, D., De la Cruz Aguilera, D. L., Barrera Villalpando, M. I., Becerril Villanueva, E., Arreola, R., Hernández Ferreira, E., Pérez Tapia, S.M., Pérez Sánchez, G., Garcés Alvarez, M.E., Aguirre Cruz, L., Velasco Velázquez, M.A., & Pavón, L. (2016). IL-8 and IL-6 primarily mediate the inflammatory response in fibromyalgia patients. Journal of neuroimmunology, 290, 22-25. doi:http://dx.doi.org/10.1016/j.jneuroim.2015.11.011
19. Ramírez, M., Martínez-Martínez, L.-A., Hernández-Quintela, E., Velazco-Casapía, J., Vargas, A., & Martínez-Lavín, M. (2015). Small fiber neuropathy in women with fibromyalgia. An in vivo assessment using corneal confocal bio-microscopy. Paper presented at the Seminars in Arthritis and Rheumatism. doi.org/10.1016/j.semarthrit.2015.03.003.
20. WHO, O. M. d. l. S. (2020). Obesidad y sobrepeso. Centro de prensa. Retrieved from https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight
21. Suárez Carmona, W., Sánchez Oliver, A. J., & González Jurado, J. A. (2017). Fisiopatología de la obesidad: Perspectiva actual. Revista chilena de nutrición, 44(3), 226-233. http://dx.doi.org/10.4067/s0717-75182017000300226.
22. OPS, O. P. d. l. S. (2017). Sobrepeso afecta a casi la mitad de la población de América Latina y el Caribe. Noticias. Retrieved from https://www.paho.org/costa-rica/index.php?option=com_content&view=article&id=348:sobrepeso-afecta-poblacion-america-latina-y-caribe&Itemid=314
23. Rivera Dommarco, J., Colchero, M., Fuentes, M., González de Cosío Martínez, T., Aguilar Salinas, C., Hernández Licona, G., & Barquera, S. (2018). La obesidad en México. Estado de la política pública y recomendaciones para su prevención y control. Salud Pública de México: Ciudad de México, Mexico. ISBN: 978-607-511-179-7.
24. Koçyiğit, B. F., & Okyay, R. A. (2018). The relationship between body mass index and pain, disease activity, depression and anxiety in women with fibromyalgia. PeerJ, 6, e4917. doi:https://doi.org/10.7717/peerj.4917
25. Bennett, R. M., Friend, R., Jones, D. P., Ward, R., Han, B. K., & Ross, R. L. (2009). The Revised Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Research & Therapy, 11. doi:https://doi.org/10.1186/ar2783
26. Salgueiro, M., García-Leiva, J. M., Ballesteros, J., Hidalgo, J., Molina, F., & Calandre, E. P. (2013). Validation of a Spanish version of the Revised Fibromyalgia Impact Questionnaire (FIQR). Health and Quality of Life Outcomes, 11. doi:10.1186/1477-7525-11-132
27. Collado, A., Gomez, E., Coscolla, R., Sunyol, R., Solé, E., Rivera, J., Altarriba, E., Carbonell, J. & Castells, X. (2014). Work, family and social environment in patients with Fibromyalgia in Spain: an epidemiological study: EPIFFAC study. BMC health services research, 14(1), 1-10. doi:https://doi.org/10.1186/s12913-014-0513-5
28. Esparza Santillán, A. K., Hernández Ramírez, A. M., Muñoz Hermosillo, D. J., & Ramírez Orozco, R. E. (2021). Relación entre la composición corporal y sintomatología en mujeres de Aguascalientes que padecen fibromialgia. Lux Médica, 16(48). Retrieved from https://revistas.uaa.mx/index.php/luxmedica/article/view/3269. ISNN 2007-1655.
29. Toker, A., Kucuksen, S., Kucuk, A., & Cicekler, H. (2014). Serum ischemia-modified albumin and malondialdehyde levels and superoxide dismutase activity in patients with fibromyalgia. Clin Lab, 60(10), 1609-1615. doi:10.7754/Clin.Lab.2014.131017
30. Fred Jiménez, R. M., Arroyo Ávila, M., Mayor, Á. M., Ríos, G., & Vilá, L. M. (2016). Clinical manifestations associated with overweight/obesity in Puerto Ricans with fibromyalgia syndrome. Journal of obesity, 2016. https://doi.org/10.1155/2016/1379289.
31. Gota, C. E., Kaouk, S., & Wilke, W. S. (2015). Fibromyalgia and obesity: the association between body mass index and disability, depression, history of abuse, medications, and comorbidities. JCR: Journal of Clinical Rheumatology, 21(6), 289-295. http://doi:10.1097/RHU.0000000000000278.

Acknowledgment

We would like to thank Edgar Felipe Lares Bayona, MSc., from the Institute of Scientific Research (IIC) of the Universidad Juárez del Estado de Durango, for his support at the beginning of this research. Also to Edgar Hernández Vargas, MD, and Carlos Francisco Martínez Ortiz, MD, for their support in obtaining participants in Durango. Verónnica Scutia, president of the civil association "Por el Derecho a Existir con Fibromialgia y SFC/EM," and M.H. Liliana Izaguirre Hernández, state representative of the civil association "CreSer Fibromialgia Bajío," for inviting more participants to join this research.

Disclosure

None reported. **MM**



Sequential pulses
to a polyp ignited a

surgical fire

in the patient's airway.

Surgical fires were among the 10 most common sentinel events reported by hospitals to the Joint Commission in 2021.*

If a sentinel event happens and a ProAssurance insured is involved, they have direct access to medical liability claims specialists and risk management consultants with experience navigating these types of malpractice claims.

We've seen the worst you can imagine and have the expertise to help reduce risk and ensure a vigorous defense from day one. The principle of fair treatment guides every action we take in defense of our physicians and healthcare providers.

PROASSURANCE®
Treated Fairly

Healthcare Professional Liability Insurance & Risk Management Services

* The Joint Commission, *Sentinel Event data released for first 6 months of 2022*. Visit: **bit.ly/3zzsloj**

ProAssurance.com • 800-282-6242

Introducing
A Malpractice Program

FOR BOARD CERTIFIED PLASTIC SURGEONS IN MISSOURI

MSMA – together with MedPro Group – has worked diligently to provide an industry-leading healthcare liability solution for Board Certified Plastic Surgeons.

Carrier Highlights:

- MedPro Group has an A++ (A.M. Best) financial strength rating
- Local defense provided by Missouri legal experts and claims managers
- A Berkshire Hathaway company that has defended physicians since 1899

Highly competitive rates matched with industry-leading coverage

- Prior acts coverage available: no tail purchase required to participate in program
- Free retirement tail after one year of coverage, regardless of age
- $50K cyber liability coverage at no additional charge
- Available policy types: Claims-made, Occurrence, and Convert to Occurrence®
- Comprehensive risk management solutions including on-site risk consultations, online courses, and free assessment tools

Reach out to Mary Hogan to find out why MedPro is the best fit for you.

Mary Hogan
MSMA Insurance Agency
636.922.9201 | 866.676.2467

A.M. Best rating as of 7/14/2022. Standard & Poor's rating as of 9/29/2021. All data is derived from MedPro Group records and calculations; claims data range is 2012-2021 unless otherwise indicated. In order to qualify for a free tail, you must have a retroactive date at least 48 months prior to the date of retirement and be insured by the company for 12 months on a mature Claims-made policy. MedPro Group is the marketing name used to refer to the insurance operations of The Medical Protective Company, Princeton Insurance Company, PLICO, Inc. and MedPro RRG Risk Retention Group. All insurance products are administered by MedPro Group and underwritten by these and other Berkshire Hathaway affiliates, including National Fire & Marine Insurance Company. Product availability is based upon business and/or regulatory approval and may differ among companies. © 2022 MedPro Group Inc. All Rights Reserved. MW-220858