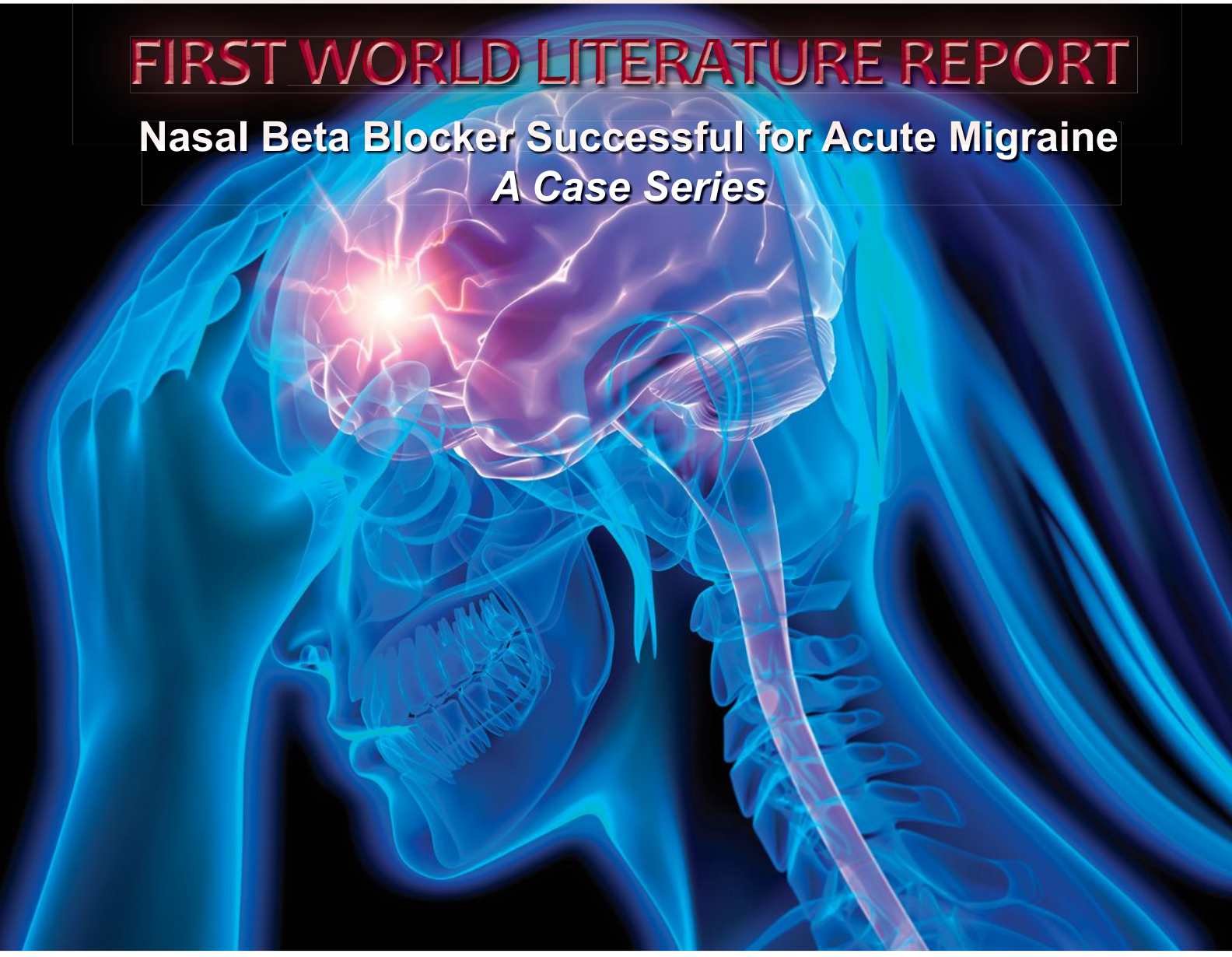
Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine January/February 2024

FIRST WORLD LITERATURE REPORT

Nasal Beta Blocker Successful for Acute Migraine
A Case Series



Kansas City University

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Pain, Depression, Opioid Use & Neurodegeneration

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MSMA member authors are bold in Table of Contents and throughout the Journal. MSMA member authors whose manuscripts are accepted to Missouri Medicine receive priority in the publication queue. Scan to join!

Missouri Medicine

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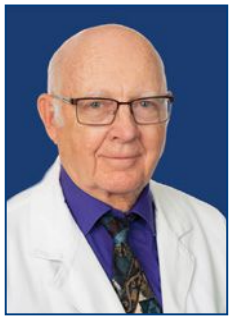
FIRST WORLD LITERATURE REPORT



Attention Pharma & Headache Researchers! Nasal Spray Timolol May Be the Next Great Thing for Acute Migraine

by John C. Hagan, III, MD

There is potential for a major new method of treating acute migraines using a nasal spray beta blocker. It is way past time for larger studies.



Migraine is the third most prevalent disease in the world and foremost among common neurological illnesses. One out of every four households in the United States has someone with migraine; there are over forty-two million Americans and more than a billion migraine headache sufferers world-wide.[1,2] Most people with migraine are not satisfied with their current headache treatment. Many are looking for something better to add to or replace their present acute migraine medications. These migraineurs and their physicians should be heartened by the article "Nasally Delivered 0.5% Timolol Beta Blocker Successfully Treats Acute Migraines in a Referral Headache Clinic: A Case Series" in this issue. It is a first world literature report; hopefully larger studies will follow and confirm our positive results and lead to an FDA approved migraine medication.

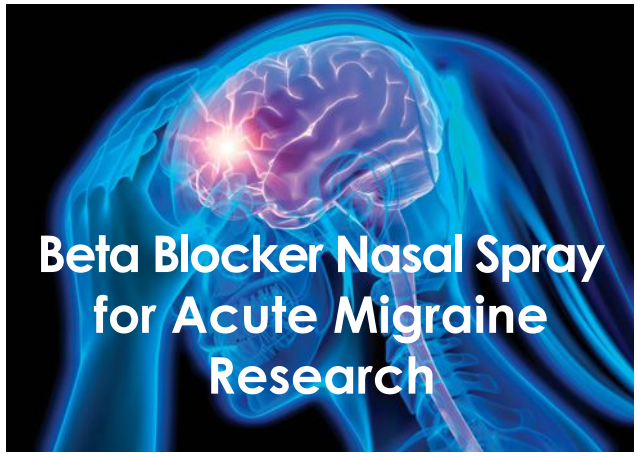
John C. Hagan, III, MD, FAAO, is a Kansas City, Missouri, ophthalmologist and *Missouri Medicine* Editor since 2000.

There is the potential for a major new method of treating migraines using nasal spray beta blockers (BB), in this study timolol 0.5%. That is there is potential if a pharmaceutical company or a group of migraine researchers develop an interest, fund, then conduct a desperately-needed large, multi-center, placebo-controlled study. That quest has been the central focus of my research efforts for the past 11 years. The glacial pace of research development is inexcusable.

In 2014, Carl V. Migliazzo, MD, and I reported the world's first case-controlled series of acute migraine responsive to timolol 0.5% eye drops applied topical to normal eyes. The mechanism is simple and forthright; the timolol travels from the external eye through the lacrimal duct into the nose where it is very rapidly absorbed by nasal mucosa. Therapeutic migraine attenuating blood levels are reached in minutes. Taken as a pill orally at first onset of acute migraine, BBs have not worked because they have slow absorption and never reach therapeutic levels. Our good results were subsequently vindicated in a small, placebo control study done at University of Missouri - School of Medicine[4] and a large, placebo-controlled study reported in *JAMA Ophthalmology* (50 patients with over 600 acute migraines).[5] In the same issue published comment about the latter article, the concept, and need for further research were endorsed by an internationally known migraine authority.[6]

Why put BB in the eye when you want BB on the nasal mucosa? Good question and one Dr. Migliazzo and I proposed in our 2014 article. We suggested direct nasal application by BB spray. For the past 10 years I have been trying to interest academia and big-small-medium size pharma in just such a study of nasal spray BB. Like most things in life, it boils down to money. For academia, at present, not enough money to fund a large study. For pharma, not enough perceived potential for over-the-top profits. As one company told me, "Why would we want to develop an effective BB nasal spray that would compete with our more expensive and profitable migraine medications?"

My disgust and rage bubbled to the surface in the *Missouri Medicine* editorial of January/February 2022, "It Should Not Be This Difficult to Engage Pharma in an Effective, Safe, Inexpensive Product for Acute Migraine, the Third Most Prevalent Disease in the World."[3] Ever optimistic, some would say naïve, I expected to hear from pharma companies anxious to fund development and/or headache researchers intent on writing a large grant proposal to NIH. The lone response I got was from Steven C. Kosa, MD, a highly regarded headache specialist at our North Kansas



SCAN CODE TO TRACK RESEARCH

- **2022 Beta Blocker Acute Migraine and Pharma Funding**
- **2018 Research Update: Beta Blocker Eye Drops for Acute Migraine**
- **2014 Beta Blocker Eye Drops for Acute Migraine**

City Hospital. Working with O'Brien Compounding Pharmacy a 0.5% timolol nasal spray was developed, and tested in Dr. Kosa's referral headache clinic. The encouraging results are reported herein.

Our hope is that based on multiple positive published studies that either pharma or a group of neurology departments will fund and conduct larger studies that are needed. I fervently believe eventually an FDA approved BB nasal spray will be available to migraine patients who live in a world of hurt.

Let's make it happen!

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Cyber Attacks on Interoperable Electronic Health Records:



A Clear and Present Danger

by Lancer Gates, DO

There is a balance between health information availability and health information security. Cyber attacks present a clear and present danger to this balance.

The Apocolypse is Upon Us

The healthcare industry is the perfect cyber-attack victim because it depends on technology for patient care and revenue cycles. Today, the healthcare industry has become the number one victim of cyber attacks. In 2022, there were 1,463 cyber attacks per week globally.



Lancer G. Gates, DO, FACOI, is President of the Missouri State Medical Association for 2023–2024. He is a Hospitalist from Kansas City, Missouri.

Once attacked, hospitals must either (1) pay a ransom to the cyber-attackers (incentivizing and perpetuating future attacks on more hospitals) or (2) go on downtime (the average downtime for hospitals in 2022 was 24 days with an average cost of $10 million). Either way, access and resources for medical services are both compromised.

The nightmare scenario is a simultaneous cyber-attack at two or more hospitals in close geographic proximity. This two-hit hypothetical would compromise access to care for patients with time-critical diagnoses such as trauma services, code strokes, and code STEMIs.

Downtime and the Rapture

In November of 2023, the Fred Hutchinson Cancer Center in Seattle, Washington, was the victim of a cyber-attack. When the Cancer Center refused to pay the ransom, the cyber criminals directly emailed the Cancer Center patients, offering to remove their personal health information from the dark web for $50. Patients who did not accept the $50 offer received a threat of swatting (the act of

reporting a false claim of a crime to law enforcement so that SWAT teams arrive uninvited at a person's home address).

On December 19, 2023, cyber criminals attacked Liberty Hospital (LH) in Missouri. The criminals faxed a ransom note to the hospital administration. LH immediately went on downtime, and the emergency department closed to trauma, code stroke, code STEMIs, direct admissions, and incoming transfers. Neighboring hospitals provided midwest hospitality for patients requiring transfer for services suddenly unavailable at LH. Akin to the rapture, more than 50% of patients were either discharged from LH or transferred to neighboring hospitals by the end of the first day of the attack.

When the Computers Failed, the People Prevailed

When a cyber-attack occurs, patient transfers and ambulance diversions inundate neighboring hospitals. Typically, employed physicians have privileges at a single hospital, restricting their ability to assist at neighboring hospitals. During cyber attacks, this results in underutilizing physicians at the hospital under cyber-attack and overutilizing physicians at neighboring hospitals. To accommodate the increased patient volume at nearby North Kansas City Hospital (NKCH), the Liberty Hospitalist group graciously admitted patients to the hospital for the privately practicing Gates Hospitalist group (members of both the LH and NKCH medical staff) so that Gates Hospitalists could redeploy to assist NKCH. LH also granted a new Gates Hospitalist physician emergency privileges during this crisis.

Downtime Becomes Uptime

United by a common enemy and faced with shared adversity, the Liberty Hospital staff and physicians dedicated themselves to teamwork, enhanced professional interactions, and grace. The bridge across the digital divide was rebuilt, with experienced healthcare providers shepherding less experienced healthcare providers to the paper side of the divide. Once across the bridge, LH administrators remedied paper charting inefficiencies by decreasing nursing-to-patient ratios and limiting the number of inpatients.

The Electronic Health Record (EHR) is the most prominent reason physicians retire. None of the LH medical staff retired during the downtime with paper charting. During downtime, physicians had more time for clinical work because there was less clerical work. Physicians gained two minutes each day by not logging into a computer. They saved time with handwritten admission and discharge medication reconciliations. (In the EHR, there is a three-second delay following each medication reconciliation, and nearly every medication is listed twice as a home and hospital medication). Physicians enjoyed a reprieve from coding and documentation queries and pop-ups, although the local Hallmark distribution center might find a way to get pop-ups back on the paper chart.

The doorway to the hospital room became the "new patient portal." Direct interactions with patients and families replaced the social isolation associated with computer charting. Contemporaneous charting was timely, concise, and meaningful, replacing the EHR-associated delayed documentation and note bloat. Later into the cyber-attack, physicians were allowed to dictate H&Ps, consults, and discharge summaries. The cyber-attack provided transcriptionists with better employment opportunities.

Physician boots on the ground replaced telemedicine physician services. New physician orientation was faster because EHR training was unnecessary. Medical students replaced their styluses with pens and learned to chart on paper and write prescriptions. A daily debriefing and town hall meeting in the hospital auditorium replaced group emails and Zoom meetings.

Nursing and ancillary staff enjoyed more desktop space without the clutter of desktop computers, keyboards, and mice. Worksite safety improved with zero blue light exposure. Staff wellness improved with intermittent biceps strengthening exercises while carrying charts that got heavier each day the patient stayed in the hospital. The chart search replaced the Google search (first finding the chart and then finding what you needed in the chart). The staff's Latin abbreviations, spelling skills, and cursive handwriting improved (our 20th-century second-grade teachers are beaming with pride). Unfortunately, crime often begets crime, and there were isolated reports of looting of paper clips, rubber bands, chart dividers, a three-hole punch, a five-hole

punch, and even a desk on wheels from medical floors that had been closed.

Once the downtime extended into the new calendar year, we quickly adapted to date orders with the new calendar year. We also anticipate future benefits, such as referrals to our hand surgeon for carpal tunnel syndrome surgery.

Liberty Hospital was without computer access for several weeks, and during this time, paper charting was impervious to another cyber-attack. The LH staff could have succumbed to the Stockholm Syndrome (captives coming to love their captors), but we did not.

To move forward, we have to look at our steps along the path that led to hospital cyber-attacks.

The March to Electronic Health Record Interoperability

In 1996, the federal government took a step to protect electronic health records. The Health Insurance Portability and Accountability Act (HIPAA) provided (1) a privacy rule that established national standards to protect patient health information and (2) a security rule that set standards for the security of electronic patient health information.

In 2009, the federal government mobilized the hospital systems and increased the cadence of the march as it promoted EHR interoperability. The American Recovery and Reinvestment Act included three components of meaningful use:

1. Utilizing the EHR for meaningful use, such as e-prescribing
2. Exchanging health information to improve the quality of healthcare
3. Reporting clinical quality data

In 2016, the federal government drafted all remaining healthcare providers into the EHR interoperability effort. The 21st Century Cures Act (CURES) promoted electronic access, exchange, and use of health data. On May 1, 2020, the Office of National Coordinator (ONC) for Health Information Technology published the final CURES Act rule for interoperability and patient access. This rule required all healthcare providers to share electronic health information by October 6, 2022.

Halt the March, Identify the Enemy, and Define the Mission

Every successful military operation starts with identifying the enemy, evaluating their capabilities, and developing a clearly defined mission.

The enemy is the cyber-attacker, and their weapon is the internet. EHR interoperability requires an internet-based platform (open system) vulnerable to cyber-attacks. Interoperability places personal information, including our health records, financial information, insurance information, social security numbers, home addresses, and phone numbers, in clear and present danger.

It is time to define the hospital's primary mission in the context of the risks and benefits of EHR interoperability. Should the hospital's primary mission be to provide interoperability of electronic medical records for the federal government, third-party payers, and other healthcare systems? Or should the hospital's primary mission be to provide reliable, accessible care, and the best medical care while ensuring patient privacy?

A Paper Shield

In the Medieval Age, Don Quixote futilely fought windmills. In the Industrial Age, John Henry beat the steam engine but died immediately following his victory. Cyber-attacks threaten to bomb us from the Technology Age to the Pre-Technology Age of pen and paper. It is not a time to fight paper mills but to celebrate Arbor Day.

Hospitals must comply with federal requirements of meaningful use and interoperability that increase their risk of a cyber-attack. Hospitals' only option to decrease the risk of damage from a cyber-attack is to dedicate more resources to cybersecurity and cybersecurity insurance. Unfortunately, hospitals have limited resources for cybersecurity because federal, state, and commercial insurance reimbursement for healthcare services is decreasing while their costs for staff, supplies, and services are rising. Hospitals have to choose between providing computer care, and providing patient care.

The Nuclear Shield: An Open and Closed Case

In the 1983 fictional movie "War Games," a teenage computer geek inadvertently hacked into a government nuclear weapons website. His computer asked him, "Would you like to play a game?" The geek, thinking it was simply a game, started playing, and a series of events unfolded, after which a worldwide nuclear war nearly occurred. In November of 2007, the non-fictional computer worm Stuxnet exploited the vulnerabilities of Iran's nuclear program. The United States of America's nuclear arsenal has not been hacked in large part because our nuclear silos are on a closed system, an intranet rather than an internet-based system. This secure system provides our nuclear weapons with the highest level of security.

Cyber attacks on interoperable EHRs are a clear and present danger to patient's access to healthcare and personal information. It is time to recognize that hospitals are "mission critical" for healthcare in America. If our hospitals are to receive the same level of security that our nuclear silos receive, then our hospitals' EHRs should be on closed systems that are not interoperable and not accessible from outside the hospital. The only way to achieve this objective is by:

1. Revoking hospital EHR meaningful use requirements
2. Exempting hospitals from interoperability requirements
3. Requiring EHR vendors to offer closed/intranet EHR products to hospitals

Patients and physicians would benefit from the security of a closed hospital EHR system; however, there would be sacrifices, including:

- Loss of Interoperability
- Loss of the patient portal
- Termination of hospital telemedicine services
- Loss of remote access by medical staff
- Loss of e-prescribing

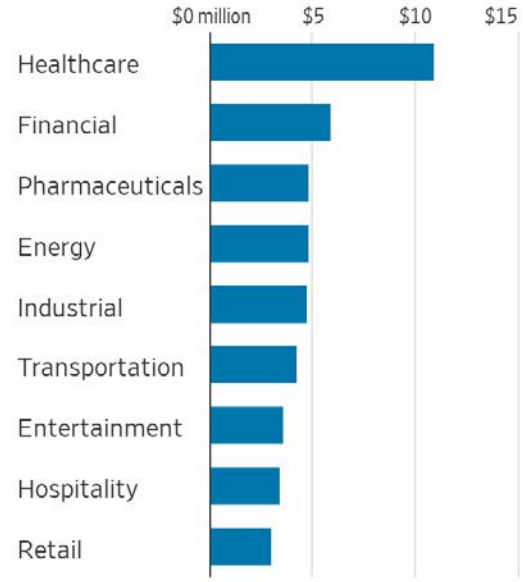
As long as hospital EHRs are interoperable, they are in clear and present danger of cyber-attacks. Having survived one of these hospital cyber-attacks, I strongly encourage our elected officials to reevaluate the risks and benefits of hospital EHR interoperability.

1 Picture = 1,000 Words

Liberty Hospital Determines Cyber-Security Incident Caused Patient Care Disruption

(December 19, 2023)

Hospital Ransom Hacks Highest Ever in 2023



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The State of Missouri's Public Health

by Paula F. Nickelson, MEd

DHSS remains committed to confronting these challenges collaboratively with all partners, including supporting individuals to take the lead in changing their personal health outcomes.

Missouri Department of Health and Senior Services (DHSS) is honored to once again offer a perspective on the 'state of the state's health' for *Missouri Medicine*, including insights into trends in our health data and current or planned initiatives to address many of these concerning statewide health outcome issues. We are grateful for the partnership of Missouri State Medical Association and members, as well as many other state-level and academic partners in this collective pursuit. It is only through the integrated and collaborative work of these strategic and vital partnerships that our state's health outcomes will improve.

Life Expectancy in Missouri

In 2022, Missouri's life expectancy rebounded from 74.6 years to 75.4 years having fallen steeply immediately following the COVID-19 outbreak. However, the 2022 life expectancy is still about two years lower than our state's life expectancy was in 2019 and remains about two years under the national life expectancy of 77.5 years in 2022. Further, the disparity in life expectancy between white and black/African-American Missourians remains substantial, with white men living 8.5 years longer than black men and white women living 4.4 years longer than black women.

Leading Causes of Mortality in Missouri

In 2022, heart disease and cancer remain the two leading causes of death in Missouri and nationwide with unintentional injuries, and COVID-19 in third and fourth positions respectively. In 2021, COVID-19 displaced unintentional injury as the third leading cause, but that has since reversed. Chronic lower respiratory disease, stroke, Alzheimer's disease, and diabetes ranked fifth through eighth, chronic kidney disease and suicide remained the ninth and tenth leading causes, both experiencing slight increases since 2021. A game show-inspired statewide multimedia campaign launched this month that brings awareness to risk factors associated with these leading causes of death among Missourians and how modifications in one's lifestyle can change one's trajectory through life.





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Obesity: Underlying Factor in Chronic Disease

Obesity is recognized as both a standalone chronic disease and a major contributor to the onset and progression of several other chronic diseases including Type 2 diabetes, cardio– and cerebro–vascular diseases, chronic kidney disease, and several cancers, underscoring a major public health concern. According to the 2022 Missouri County Level Study, with an obesity prevalence rate of 36.5% in adults, Missouri continues to outpace the national average of 33.6%. There is a complex interaction between several socioeconomic factors and chronic disease rates. In 2022, individuals from households earning under $50,000 annually were 40% more likely to experience obesity than those with household incomes of more than $150,000.

Aging Population in Missouri

Missouri's population is growing older. The number of Missouri citizens who are 65 years and older has grown nearly 23% from 2012-2022, and the median age has increased from 38.0 to 39.2 over the last 10 years. Missouri's median age is also older than the US median age overall (39.2 versus 38.8). Health conditions that occur with increased aging are also on the rise. Alzheimer's disease is the sixth leading cause of death rising by 143.1% in Missouri between 2000-2019.

Unintentional Drug Overdose Deaths in Missouri

Out of the top 10 leading causes, unintentional injury deaths have experienced the greatest increase when comparing 2012-2022, with a total increase of 59.4%. Unintentional drug overdose, a sub-category of unintentional injury, is the primary driver of this increase. More than 90% of the opioid deaths are fentanyl-related. Just over half (52%) of all opioid-related deaths occurred in St. Louis metropolitan residents. However, other areas of the state are increasing at much faster rates. Opioid-related Jackson County (Kansas City area) resident deaths have nearly tripled from 2019 to 2022.

Public Health and Healthcare Workforce Investments

A standing advisory council under the leadership of DHSS and the Office of Workforce Development within the Missouri Department of Higher Education and Workforce Development (DHEWD/OWD) was established to coordinate workforce initiatives statewide relative to titles in the fields of public health, healthcare, oral health and behavioral health.



State Health Assessment: https://health.mo.gov/healthplans/pdf/state-health-assessment.pdf

Workforce investments from the FY24 legislature included funding for Graduate Medical Education positions to existing residency programs seeking to expand and dedicated to assuring sustained support of new residency slots above their existing Medicare-capped positions. As well, DHSS has led a planning effort in collaboration with various partners and in consultation with a federal contractor to develop a state strategy to expand our existing residency capacity which currently only offers adequate residencies to about two-thirds of the medical students graduating from Missouri-based medical programs. Research has proven that students who train and conduct their residency in a specific geographic region are about 75% more likely to remain in that geographic region to practice so it is highly beneficial to us to increase our residency positions in the state. Missouri would currently require approximately 600 primary care

physicians and 160 psychiatrists to eliminate the Health Professional Shortage Area (HPSA) designations statewide.

The legislature changed an existing statute and dedicated funding to allow DHSS, in collaboration with the Missouri Department of Mental Health and the Office of Workforce Development, to annually designate specific titles within public health, healthcare and behavioral health for general revenue-funded local reimbursement based upon workforce data. FY24 budget also included funding for assistance to training programs for certified nursing assistants.

Maternal Mortality in Missouri

Missouri continues to experience one of the highest rates of maternal mortality in the US. The 2023 report of the Missouri Pregnancy Associated Mortality Review Board for 2018-2020 found an average of 70 Missouri women per year died while pregnant or within a year of pregnancy. As recommended by the Governor, the legislature appropriated funding to DHSS to implement evidence-based practices to address maternal mortality including the establishment of a perinatal health access collaborative to allow access to psychiatric expertise, training for maternal care providers and the establishment of a maternal and child health dashboard.

The FY24 legislative session also included extended post-partum Medicaid coverage for twelve months following pregnancy. In late 2023, a new website was launched called "Healthy Moms, Healthy Babies" with the mission of connecting women to quality healthcare and supportive resources that will provide healthy, successful pregnancy and post-partum experiences for both mom and baby. The site is a collaboration between several Missouri state agencies: DHSS, the Department of Social Services, MO HealthNet Division, the Department of Mental Health, and the Department of Elementary and Secondary Education.

Infant Mortality in Missouri

Missouri is one of only four states along with Iowa, Georgia, and Texas that experienced a statistically significant increase in the overall infant death rate (classified as death of children under the age of one) between 2021 and 2022. African-American non-Hispanic infant death (13.2 per 1,000 live births) was more than twice the white rate in Missouri (5.5 per 1,000 live births), a consistent trend in Missouri for over a decade. The persistent racial disparity among infant/maternal deaths underscores the need to address these issues from a health equity and social determinants of health perspective rather than solely from a health care access perspective. One policy intervention which should be considered in Missouri is implementation of a standardized, state-wide Fetal Infant Mortality Review process to anonymously review all infant deaths to identify root causes and then implement policies to address those root causes.

Firearms Deaths Increase for Missouri Children and Teens

Violent deaths are affecting younger populations at higher rates and have been increasing in Missouri. When comparing to past years, suicide increased by 31.4% from 2012 to 2022 while homicide increased by 68.2% in the same timeframe. The increases in both the homicide and suicide death rate in Missouri were higher than the national homicide and suicide death increases. About 66% of suicides and 85% of homicides were firearm–related in 2022.

New Model for Public Health in Missouri: Foundational Public Health Services

In the January 2023 *Missouri Medicine* article, DHSS reported that our state's governmental public health system is moving toward a new model of delivering services entitled Foundational Public Health Services. In 2019, by self-report more than half of our state's 115 local public health agencies reported not having the capacity to conduct the core components of public health. It is our philosophy that no one is safe until we all are safe, and thus every public health agency in the state should have the capacity to perform all components of public health as depicted in this graphic.

DHSS is currently conducting a cost–analysis process in collaboration with the University of Missouri–Columbia and all local public health agencies to provide a cost estimate to legislators for a fully functioning, statewide public health system. As well, a concurrent process of identifying key performance measures for such a public health system is underway and includes key stakeholders such as county and state policy makers, local public health and MO HealthNet.

Other positive developments for the Missouri public health system include the establishment of a

Missouri Department of Health & Senior Services Resources

Life Expectancy
https://health.mo.gov/data/focus/pdf/2022-focus.pdf

Preventing Leading Causes of Death
https://health.mo.gov/living/

Unintentional Drug Overdose Deaths
https://health.mo.gov/data/opioids/

Health Resources for Moms
https://healthymomsbabies.mo.gov/

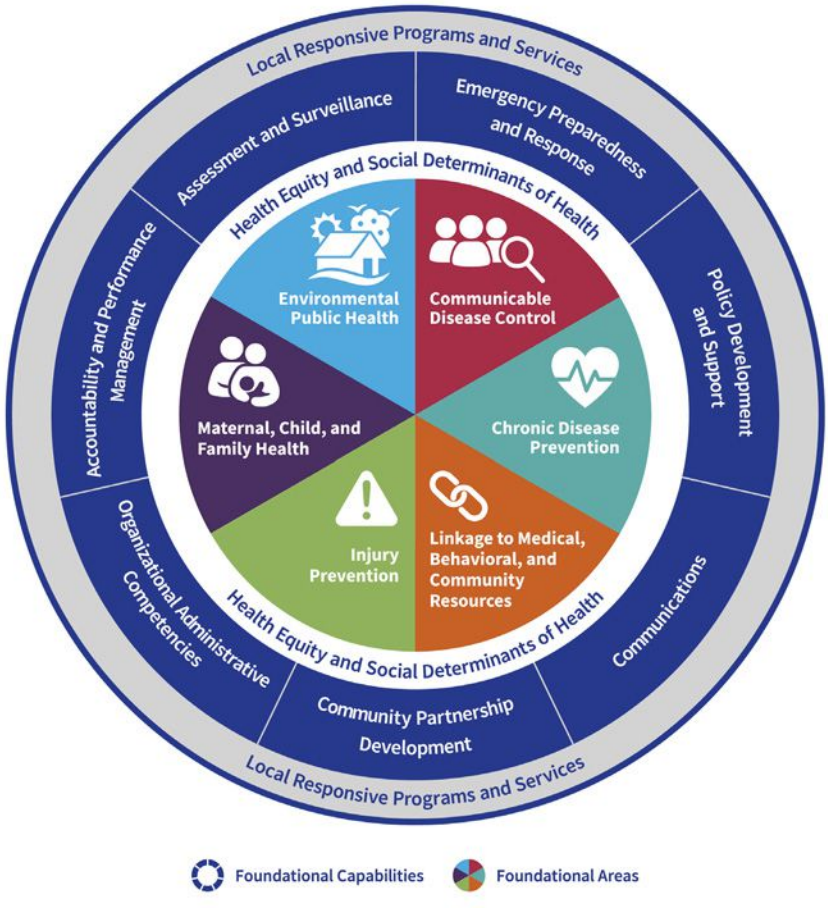
Foundational Public Health Services
https://nnphi.org/

State Health Improvement Plan
https://health.mo.gov/healthplans/pdf/state-health-improvement-plan.pdf

DHSS Strategic Plan
https://health.mo.gov/healthplans/pdf/strategic-plan.pdf

public health institute recognized by the National Network of Public Health Institutes. Missouri's public health institute, Missouri Center for Public Health Excellence, received start-up funding from the Missouri Foundation for Health and has continued to expand on that base funding. As well, the FY24 legislature appropriated incentive funding for local public health agencies pursuing accreditation and participating in annual training for their administrators and governing bodies.

Further information regarding Missouri's health indicators and the state plan to improve our health outcomes are available in the recently released State Health Assessment and the State Health Improvement Plan. Readers may also view the DHSS strategic plan outlining the initiatives underway in our role as the state health authority to improve Missouri's health outcomes.



Missouri continues to face many challenges to improving our state's health. DHSS remains committed to confronting these challenges collaboratively with all partners, including supporting individuals to take the lead in changing their personal health outcomes. We look forward to our continued work together to achieve optimal health for all Missouri citizens. **MM**

Mental Illness and Violence Among People Experiencing Homelessness: An Evidence-Based Review

by Kevin Y. Xu, MD, Jessica A. Gold, MD, Hannah S. Szlyk, PhD, Stephanie A. Rolin, MD & Morgan C. Shields, PhD

The US media is saturated with coverage of perceived threats to public safety by people experiencing homelessness (PEH) with purported "mental illness." In a prescient 2017 article in the Journal of the American Medical Association (JAMA), then-Los Angeles health commissioner, Mitchell Katz, noted a sense of public "frustration with some of the behaviors of some homeless people," ranging from "sidewalks being blocked by shopping carts, aggressive panhandling, and urination and defecation in public."[1] Such sentiments have intensified in recent years, as the number of PEH (Table 1) has surged, with frustration increasingly turning into fear. With regards to media coverage, a series of articles suggested that nearly half of commercial sidewalks in San Francisco were "covered in feces," leading to widespread public outrage.[2] Meanwhile, a content analysis of 6,400 tweets regarding PEH collected over three months showed widespread generalizations that PEH posed a high risk of violence and that homelessness was caused by untreated mental illness.[3]

The framing of these narratives have been identified as further entrenching the dehumanization of PEH, contributing to oversimplified understandings of PEH and mental illness, and motivating policy interventions that are not evidence-based.[4] Physicians' lack of specific training in working with PEH can create additional barriers to accessing care,[5] especially since PEH may perceive negative attitudes in their physicians,[6] exacerbating feelings of alienation.[7] Stigma is pervasive,[8] and that experience is often compounded by PEH's past negative experiences with medical care and ongoing structural barriers to engagement (e.g., transportation, payment).[9] Against this backdrop, this review seeks to harness our expertise in forensic psychiatry, addiction science, health policy research, social work, and adult psychiatry to highlight potential misinformation and provide an evidence-based update for clinical generalists. We will also discuss evidence-based solutions for PEH, describing why long-term custodial psychiatric care and involuntary psychiatric hospitalization is unlikely to solve the ongoing crisis.



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Mental Illness and Addiction Can Be One of Many Precipitants of Homelessness and Should Not Be Seen as the Underlying Cause

Mental illness is commonly assumed to be the cause of homelessness. However, homelessness is a complex health equity problem, as it is embedded in a web of structural determinants of health and has potential solutions that are often misrepresented to the public. Extensive research has shown that the strongest drivers of homelessness are related to poverty and housing affordability.[10] People of color experience among the highest rates of housing instability (Table 1), attributable to unequal access to mortgages and race-based exclusionary tactics in real estate (redlining), among myriad other factors.[11]

While a person's current state while homeless may be conflated as the cause of homelessness, homelessness itself can lead to trauma, victimization, problematic substance use, and serious mental illness, exacerbated

Table 1: Key Information About People Experiencing Homelessness (PEH)

People experiencing homelessness (PEH) are defined by the U.S. Department of Housing and Urban Development as individuals who lack or are at imminent risk of losing fixed, regular, or adequate nighttime residence.[71]

The number of PEH in the U.S. reached a record high in 2022 of 582,620.[72]

Unmet medical needs are common in PEH:
- About 30% of PEH have a mental health condition.[73]
- Approximately 50% of PEH have problematic substance use.[73]
- PEH have higher rates of non-psychiatric medical conditions like heart disease (the leading cause of morbidity and mortality in PEH), tuberculosis, hepatitis, cancer, and skin diseases.[11]

Multiple states have begun passing legislation attempting to criminalize homelessness.
- Missouri passed laws that rendered sleeping on state-owned land a misdemeanor while becoming the first state to bar federal and state funds for homeless services to be used on permanent housing.[74]
- Arizona has considered legislation that would cause panhandling to be punishable by up to 6 months in jail on the third offense.[75]

Much attention has focused on PEH in major cities along the West Coast, with California having the largest population of PEH for over a decade. Yet, Midwestern states have also seen a large increase in PEH, with Missouri having the greatest increase in unaccompanied and unhoused young people and minors in the US from 2019 to 2020.[76]

People of color are overrepresented among PEH. In an analysis of federal data, the overall prevalence of homelessness for Black individuals in the US was 3-fold greater than the rates of White peers,[77] with the disparity as high as 4-fold in St. Louis[78] and 10-fold in San Francisco.[79]

by the dearth of community-based resources[11] and, more recently, the COVID-19 pandemic.[12] Moreover, cognitive disorders such as dementia and traumatic brain injury (TBI) are overlooked consequences of violence towards PEH. A recent systematic review showed that 53% of PEH had a TBI of any severity, noting that past TBI was associated with increased risk of victimization and intimate partner violence. Especially since it can contribute to worse psychiatric outcomes, TBI can be challenging "to manage in the best of circumstances and may complicate efforts at sobriety or housing stabilization."[11] To date, evidence-based strategies to diagnose and treat cognitive disorders in PEH are lacking.[11,13]

The interplay between homelessness and addiction is particularly complex. Longitudinal analyses show that relationships among addiction, mental illness, and homelessness are unlikely to be causal.[14,15] For instance, in people with problematic substance use, adverse childhood experiences and trauma were stronger predictors of homelessness than addiction.[16,17] Data collection on substance use statistics in PEH, already lacking, is further complicated by the fact that "substance use" does not equate "addiction," especially as PEH may have consumed fentanyl and other potency-enhancing drugs unknowingly. Importantly, while the proliferation of fentanyl, methamphetamine, and other adulterant use in PEH have garnered much media coverage, alcohol use disorder is the most common substance use disorder in PEH[18] (prevalence of nearly 40%[11]). While studies have shown important racial and socioeconomic disparities in alcohol use disorder screening and treatment in general adult populations in the US,[19] PEH are not included in national surveys of substance use disorders, constituting a major research gap.

Homelessness and Mental Illness Are Not Driving Surges in Violent Crime

Homelessness and mental illness are often a public safety concern. However, PEH are more likely to be victims of crime than perpetrators,[20] and rates of violent crime among PEH are lower compared to other types of crime (e.g., drug-related charges).[21] A 2020 US Department of Justice study showed that approximately half of PEH surveyed reported being

victims of violence, compared to 2% of the general population.[22] When violence does occur in PEH, studies have suggested they often serve as a function of self-protection.[23] PEH are at particularly high risk of being victims of both domestic violence, particularly women and LGBTQIA+ people,[24] and are also at elevated suicide risk.[25-27]

Furthermore, although media depictions of violence in people with mental illnesses like schizophrenia are common,[28] studies have not found significant relationships between most serious mental illnesses and future violent behavior.[29] A major analysis led by Paul Appelbaum (The MacArthur Violence Risk Assessment study) involved longitudinal follow-up data on people who were discharged from inpatient psychiatric facilities. Appelbaum and colleagues showed that the prevalence of violence among people with serious mental illness—and no co-occurring addiction—was virtually indistinguishable from control subjects selected from the same neighborhoods. The authors suggested that when neighborhoods are unsafe and high in socioeconomic distress, violence risk was comparable in people with and without serious mental illness.[30,31] Another notable study analyzed data from the social network of 169 people with serious mental illness for over 30 months, finding that among >3,000 social network members, only 1.5% were ever the target of violence, with the majority of them being family members and peers, not members of the general public.[32]

Problematic substance use has been hypothesized to confer a greater risk of perceived "violence" than other psychiatric conditions.[33,34] While recognizing that PEH who use drugs may exhibit "challenging behaviors" that may be "perceived as but not necessarily result in violence," researchers have suggested that 1) most violent acts are not committed by people with mental illness; and 2) addictive disorders may explain some of the increased risk of violence associated with psychiatric disorders.[35] While there is a robust body of literature on the relationship between alcohol use disorder and aggression,[36] studies have found that permanent supportive housing with access to mental health professionals—for PEH with alcohol use disorder have contributed to longitudinal decreases in use.[37] Studies investigating the role of supportive housing for PEH who struggle with addiction have also observed decreased reoffending rates and criminal justice involvement with supportive housing placement.[38] Importantly, access to supportive housing is associated with decreased risk of violence towards PEH, evidenced by programs that integrated suicide prevention, trauma-informed care,[39] and case management with supportive housing.[40]

Permanent Supportive Housing is Cost-Effective and Associated with Better Outcomes for PEH

In addition to improving health outcomes for PEH, permanent supportive housing has been found to be cost-effective. For instance, a 2019 study randomized nearly 1,200 PEH in four large Canadian cities to either permanent supportive housing with intensive case management compared to treatment as usual, finding an incremental cost-effectiveness ratio of $56 per additional day of stable housing.[41] The authors noted that the cost of the intervention, approximately $40 per participant daily, was within the range of costs for currently funded forms of shelter and supportive housing, and that costs for permanent supportive housing were offset by reductions in costs of shelters and emergency admissions.[41] A separate economic valuation study noted that the benefit-to-cost ratio for permanent supportive housing studies in the US was 1.8 to 1, with a median averted cost of $14,193 per year from the judicial system or health care expenditures. (For reference, a recent estimate showed that it may cost local governments more than $30,000 per person experiencing homelessness annually in legal system, cleanup, and medical fees in Springfield, Missouri, via treatment as usual.[42])

Unfortunately, efforts to provide permanent supportive housing and comprehensive interventions to prevent homelessness in the first place have been meager. Furthermore, the elevated rates of victimization and trauma in PEH would suggest a need for trauma-informed care, case-management, wrap-around services, and comprehensive psychiatric treatment. Yet instead of investment in these programs, supportive housing-first programs with case management, counseling, job training, and health care services have struggled to procure sustainable funding for renovations and expanded capacity, relying on small COVID-19 emergency funds.[43]

Putting People Away Without Essential Care and Basic Needs

We are seeing a push for locking people away (and out of sight) without increasing access to essential health care and basic needs. However, coercion is not a substitute for permanent supportive housing.

In public media, narratives on homelessness, mental health, and violence often suggest that involuntary psychiatric commitment and the use of law enforcement to implement involuntary holds are solutions for homelessness. Consequently, there is driving a public interest in the use of law enforcement and involuntary psychiatric care to address homelessness despite a lack of evidence for these measures. Specifically, involuntary psychiatric hospitalization is usually short-term whereas addressing either substance use or homelessness would require a long-term intervention. Yet, leaders in California and Oregon have discussed using involuntary holds to "combat homelessness."[44] New York City, in particular, has been in the spotlight for directing police and emergency personnel to hospitalize people deemed too mentally ill for themselves, even if they posed no threat to others,[45] sometimes described as the "forced removal of mentally ill" people.[46] Despite this push to use the threat of arrest and citation to compel people to seek treatment,[31] studies show that law enforcement presence at substance use treatment sites may discourage people who use drugs from accessing health services.[32] Overall, involuntary treatment for substance use is not supported by most psychiatrists.[47]

Importantly, the debate surrounding the merits of involuntary psychiatric treatment for PEH who are mentally ill—and the framing of untreated mental illness as a public safety problem—is not a new one. It can be helpful to consider the historical legacy of deinstitutionalization largely starting in the 1960s, which can be defined as the depopulation of psychiatric hospitals. Deinstitutionalization was motivated by a value for community integration and concern over the dehumanizing conditions within institutions, as well as by fiscal considerations. However, instead of reorienting psychiatry towards a community-based healthcare model, government support for comprehensive outpatient services, including for many PEH with serious mental illness, did not materialize.[48] Meanwhile, the push for using law enforcement to involuntarily hospitalize PEH with a reported history of mental illness and psychiatric hospitalization who had not been convicted or charged in a crime has been gaining steam. In 1999, following the murder of Kendra Webdale by Andrew Goldstein, New York State passed the first assisted outpatient treatment (AOT) law ("Kendra's Law") in the US. As noted in a 2010 special section on AOT in Psychiatric Services, it was noted that "a judge may order a person with mental illness to adhere to recommended outpatient treatment" and that "nonadherence with a treatment plan may lead to a request that law officers transport the consumer to a treatment facility for encouragement to comply with treatment or evaluation for inpatient commitment."[49] In many cities, the encoding of AOT has authorized law enforcement officers to bring people with a reported history of mental illness to emergency rooms for treatment. While media narratives have suggested that Mr. Goldstein was not in "compliance" with his treatment, Mr. Goldstein had, in actuality, twice attempted voluntarily to participate in a Bellevue pilot program for psychiatric treatment but was turned away due to limited space.[50]

Even as AOT has expanded across the majority of US states,[51] the results of AOT have been mixed at best. A highly controversial 2001 study by Swartz and colleagues sought to randomize involuntarily-hospitalized people to either be released from civil commitment or undergo outpatient commitment, with the authors contending that outpatient commitment lasting more than six months was associated with decreased hospitalization, arrests, acts of violence, and incidents of victimization.[52] While the study was well-received by proponents of AOT, it was widely criticized for ethical issues, lack of blinding, as well as attrition, selection, and reporting bias.[53] To this day, there remains concern that the effective ingredients in AOT are not necessarily compulsion, but rather the influx of money, resources, and staff support[54] that often come along when AOT state laws are implemented. For instance, AOT in New York was accompanied by an infusion of new service dollars and featured "more comprehensive implementation, infrastructure and oversight of the AOT process than any other comparable program in the United States."[54] Further, AOT programs effectively allow people to "jump the line" ahead of others waiting for services voluntarily, potentially having the unintended consequence of further limiting voluntary treatment; this is amplified by the limited caseloads that case managers will have when serving AOT clients, as mandated in AOT

statutes and regulations in many states so as to ensure that each AOT client receives comprehensive care.[55] Meanwhile, a severe dearth of supportive housing and treatment capacity have limited the utilization and effectiveness of AOT throughout the US.[56]

In addition, acute psychiatric treatment via AOT does not equate long-term community-based care, as many people who are sent to the emergency room for acute stabilization are discharged with inadequate follow-up. Moreover, inpatient psychiatric hospitalization as a place for even brief psychiatric stabilization has been debated for lacking a robust evidence-base of its own; studies have noted that inpatient psychiatric admissions can be traumatizing for many patients,[57,58] while also introducing disruption in economic, employment, interpersonal, and therapeutic domains.[59] A recent study noted that young adults reported negative effects of involuntary psychiatric admission on trust, help-seeing, and engagement with clinicians, evidenced by the selective non-disclosure of suicidal ideation.[60] Another analysis showed a widespread lack of electronic health information exchange at discharge from inpatient psychiatric care, hindering outpatient care coordination. [61] In addition, as noted in a recent review of the risks and benefits of psychiatric admissions, inpatient hospitalization may exacerbate employment instability and come with hospital bills that pose high financial burden to patients with unstable insurance coverage.[59] Finally, the number of inpatient psychiatric beds owned by systems, for-profit companies, and behavioral health hospital chains have increased substantially in the last decade, per a recent analysis of the National Bureau of Economic Research's Health Systems and Provider Database.[62] Particularly amid the current enthusiasm surrounding the use of involuntary psychiatric hospitalization to combat homelessness, it is imperative for payers and policymakers to institute safeguards against profiteering, while monitoring trends in quality of inpatient care moving forward.

Learning "From the Misses" Does Not Breed Compassion

As complex as is the relationship between homelessness and mental illness, the provision of non-psychiatric medical care for PEH is not routinely included in clinical training. A systematic review and meta-ethnography on substance use treatment for PEH showed that compassionate support from medical staff was the most consistently mentioned component of effective treatment services.[24] Yet, an analysis of emergency medicine residents illustrated a lack of didactic hours and formal curricula dedicated to learning about PEH, trainees reported feelings of frustration and futility amid a sentiment that they were primarily learning how to treat PEH "from the misses," defined as cases where PEH had bad outcomes.[63]

While some studies have shown that medical trainees have adopted increasingly negative attitudes towards PEH over the course of medical training,[64] there are nonetheless some signs of progress, as traditional academic medicine increasingly embraces health care for PEH in its formal curricula, both through clinical training and didactics illuminating health systems' structural violence.[65] Academic programs like Boston Health Care for the Homeless and Yale Street Psychiatry have been successful in integrating educational experiences surrounding PEH into clinical training.[66,67]

Yet, there is mounting concern about negative public opinion[68] and compassion[69] wearing thin amid perceptions of US cities being "taken over" by encampments.[70] Meanwhile, resources that PEH may benefit from are often unavailable (i.e., trauma-informed care, permanent supportive housing, diagnosis and management of cognitive impairment). Since we cannot write a prescription for housing, it may be tempting for health care providers, when working with PEH, to "call for a psychiatry consult" to consider involuntary institutionalization, which may feel akin to the most immediate tool available to physicians seeking to help PEH.

Ultimately, we must not conflate the tools available to us in the hospital (i.e., involuntary psychiatric hospitalization for persons at imminent risk of harm to self or others) with structural solutions that address the underlying drivers of homelessness. As we have seen throughout history, carceral logic has bred carceral solutions. Decreasing the visibility of PEH does not make the problem go away.

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Medical Illustration State of the Art & Future Considerations

Illuminating Medicine & Science Part II

by Mark M. Miller, MA



The Association of Medical Illustrators

As the number of medical illustrators grew, the need for a professional organization became apparent. In 1945, 30 delegates gathered in Chicago to write a Constitution and By-laws, and the following year the first Association of Medical Illustrators (AMI) meeting was held in Philadelphia, with 40 members attending. Tom Jones was the organizations first president.

To paraphrase the stated goals of those early delegates, the AMI would promote the study and advancement of medical illustration, and encourage the cooperation with medical professionals. Today the AMI boasts more than 800 national and international members in multiple categories, including professional and student members. The annual meeting continues, relocating each year. The AMI certification program (CMI) insures standards of competency.

Pencils to Pixels

The goal of the medical illustrator, in our role as educators, is to impart information in an unambiguous and efficient manner. We are taught that the illustration's (animation's, etc.) "message" is of upmost importance, that no matter how aesthetically pleasing, the illustration is a failure if the message is ambiguous, challenging to decipher, or much worse, inaccurate!



Mark M. Miller, MA, is Scientific Illustrator at the Stowers Institute, Kansas City, and owner of Miller Medical Illustration. His work and contact information can be found at www.millermedart.com.

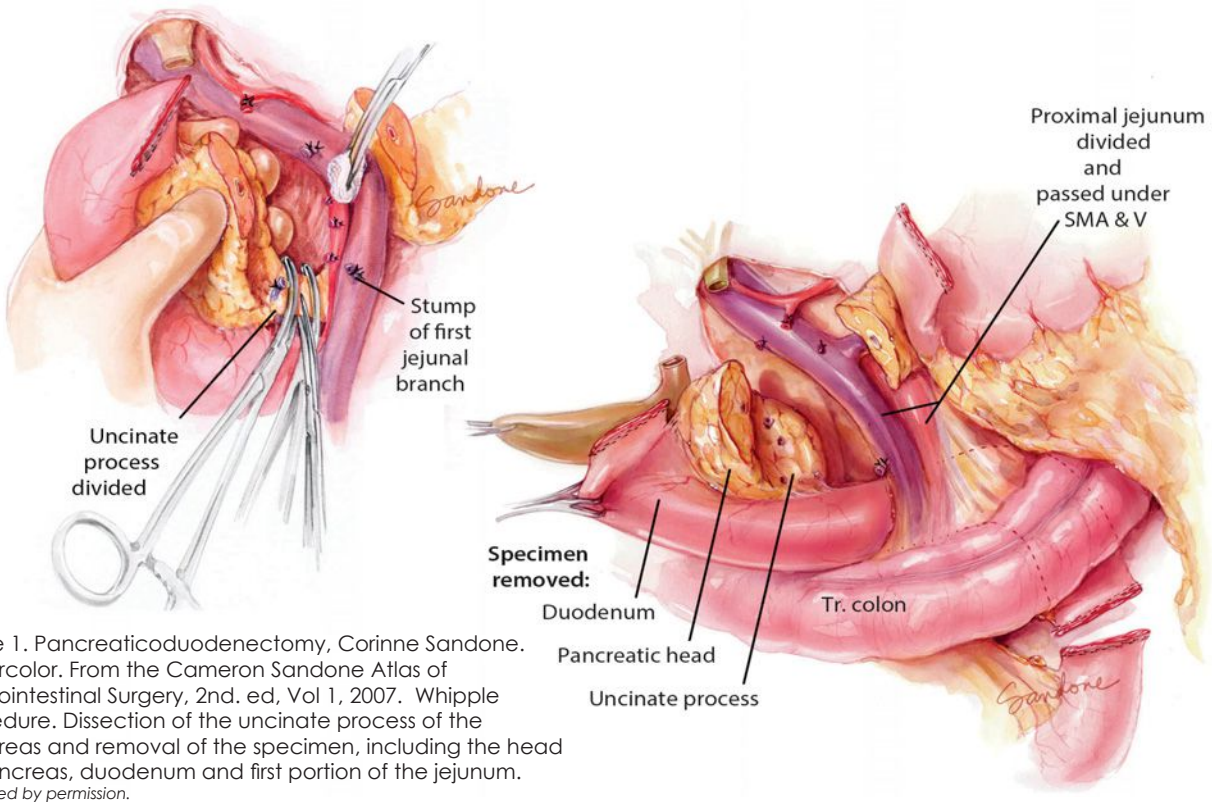


Figure 1. Pancreaticoduodenectomy, Corinne Sandone. Watercolor. From the Cameron Sandone Atlas of Gastrointestinal Surgery, 2nd. ed, Vol 1, 2007. Whipple Procedure. Dissection of the uncinate process of the pancreas and removal of the specimen, including the head of pancreas, duodenum and first portion of the jejunum.
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Prior to the 1980s, this goal was pursued via "natural" media, using simple, but time-tested tools and techniques. "Pen and ink" is an example. Using a flexible pen nib dipped in India ink, variable thickness lines are drawn on a clay-coated board in manner, according to line density and thickness, suggesting "tone," that is, varying shades of grey. Dark areas are painted on the board with a wash of diluted ink, and then modulated by stroking into the underlying clay surface with a specialized sharp instrument, re-exposing the white of the board. From skilled hands, complex and visually rich illustrations can be made (Figures 3 and 6, Part 1, November/December 2023 *Missouri Medicine*).

In the pre-color reproduction era, pen and ink, graphite, charcoal, wash, and a beautiful but challenging medium called carbon dust (invented by Brödel), were the tools of the trade (Figure 4, *ibid*). With color lithography came colored pencils, watercolor and gauche (opaque watercolor), applied by brush or airbrush (Figures 1, 2). With the invention of polymers, some artists made masterful works with acrylic paint, also applied by "hand" or with an airbrush.

Though there are professionals who continue to employ traditional techniques, the introduction of the personal computer slowly, but inextricably, ushered in the digital era of medical illustration. (My career spans eras. I worked traditionally for seven years, but transitioned during the early 1990s). The evolution of software for images is similar to the evolutionary tree of life, with simple, basic programs growing ever more complex and branching out into distinct areas of functionality, though with many of the same genetic (code) underpinnings. Without delving too deep into that evolution, Adobe Inc. software, (incorporated 1982) and Apple Macintosh computers (released 1984), were the dance partners that began the revolution. In truth however, the early products from both companies were quite limited.

Medical illustrators adopted digital technology at varying rates, with some jumping onboard immediately, some slowly, and some never. The general view however, is that digital technology is simply another tool for the making of visuals. The same skills, namely, knowledge of the subject matter, an understanding of the most effective approach to best present that subject matter, and the artistic skills

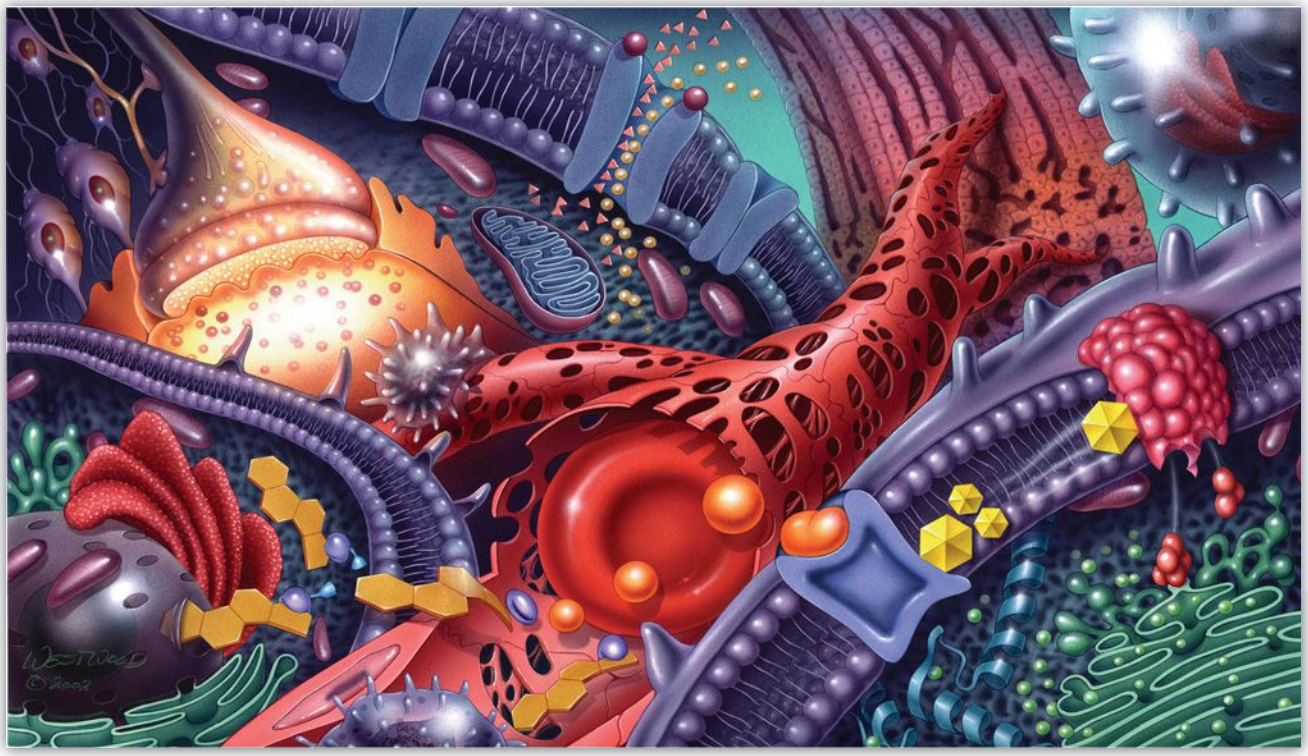


Figure 2. Physiologic Regulation at the Cellular Level, © 2002 Bill Westwood, MS, CMI. Watercolor, and gouache with airbrush on illustration board. Wrap around cover illustration for the textbook Human Physiology. McGraw-Hill.
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to make it all happen, are the same, regardless of the media chosen. Today's medical illustrators work in all manner of digital media, including 3D modeling (and printing), 2D and 3D animation, and more recently, virtual reality (VR), where a surgeon in training, for example, can "enter" a virtual operating suite and practice a skill.

Education and Careers

Five institutions offer accredited Master degree programs in medical illustration (see www.ami.org). Though there are undergraduate programs available, graduate degree level competency is strongly encouraged. Acceptance rates are limited, as entrance is highly selective. Exceptional artistic skills, particularly realistic drawing, and strong science proficiency are required. Undergraduate prerequisites are also required, but not a specific undergraduate degree. It's not uncommon for some already working in a medical or science profession to apply. In all graduate programs, curriculum is divided between studio art techniques, with emphasis on digital media, and medical school level courses in anatomy (including cadaver dissection), histology, and other core medical education disciplines. Fifty to sixty graduates with Master's degrees enter the profession each year, with many more having earned an undergraduate degree.

Jobs for graduates are wide and varied. Many become staff illustrators and/or animators for major medical and research institutions, especially those with a strong teaching focus. Foundational bioscience research entities, both governmental (NIH, CDC) (Figure 3), and private, such as the Stowers Institute in Kansas City

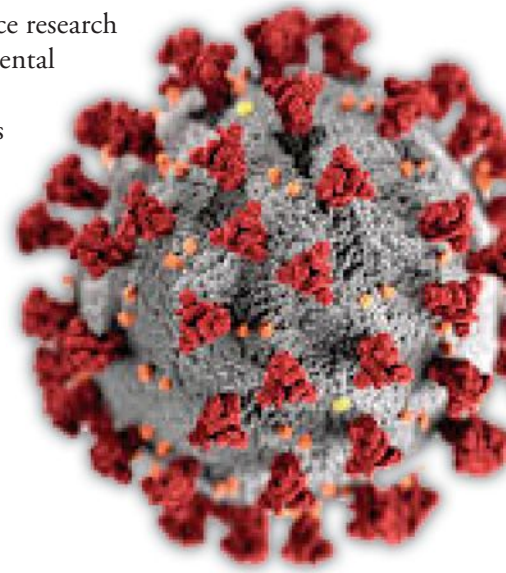
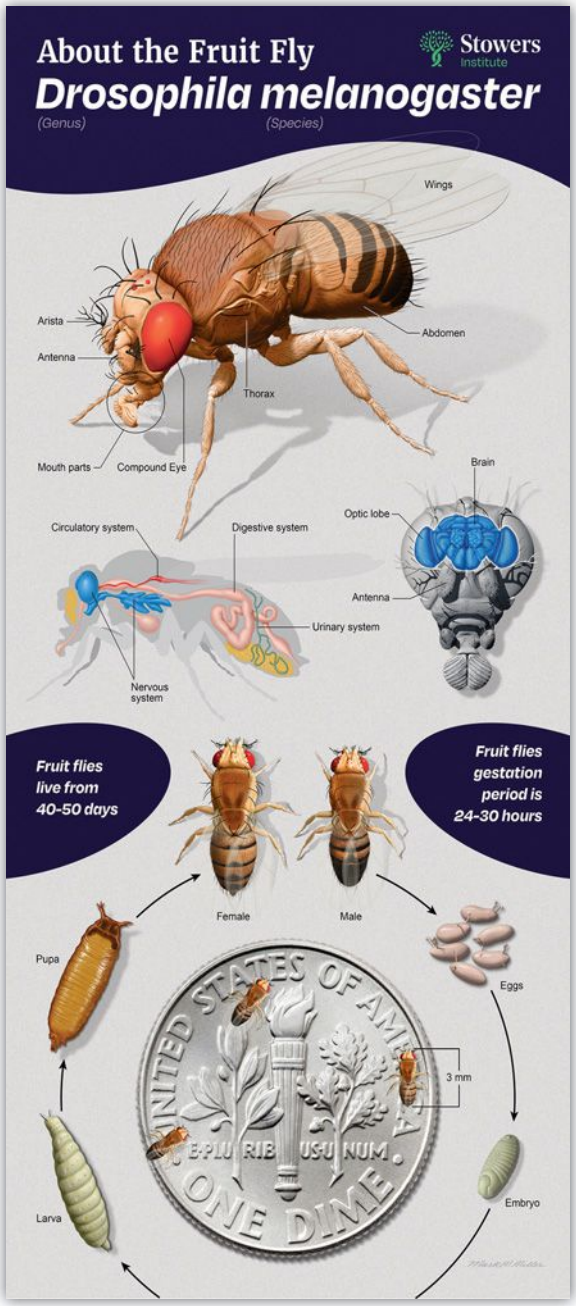


Figure 3. Ultrastructure Morphology of Coronaviruses, Alissa Eckert, MSMI and Dan Higgins, MAMS. Centers for Disease Control and Prevention (CDC), 2020.



How would have Max Brödel responded to the digital revolution in medical illustration? A student of his confidently stated that Brödel would have energetically accepted the challenge, and in no short order would have coaxed amazing art from the silicon.



(Figure 4), recruit medical-scientific illustrators and animators, where molecular visualization might be one of the tasks required. Industry jobs, the creation of visuals for marketing medical and pharmaceutical products, are offered by several companies dedicated to that niche, companies often launched by medical illustrators (Figure 5). Careers developing virtual or augmented reality suites (VR, AR) are growing. A subset of graduates find work in the medical-legal field, creating illustrations and animations for legal proceedings.

The historic roots of medical illustration, namely textbook and journal illustration, continues, as does editorial work for publications (Figure 6). Roughly a quarter of medical illustrators in the AMI find self-employment fulfilling, where project diversity is common. Some even find their way to the gaming industry. A related field is Clinical Anaplastology. Using many of the same skills as medical illustrators (color theory, 3D modeling and printing, sculpting, painting and materials science), individuals create custom, life-like facial and somatic prosthetics for those disfigured by injury or the surgical resection of disease.

Technology Giveth. Technology Taketh Away?

I distinctly recall a conversation with then fellow faculty member Ranice Crosby, about how Max Brödel would have responded to the digital revolution in medical illustration. Crosby confidently stated that the man she knew would have energetically accepted the challenge, and in no short order would have coaxed amazing art from the silicon. How would Brödel have reacted to the advent of Artificial Intelligence (AI) and the machine generation of images?

Today it is possible, with a prompt and "trained" software, to create *de novo* artworks, which simultaneously are novel, yet, derivative. Derivative in the sense that no

Figure 4. Fruit Fly Educational Poster, © Mark M. Miller, MA. First of three large infographics describing the purpose and function of the Fly Transfer Robot. Stowers Institute, Kansas City, Missouri, 2022.
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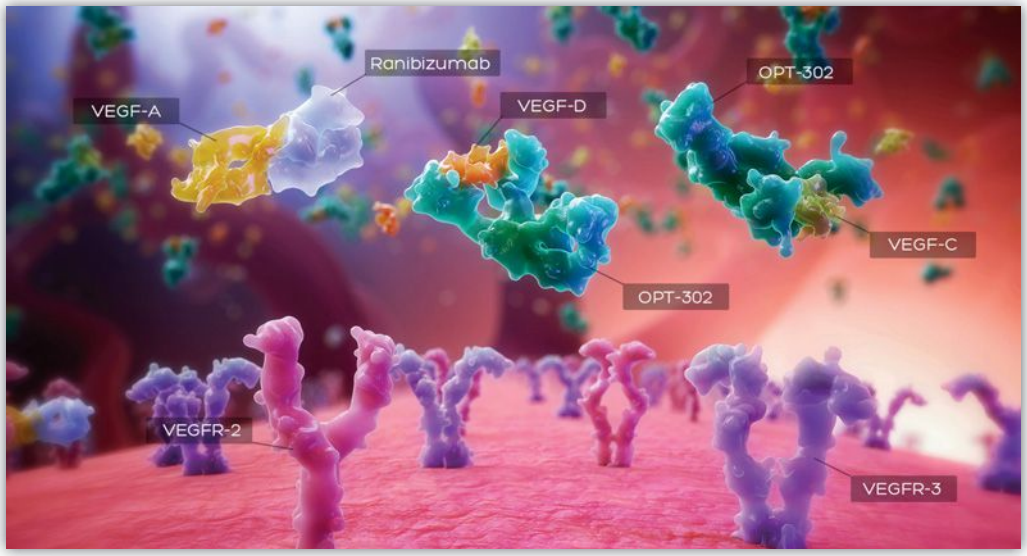


Figure 5. Image from an animation created for Opthea Limited. iso-form LLC.
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Figure 6. Gastrointestinal Conditions, © Mark M. Miller, MA. Editorial cover illustration using Adobe Photoshop, Illustrator and Pixologic ZBrush. The Academy of Family Physicians, FP Essentials, 2019.
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AI fabricated image is created in a vacuum, but rather is the synthesis of millions of "samples," taken (stolen?) from online sources, often copyrighted work. Does one need an anterior view of the heart in a specific style? That's now obtainable in a matter of seconds with the right prompt. What implication does this have for intellectual property, and more profoundly, the field itself? Like the digital revolution of the 1980s, we currently are at the vanguard of an epoch-defining era where there is appreciable angst, not only among medical illustrators, but all creatives.

The optimist in me believes AI will find its limited place, becoming yet another tool in the toolbox. But it is so new, revolutionary, and rapidly evolving, that like the mid-century futurists who envisioned flying cars in everyone's driveway (I still want one), predicting the future is tricky business. There is certainty however, that as long as there are advancements in medical, scientific, and biological knowledge, there will remain a powerful need to help explain that knowledge visually. Whether it's referred to as medical, scientific, or biological illustration, biomedical or data visualization, it's hoped and expected that talented and well-trained organic minds will continue to lead the path, extending this rich history.

For further information on medical illustration, educational programs, and careers, please visit www.ami.org. To support medical illustration education, please visit www.vesaliustrust.org. Part 1 of this two-part series was published in the November/December 2023 *Missouri Medicine*.

Source

History of the Association of Medical Illustrators. Demarest, R., ed. Association of Medical Illustrators. © 1995

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From Aspiration to Impact: Paving the Path in Healthcare and Inspiring Future Generations

by April Tyus-Myles, MD

I remember walking down my pediatrician's office hallway with my mom when I was about five. As we walk out, my mom states: "April, I bet this is something that you would like to do when you grow up." I told my mom: "Yes, I want to do that! I want to be a doctor!" It was at that moment that I first realized not only that I wanted to be a doctor; but I wanted to be a "kid doctor."

Throughout my elementary, middle school, and high school years, I studied hard and aimed for excellence. My parents taught me at an early age that education was the foundation for success. My sisters and I loved to read books, and over the summer, we would go to the library and get large stacks of books to read at home. This love of reading enhanced my academic success. One of my proudest moments in high school was becoming the first black valedictorian at Stephen Decatur High School, Decatur, Illinois, in 1991.

My biggest mentors were my parents. As long as I can remember, they set a standard of excellence for myself and my sisters. They always expressed the importance of education. It was expected that my sisters and I would work hard in school, get good grades, and go to college. With that expectation, combined with their nurturing and guidance, we all rose to the occasion.

After finishing high school, I headed off to Washington University in St. Louis to attend college. What a rude awakening! I, one of the smartest kids at my high school, was now amongst everyone else who was also the smartest kids at *their* high schools. However, I did not let that intimidate me. I buckled down and studied hard and went to every pre-med study and tutoring session that was available. I followed the pre-med track and majored in biology, with a minor in African and African American studies. I graduated, with honors earning a BA degree in 1995.

I started medical school at Saint Louis University School of Medicine soon after. As I was rotating through the different medical specialties, I kept an open mind regarding which area of medicine I might like to pursue. However, I found that the only rotations that I really loved were the pediatric rotations. That sealed in my mind what I had always known from the time I was five-years old: I really wanted to be a pediatrician. Helping children gave me joy.

I began my pediatrics residency at the Southern Illinois School of Medicine in Springfield, Illinois in 1999. This residency program provided me with an intense training ground for sharpening and enhancing my general pediatric clinical skills. Because it is a smaller program, I had the advantage of getting more hands-on procedures and individualized teaching while rounding with the pediatric general and specialist attendings. I found this to be of great benefit in my future career.



April Tyus-Myles, MD, FAAP, MBA, is a Pediatrician with SSM Health Medical Group in St. Louis, Missouri.



Starting at Rainbow Pediatrics.



Dr. Tyus-Myles with one of her COPE residents from St. Louis Children's Hospital.

After my pediatrics residency finished in 2002, I returned to St. Louis and joined Anita Stiffelman, MD, at her private practice, Rainbow Pediatrics, in Florissant, Missouri. After several years, I became a managing partner/co-owner. I was finally able to reach the goal that I set for myself at age five! I continued to work at Rainbow Pediatrics for the next 16 years. Over that period, the thing that I loved the most was the long-term relationships with my patients and their families, along with the great working relationship with our staff. In addition, being in private practice not only helped further develop me as a clinician, but I also learned the business administrative skills needed to successfully manage an office.

During that time, I also became an Instructor of Clinical Pediatrics and served as a pediatric clinical preceptor for the WU-SOM's Clinical Pediatrics Community Outpatient Practice Experience (COPE) program from 2003-2021. This program allowed me to teach one pediatric resident in my office for the entire three years of his/her residency. I loved being able to teach and impart the knowledge that was given to me by my pediatric instructors. I formed lasting relationships with all the residents that I precepted, and I still, to this day, stay connected with many of them. During my time at Rainbow Pediatrics, I was also involved as a collaborator with WU-SOM in the clinical study "Asthma Symptom Based Adjustment of Inhaled Steroid Therapy in African American Children (ASIST) that aimed to improve the clinical treatment of African American children with asthma.

Due to the changing landscape in healthcare insurance reimbursement rates for independent private practice practitioners, we decided to sell Rainbow Pediatrics and joined SSM Health in 2018 where we moved just a few blocks from our previous location in Florissant into the brand new SSM Cardinal Glennon Pediatric Multispecialty Center in Ferguson. It was a big transition moving from a private practice setting, which is all that I had known for 16 years, to a large corporate



Graduating from George Washington University with one of Dr. Tyus-Myles' mentees and former patient.

setting. However, I jumped right in and began serving on the SSM Health Pediatric Leadership Council and the SSM Health Medical Group Pediatric Service Center Advisory Board. On the Leadership Council, I aided in establishing and improving quality metrics for the pediatric group as well as finding solutions to any problems. On the Service Center Advisory Board, I helped to establish guidelines for the Call Service Center to provide quality triage for the patient families. We also monitored quality measures for the call center and looked for solutions.

While acclimating to the corporate system health setting, I began to study healthcare trends and learned about the transition from the fee-for-service model to the value-based care model. I realized that the world of medicine was changing, and it was no longer sufficient to be an expert in the field of medicine clinically. To be competitive, one must also understand and be able to master the business side of medicine. Thus, I began my search for healthcare MBA programs.

In 2019, I began my MBA program at the George Washington University (GWU) School of Business. Little did I know that the world would soon be forever changed by the COVID-19 pandemic in 2020. However, I was able to endure the challenges of working full-time and taking MBA classes while bearing the fears and stresses caused by the COVID pandemic. In May 2022, I graduated with my MBA along with a Graduate Certificate in Clinical Operations and Healthcare Management.

Because of that knowledge, I was able to gain greater insight into value-based care and meeting the goals of the Triple Aim. I now understand the principles of accounting, finance, marketing, economics, and strategic management, along with many other business principles. One of the biggest takeaways is that to improve the healthcare of populations, and to follow evidence-based guidelines to control costs and increase the quality of care, we must also focus on addressing the social determinants of health and healthcare inequities that affect the health of populations. My wonderful professors at GWU provided me with a first-class education and stressed the importance of using the information that I learned to serve others.

In November 2022, I was appointed as the part-time Medical Director of SSM Medical Group pediatric department. In this role, I develop and oversee strategies, policies, and procedures for primary care and population health. I act as the physician lead in discussions with insurance plans for population health initiatives and work in collaboration with our administrative leaders on value-based contracts with federal, state, and commercial groups. I am also working to expand a program that is already established in the Cardinal Glennon DANIS clinics, that identifies and addresses the social determinants of health of patient families to six of our pediatric medical group locations.

As I look back over my career, I realize that one of my biggest sources of joy was the relationships that formed over the years between myself, my patients, and patient families that I served. Having worked in St. Louis for over 20 years, I have had the pleasure of taking care of children from the time they were newborns until the age of 18. In addition, some of the teens that I saw when I first started are now parents themselves, and they bring their children to my office. I have known many of the families for so long that I feel they are a part of my family.



As I continue my career, I lean on a set of principles to guide in decision-making as I continue to pursue my purpose in life.

"Our prime purpose in this life is to help others. And if you can't help them, at least don't hurt them."
– Dalai Lama

"Earn your success based on service to others, not at the expense of others."
– H. Jackson Brown, Jr

"I am only one, but I am one. I cannot do everything, but I can do something. And I will not let what I cannot do interfere with what I can do."
– Edward Everett Hale

I realize that I serve as a role model for the next generation of youth, especially those who are considering a career in healthcare. That is another source of joy for me because my purpose in life is to help others.

So, my advice to those who ask:

- What can we, as health professionals, do to help inspire the next generation of youth that are considering a career in healthcare?
- Share your journey. Over the years, I have visited various elementary schools and college university settings to share my career journey with students. I also partnered with the UMSL Bridge Summer Program, the Girls Inc. Eureka Program, and the St. Louis Internship Program at St. Luke's Hospital to speak to middle and high school students about my career path.
- Volunteer in local organizations/non-profits so that you are visible in the community. For example, over the years, I participated in various health fairs throughout St. Louis, organized blood drives in collaboration with the Red Cross and Mississippi Valley Regional Blood Center, and organized bone marrow drives in collaboration with the National Marrow Donor Center and Sickle Cell Sabbath program at WU. I also volunteered in the "Think, Learn & Study" program, which provided educational and fun activities for St. Louis inner-city children, served as a Board Member for United 4 Children and Build-A-Body Kids Fitness, and participated in "Doctors on the Runway," a charity physician fashion show in which the proceeds were donated to a local children's hospital.
- Support pipeline efforts (programs, scholarships) to help more students enter healthcare. I chose to do this by donating to non-profits such as the Scholarship Foundation of St. Louis and via medical society scholarship funds.
- Be a mentor. I have had the opportunity to serve as a mentor to many students. One of my proudest moments was when I graduated from GWU at the same time as one of my mentees who was also one of my former patients. I graduated with a MBA in Healthcare, and he graduated with dual degrees: BS in Biological Sciences and BA in Psychology. Now he is planning to enter the healthcare arena and is pursuing a Masters in Public Health at GWU. **MM**



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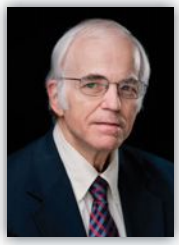
James R. Blaine, MD, Springfield, Emergency Medicine, is a new Contributing Editor. A long-time writer and editor for the *Greene County Medical Journal*, he replaces **Betty M. Drees, MD**, Kansas City, who has written articles and served the Committee on Publication for eight years.

Joanne Loethen, MD, Kansas City, and **Stephen T. Keithahn, MD**, Columbia, are switching Editorial Board positions. Dr. Loethen will represent Internal Medicine/Pediatrics and Dr. Keithahn will represent Physician Wellness.









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Nasally Delivered 0.5% Timolol Beta Blocker Successfully Treats Acute Migraines in a Referral Headache Clinic: A Case Series

by Steven C. Kosa, MD & John C. Hagan III, MD

Ten of 16 patients (62.5%) with refractory acute migraines responded favorably to novel, nasal delivery of 0.5% timolol. and successfully continue its use. Larger, placebo-controlled, multi-center studies should be done expeditiously.



Steven C. Kosa, MD, (pictured) is a neurologist with interest in headache treatment. **John C. Hagan, III, MD,** is an ophthalmologist and editor of *Missouri Medicine*. Both practice in North Kansas City, Missouri.

Abstract

This is the first reported case series of nasally delivered beta blocker (timolol 0.5%) for the treatment of acute migraine. In a retrospective chart review, 16 patients were found who had received intranasal timolol for sub-optimally treated acute migraines. Of these, 10 (62.5%) reported to their provider that the medication was helpful. Encouragingly, the treatment was beneficial even for patients previously refractory to other medications. Intranasal timolol was well tolerated, with only one patient reporting mild nasal congestion and no other side effects reported. These findings suggest the need for a prospective pilot study followed by a larger double-blind randomized placebo-controlled trial to determine the overall efficacy and safety of nasally delivered beta blockers for acute migraine treatment.

Introduction

Oral beta blockers, taken daily, have been proven useful in migraine prevention; propranolol and timolol are FDA approved for this indication.[1] Episodic oral beta blocker treatment of acute migraine has not been successful. It is hypothesized that the difference in responsiveness is the prolonged time to achieve therapeutic beta blocker blood levels by oral administration at first onset of acute migraine.[2]

In 2014, Migliazzo and Hagan[3] reported the first case series of successful treatment of acute migraine using topical 0.5% timolol eye drops. Findings were validated in subsequent placebo-controlled studies.[4,5] A single study purported to show that topical timolol eye drops were not effective for acute migraine treatment.[6] This study was later challenged as having flaws in trial design and implementation.[7]

Therapeutic application of timolol eye drops for acute migraine requires a dexterous patient with functional eyelids and patent lacrimal duct drainage onto normal nasal mucosa. Additionally, the patient must first be examined by an ophthalmologist and found to have no ocular contraindication.[3]

Nasal spray delivery of beta blockers has been postulated to be easier, more effective and more suitable for migraine patients than topical drops to the eye.[8]

This retrospective chart review outlines the clinical experience with the use of nasally delivered 0.5% timolol solution in 16 patients. A single representative case report is presented.

Case Report

A 39-year-old female initially presented to the author's (SCK) headache clinic after a fall causing head injury that substantially worsened her baseline migraines. She presented with status migrainosus which was successfully treated with occipital and trigeminal branch nerve blocks and changes to her preventive medication regimen. She was a poor responder to triptan medication and was overusing over-the-counter (OTC) analgesic medications. Due to poor insurance coverage and excessive patient co-pay, she had difficulty getting access to newer CGRP blocking medications. Timolol 0.5% nasal spray was prescribed for acute migraine treatment. She reported this to be quite helpful in aborting migraine attacks that broke through her preventive medications. Over time, she has used nasal timolol spray for multiple migraines with recurring success. She continues to use timolol nasal spray as a first line acute treatment option. She has reported no side effects. The preventive medication adjustments, along with this novel acute treatment option, led to cessation of her overuse of OTC analgesics. She reports a notable improvement in her personal and professional life.



Figure 1. Sample nasal timolol 0.5% prescription (figure used with permission from Tyler Chamberlain, PharmD).

Figure 2. Migraine Intractability Score

1. Episode migraine, prescription treatment naive.
2. Episodic migraine, not on preventive therapy, tried and failed one triptan for acute treatment .
3. Episodic or chronic migraine, on first or second preventive medication, tried and failed two triptans for acute treatment.
4. Chronic migraine, failed 2 or more preventive medications and multiple acute medications (triptans, CGRP antagonists, NSAIDs).
5. Chronic refractory migraine, poorly responsive to most preventive and acute medications.

Methods

The referral headache neurology practice of one of the authors (SCK) has previously worked with a compounding pharmacy to be able to prescribe nasal timolol to patients not satisfied with their current acute treatment regimen. The compounding pharmacy, O'Brien Pharmacy, produces a solution of 0.5% timolol combined with Mucolox™ to enhance nasal absorption which is given in a nasal aerosol delivery device (Figure 1). Each metered 0.1 ml spray delivers 0.5 mgs timolol to the nasal mucosa. When prescribed, patients are advised to use one spray in each nostril as quickly as possible at the onset of an acute migraine. If necessary, they are told they can use a second set of nasal sprays 15 minutes later. No more than four sprays are allowed within a 24-hour period. Because this treatment is novel and they report dissatisfaction with their previous abortive options, patients have been asked to use timolol solely as their rescue medication. Also because of the novelty of treatment, patients have been routinely asked in their follow-up clinical visits whether they felt the treatment was effective and whether they had any side effects. Patients are not offered timolol nasal spray if they are already on a beta blocker or if they had contraindications to the medication.

The charts of all patients who received nasal timolol from May 2022 to August 2023 were reviewed. Based on their headache history, the first author (SCK) assigned patients an "intractability score" (Figure 2) to delineate how refractory their migraine headaches were to previous treatments. This score ranged from one to five with five being the most refractory migraines. The score factored in the number of migraine days

Table 1. Abbreviations: CM-chronic migraine; EM-episodic migraine; w/-with; w/o-without; F-female; M-male

Positive response to timolol			No response to timolol		
Sex, age	Diagnosis	Intractability Score	Sex, age	Diagnosis	Intractability Score
F, 39	CM w/o aura	4	F, 38	CM w/o aura	3
M, 53	CM w/aura	5	M, 66	CM w/o aura	5
F, 51	CM w/o aura	3	M, 67	CM w/o aura	3
M, 45	EM w/ aura	2	F, 42	CM w/aura	4
F, 65	CM w/o aura	5	F, 43	CM w/aura	5
F, 39	CM w/aura	4	F, 54	CM w/o aura	3
F, 26	CM w/o aura	3			
F, 42	CM w/o aura	4			
F, 32	CM w/o aura	4			
M, 54	CM w/ aura	5			

per month (episodic – less than 15 headache days per month or chronic – greater than 15 headache days per month) and medication response history (acute and preventive therapies).

Results

Thirty acute migraine prescriptions for nasal spray timolol 0.5% were generated from May 2022 to August 2023. Of these, 16 patients ultimately filled the prescription. Reasons for not filling the prescription included: lack of insurance coverage for compounded prescriptions, lack of familiarity with compounding pharmacies, or intolerance of nasal spray medications. Out of pocket-cost was an uncommon reason for not filling. Notably, the pharmacy price for a single, 15 ml compounded 0.5% timolol nasal spray is $77.45 and $112.03 for 30 ml (January 2024).

Of the 16 patients that filled and tried the prescription, 10 reported a favorable response (62.5%) and added the new therapy as an ongoing supplementary acute migraine treatment option. Six patients (37.5%) reported they did not perceive any favorable response (Table 1). Only one patient reported side effects of the medication, and this was mild nasal congestion. Notably, this patient also reported a positive response and chose to continue the medication. In the patients who responded favorably, the intractability score ranged from 2 to 5 with an average of 3.4. The score in those who did not respond ranged from 3 to 5 with an average of 3.8.

Discussion

Oral beta blockers are an established preventative therapy for migraine, but these require daily dosing to achieve and maintain therapeutic blood levels. Previous studies examining oral beta blockade as an acute treatment for migraine were unsuccessful,[9] likely because the extensive first pass metabolism prevented rapid achievement of the therapeutic level. Beta blockers, in solution form, applied to normal nasal mucosa achieve blood levels comparable to intravenous injection.[10] The previously reported effectiveness of timolol applied topically to the eye for abortive migraine treatment has been proposed to be due to drainage of the beta blocker through the lacrimal system onto the nasal mucosa.[3]

In this small retrospective series, 10/16 (62.5%) of patients reported improvement in migraine after trying timolol 0.5% by nasal spray at the onset of their migraine. It is not clear how many times each patient tried the medication or how much improvement was achieved, but these 10 patients did choose to continue with the medication long term. Encouragingly, this series included patients that were previously refractory to other treatments. The nasal application of timolol was well tolerated, and negated contraindications for topical eye medication, such as eyelid ectropion or lacrimal system dysfunction. While this series demonstrates the promise of another option for abortive migraine treatment, additional larger randomized placebo-controlled trials are required.

Conclusion

Despite the growing number of treatment options, there continue to be migraine patients with no response to the current available medications. As science continues to explore new drug targets through translational research, it is also reasonable to revisit older generation medications while exploring



SCAN CODE TO TRACK RESEARCH

- **2022 Beta Blocker Acute Migraine and Pharma Funding**
- **2018 Research Update: Beta Blocker Eye Drops for Acute Migraine**
- **2014 Beta Blocker Eye Drops for Acute Migraine**

novel delivery systems. In the period since the 2014 Migliazzo-Hagan case series,[3] there has been growing interest in the therapeutic promise of rapidly absorbed beta blockers.[11,12,13,14,15,16,17,18,19] This study adds to the growing body of literature supporting topical timolol as an option for acute migraine treatment.

Note

The compounded, prescription only, nasal timolol spray is available from O'Brien's Pharmacy, 913-322-0001, 800-627-4360, 913-322-0002 (fax), mail@obrienrx.com; website: https://obrienrx.com.

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MM

Brain Imaging in Routine Psychiatric Practice

by Alecia C. Vogel, MD, PhD & Kevin J. Black, MD

As psychiatrists, we love to look at the brain—but we're not going to put you through the time, cost, and risks of brain imaging unless there's evidence that it is likely to benefit you.



Alecia C. Vogel, MD, PhD, (pictured), is Assistant Professor of Psychiatry (Child) and Kevin J. Black, MD, is Professor of Psychiatry, Neurology, Radiology, and Neuroscience; both are at Washington University School of Medicine in St. Louis, Missouri.

Abstract

Technologies in the 21st century provide increasingly detailed and accurate maps of brain structure and function. So why don't psychiatrists order brain imaging on all our patients? Here we briefly review major neuroimaging methods and some of their findings in psychiatry. As clinicians and neuroimaging researchers, we are eager to bring brain imaging into daily clinical practice. However, to be clinically useful, any test in medicine must demonstrate adequate test statistics, and show proven benefits that outweigh its risks and costs. In 2024, beyond certain limited circumstances, we have no imaging tests that can meet those standards to provide diagnosis or guide treatment. This cold fact explains why for most psychiatric patients, neuroimaging is not currently recommended by professional organizations or the National Institute of Mental Health.

Introduction

Contrary to a popular myth,[1] psychiatrists routinely look at the brain for some aspects of patient care. For instance, PET is increasingly used for dementia assessment,[2] and MRI is recommended for some patients with new-onset psychosis.[3] However, we still do not recommend brain imaging for most of our patients. This leads to some consternation, with patients asking questions like:

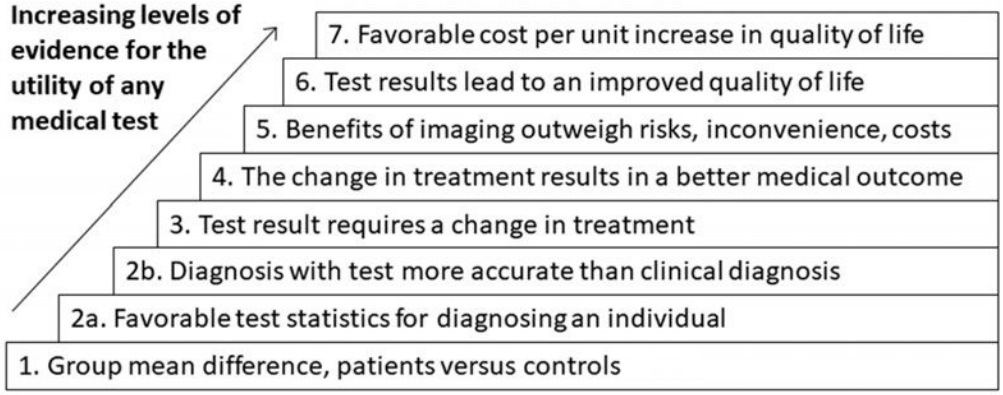
'If this is a brain disorder, can't you tell what's wrong by looking at my brain?'

'Are you sure this is the right diagnosis? Isn't there some kind of brain scan you can do?'

'How do you know this is the right medication for me?'

As psychiatrists who are also NIH-funded researchers using neuroimaging to understand psychopathology, these questions are understandable but the answer is as frustrating for us as it is our patients: "We don't have any brain imaging techniques that can reliably diagnose you or guide your treatment." Medicine in general, and psychiatry specifically, has made amazing strides in understanding the neurobiological basis of psychiatric symptoms and disorders over the last 50 years. We have learned that essentially all psychiatric diagnoses are caused in part by genes the patient carried,[4] sometimes with higher genetic contributions than many non-psychiatric conditions.[5,6] We know that brain lesions can

Figure 1. Hierarchy of clinical utility of medical tests.



produce psychiatric symptoms.[7,8] We have even identified neurobiological mechanisms by which social and psychological stress affects the brain.[9] Yet, there are still no standard lab or imaging tests to diagnose psychiatric disorders, sometimes leading to frustration and confusion as well as opening the door to potentially exaggerated claims. Here, we review what is needed to make any medical test clinically useful, then overview various neuroimaging methods and how they have contributed to our understanding of the neurobiology of psychiatric illness and how these techniques may fit into the framework of medical testing for individual patients in the future.

Demonstrating the Clinical Utility of Any Test in Medicine

As with any diagnostic test in medicine, differentiating patients and unaffected persons is important, but is only the first hurdle the test must pass to be clinically useful. One may view the needed steps as a hierarchy, each step building on the previous step, as shown in Figure 1. After first defining whether any group mean difference exists, it is then important to know if the statistical differences are actually meaningful in diagnoses. The test must be consistent and replicable enough in a single individual to allow for a single measurement to reflect that person's disease "state".

For example, in a patient with non-insulin dependent diabetes when a single blood glucose level (BGL) is checked, it may or may not be within the normal range at that given time. Thus, the single BGL is not a reliable diagnostic test and measures that are integrated over time are necessary. Moreover, there must a reliable separation between the test results in someone with and without the diagnosis.

For example, the presence of antinuclear antibodies, particularly with mild abnormalities, shows overlap between the range seen in those with and without autoimmune diseases and is better seen as only one part of a diagnostic assessment.[10] Moreover, even if a test can reliably distinguish between those with and without a certain diagnosis, it must add value to the clinical assessment or treatment algorithm. It should be more accurate than, or at least add diagnostic accuracy to a clinical diagnosis and/or result in a change in treatment.

Moving up in the hierarchy, an increasingly useful test not only provides a reliable diagnosis or dictates a change in treatment but does so in a way that results in a better medical outcome or, even better, and improved quality of life. Moreover, it should do so in a cost-effective way, in that both the personal costs of inconvenience and potential harm, as well as the financial costs are outweighed by the benefit. Let us now review neuroimaging techniques and how they might fit into this framework.

What is Neuroimaging and How Has it Been Used in Psychiatry?

Broadly speaking, neuroimaging methods can be defined into those that assess structure, or what the brain looks like (often in considerable detail), and those that assess function, which measure what parts of the brain are most active at a given time, or locate and measure specific neurotransmitters

Table 1. Selected structural brain imaging findings in primary psychiatric disorders

- Lateral ventricles are enlarged in schizophrenia.[31]
- Subgenual cingulate cortex volume is reduced in major depressive disorder, leading to discovery of glial cell number reduction in the same region.[14,15]
- Frontotemporal dementia clinical subtypes correspond to differential atrophy patterns.[32,33]
- Primary motor cortex is thinner in Tourette syndrome.[34]

Table 2. Selected functional brain imaging findings in primary psychiatric disorders

- EEG and fMRI studies consistently show decreased response to anticipating and receiving rewards in people with depression.[35]
- Patients with schizophrenia show decreased activations in fronto-temporal regions during learning and memory tasks in fMRI.[36]
- Clinical anxiety is associated with increased activity in the insula, medial temporal lobe, and anterior cingulate cortex.[37]
- In depression, resting state networks show decreased connectivity between cognitive control and emotion regions.[38]

or their receptors. For each of these, neuroimagers can use radiation (i.e., computed tomography (CT) scans) and/or radiolabeled markers (i.e., positron emission tomography (PET) and single photon emission computed tomography (SPECT)), magnetic field-based imaging (i.e., magnetic resonance imaging (MRI), functional MRI and magnetic spectroscopy), or measurements of changes in the electrical field (i.e., electroencephalography (EEG)). First, we briefly review each of these techniques and how they have contributed to our understanding of psychiatric disorders.

Structural Neuroimaging: CT, MRI, and DTI

Structural neuroimaging, looking at the structure of the gray matter and white matter of the cortex, subcortical areas, the cerebellum, ventricles, and blood vessels has become increasingly high resolution. Currently, CT scans can accurately render single millimeter slices and MRI can give sub-millimeter details.[11] CT scans utilize x-ray based technology, meaning there is a small but measurable dose of radiation for each CT scan done, and images are reconstructed to a 3D model. MRI does not utilize any ionizing radiation, but rather capitalizes on differential changes in the magnetic field produced by the water content of diverse tissues. While there are no radiation risks, as the magnet strength increases above 3 tesla, patients can experience some discomfort during scans. Special techniques, such as diffusion tensor imaging (DTI), utilize MR-based imaging to assess the integrity of the white matter tracts.[11]

Together, structural imaging techniques allow us to see many types of brain injury, including both ischemic and hemorrhagic strokes, congenital malformations, malignancies of all types, and even some traumatic brain injuries, when these are large enough to be accompanied by white matter damage. Some key findings in primary psychiatric disorders are shown in Table 1.

Functional Neuroimaging: EEG, PET, fMRI, SPECT

In contrast to structural neuroimaging, functional neuroimaging attempts to discern the neural activity in the brain at a given time. A variety of techniques for measuring function exist, capitalizing on the changes that occur in the brain when neurons are firing or are in activated and/or deactivated states. We will review many of these techniques and some major contributions they have provided in our understanding of psychiatric disorders in Table 2.

Electroencephalography (EEG) is one of the oldest and also the most direct non-invasive measure of function. EEG measures electrical field changes from neural activity—both the neurons firing as well as more general changes in local field potentials which allow neurons to be in a state where they are more or less likely to fire.[11,12] Unfortunately, as EEG uses electrodes that are on the scalp, it has limited ability to determine the specific part of the brain causing any particular signal as each electrode is receiving information from many parts of the brain. Placing the electrode directly on the dura, as is done for neurosurgical assessments, improves

spatial resolution, but is clearly not a good solution for use as a diagnostic test.

To improve spatial resolution in the 1980s, researchers, including those at Washington University, developed positron emission tomography (PET) imaging for use in studying neural activity. In the most common application of PET, radiolabeled glucose is injected into patients, which can then be measured to see which parts of the brain are most metabolically active at that time, or when performing a specific task, though other radiotracers can be used as well.[13] PET can also measure neurochemical receptors on neurons. PET imaging provided the foundation for assessing anterior cingulate cortex dysfunction in MDD.[14,15] Further psychiatric research has utilized PET to understand serotonin and serotonin receptors in mood disorders.[16] However, use of PET in psychiatric research is limited by exposure to ionizing radiation, expense and limited spatial resolution.[11]

Single-photon emission computer tomography (SPECT) is a highly-related technique, also utilizing a radiomarker.[12] Often SPECT in neuroimaging utilizes technetium-based isotopes to assess blood flow, though as with PET, other compounds can be used as well. This technique does carry some radiation risk and by measuring the emission of single photons, spatial resolution in limited to around 1cm; temporal resolution is also limited.[11]

In the 1990s it was recognized that MRI could provide similar information on regional brain activity without the radiation exposure inherent to prior imaging modalities. Magnetic resonance based functional neuroimaging most often uses changes in the level of oxygenated and deoxygenated hemoglobin in blood to determine which areas are most metabolically active. The MRI detects the differential magnetic field properties of oxygenated vs deoxygenated blood at a spatial resolution of a about a millimeter, much higher than any prior neuroimaging technique.[11,12] This method is called BOLD (blood oxygen level–dependent) fMRI.

MRI can also measure local blood flow. Perfusion MRI has lower spatial and temporal resolution than BOLD, but is quantitatively much more stable over time, making it potentially more useful to examine slow changes in the brain such as between wakefulness and sleep. The temporal stability of perfusion MRI has also been exploited to quantify drug activity and receptor sensitivity in the brain, since pharmacological effects often require measurements separated by hours or days in time.[17]

Magnetic spectroscopy, like MRI, capitalizes on the magnetic properties of excited protons, for example in the amino acid neurotransmitter glutamate. However, to do so reliably, the overwhelming water signal must be suppressed in data analyses. Practically, this means that to get good signal to noise, MRS must focus on very small areas of the brain, on the order of several square centimeters and/or utilize long scan times to maximize the number of measurements taken.[11] The potential to measure neurotransmitters such as GABA and glutamate have made it an appealing methodology for psychiatric research.

Around 20 years ago, researchers recognized that not only could fMRI be used to assess which brain regions were most active when doing specific activities, but that regions intrinsically varied (at rest) in how metabolically active they were in interesting and consistent ways. For instance, the left and right motor cortex tend to be active more often than not at the same time. Assessing the relationships between which regions were consistently co-activated is the basis of resting state functional connectivity, one of the most commonly used neuroimaging techniques in modern psychiatric research.[18]

How Has Neuroimaging Fallen Short?

While neuroimaging has given us a multitude of information about how the brain is generally affected in psychiatric diagnoses, the neuroimaging techniques described above are not yet meeting the criteria for a useful or high quality medical test as defined above. First, all of the neuroimaging techniques described above generally rely on group-based analyses. That is to say that in order to get a reliable enough signal to see differences related to depression, for example, researchers measure which areas differ on average between those with depression and those without. Second, the distribution of values for those who have a diagnosis and those who do not often overlap.

First, while large deviations from typical neuroimaging values or patterns may be more indicative of pathology, there are people who will

have psychopathology but no abnormalities in brain imaging and those with differences in neuroimaging that have no specific psychiatric diagnosis. In this way, neuroimaging techniques struggle to meet criterion 2a in the above referenced hierarchy of clinical test utility – they often cannot reliably distinguish between those with and without a diagnosis. Moreover, there is considerable overlap in neuroimaging findings across psychiatric diagnoses. To draw another analogy to anti-nuclear antibody testing, ANA can be elevated in multiple autoimmune conditions and cannot alone be used to give a particular diagnosis but only in conjunction with other tests and the clinical picture. Neuroimaging abnormalities such as decreased anterior cingulate cortex activity is seen across psychiatric conditions from depression and anxiety to bipolar disorder and obsessive-compulsive disorder[19] and cannot be used to give a specific diagnosis. Abnormalities in reward processing occur in both depressive disorder and attention deficit hyperactivity disorder.[20] For both, it is the context in which these abnormalities occur (meaning other symptoms and time course) that provide the diagnosis.

Second, in functional neuroimaging, the signal itself is not reliable enough to get a single (or even several) time measurement in an individual person and determine where that sits on the spectrum of "normal" or even "depression." As referenced above, by failing to reliably differentiate between a person with and without a disorder at any given time, these techniques fail step 2a in the hierarchy of clinical utility in medical testing. While resting state neuroimaging techniques are less affected by the individual measure or "state" as they either are thought to reflect a variation overall, "average" patterns of neural activations across the brain, there remains considerable variability in these measurements as these patterns can systematically change throughout the day and with training or experience.[21,22] Even state-of-the-art machine learning algorithms, which have excellent performance differentiating between groups of people with and without symptoms (i.e., psychosis), struggle to reliably label an individual as one experiencing psychosis.[23] Moreover, current imaging "diagnoses" are still being compared to clinical diagnoses, indicating that at the current time these tests also fail 2b in the hierarchy as they are using clinical diagnoses as the "gold standard," not performing better than or even adding to these diagnoses in most studies.

Last, a number of the neuroimaging techniques discussed above do carry small but significant risk. PET and SPECT all include exposure to radiolabeled markers and exposure to ionizing radiation (albeit in relatively small quantities) as well as intravenous access. Research indicates that more than 20 minutes of high quality resting state scans are needed to be able to reliably asses an individual's functional connectivity patterns.[24] The long amounts of time needed to obtain MR imaging in a small, contained space where patients must lie flat results in significant inconvenience. Furthermore, relative contraindications to MRI exist, from pacemakers to tattoos to claustrophobia. The use of these expensive imaging techniques, which require trained technicians and intensive computational analysis, also makes these techniques currently much more expensive than clinical diagnoses, indicating an additional failure in step 5 of the testing hierarchy.

To put this all together, consider the example of perfusion SPECT, which some have advocated to diagnose and guide treatment in children with ADHD and related symptoms. Some patients and clinicians are already convinced that the scan was useful in that setting. However, for these judgments, the quality of the evidence must be high, because a happy outcome after a test may be chance. As the old saying puts it, even a stopped clock is right twice a day. Furthermore, since patients and doctors both are hoping for the test to mean something, they are likely to interpret their experience with favorable bias. Therefore we can trust only research that keeps them both from knowing whether the test results are real or simulated until the outcome of interest is recorded without bias. Judged in this light, what does the evidence say?

Average brain activity probably differs in ADHD compared with people without ADHD (step 1 in the box). However, there is no reliable published information on step 2a, e.g., what is the positive predictive value of a specific finding on the SPECT scan for diagnosis? And given that the current standard for diagnosis of ADHD is driven by clinical assessment, it is not surprising that step 2b is hard

to achieve. Even if the scan could provide clinically important superior diagnostic information, that information is largely irrelevant to the patient unless it makes a difference to treatment (step 3) and ultimately to the effect on the patient of changing treatment (step 4). Any such benefits must of course be weighed against the downsides of imaging, such as financial cost, time and inconvenience, and in this example involving irradiating children, risks to health (step 5). Furthermore, ideally the downstream effects of improving a diagnosis by imaging would change not only a medically measurable outcome but raise the quality of the patient's life (step 6). Finally, from a public health perspective, test results should improve quality of life at least as much as other interventions of similar cost (step 7). Collectively, these points remind us that any medical diagnostic test needs to pass quite a high bar for us to conclude that they are worth it to the patient (step 6) or to society (step 7). Unfortunately, at this time, imaging tests for common psychiatric illnesses are almost all stuck at step 1.

Where is Neuroimaging Going?

Ultimately, this is not an indictment of the use of neuroimaging in psychiatry—it's an acknowledgment of the complexity of the human brain and psychiatric conditions, which are themselves part of the human experience. There are 100 billion neurons in the human brain and the activity patterns that correlate with "normal" or "typical" human experience is not fully understood. Those activity patterns we do see differ across people and types of tasks themselves can differ depending on the context—in what part of the circadian cycle the data is collected, how sleepy the participant feels, whether another person is in the room, or whether they have just experienced intense emotions. This is consistent with the human experience, but makes measurement extremely difficult. Additionally, our current psychiatric diagnoses are (well validated) conjunctions of symptoms. While this does capture important information about the diagnoses, there are also more than 100 combinations of symptoms that can result in a diagnosis of major depressive disorder.[25] Between the complexity of the human brain and the variety of symptoms, it is not surprising that neuroimaging findings related to a specific diagnosis have produced variable results. As a result, the field, guided by the NIMH, has increasingly moved to investigating neuroimaging markers of individual psychiatric symptoms rather than diagnoses.[26] While this approach holds promise, the difficulty in identifying reliable, specific markers continues.

As reviewed in this journal by Siegel et al., in July 2023, researchers continue to work to identify patterns of brain responses that may indicate a particular diagnosis or possible treatment response to improve our ability to "personalize" psychiatric medicine. Much of this research is focused on using complex computer algorithms and machine learning to identify complex spatial or temporal patterns of resting state functional connectivity associated with disease states or treatment response, or on combinations of imaging modalities.[25] However, even when initial studies have found patterns consistent with subtypes of depression,[27] follow up studies using different populations have often found the initial results are not generalizable.[28]

Further work in these areas promises to improve on these limitations,[29] but currently the results reported in neuroimaging studies can tell us about a group, but cannot reliably tell us about an individual within that group.

What Do I Tell My Patients?

When patients ask us: "Isn't there a brain scan you can do?" using the knowledge reviewed here, we tell them: "I wish we could—it's something we're working on in our research studies. Unfortunately, right now all types of brain imaging cannot reliably give you a diagnosis or tell us which treatment will be best for you."

Walking through the information above can also help patients understand why such tests, when offered, are not recommended by most psychiatrists or the National Institute of Mental Health, are not FDA approved, and are not covered by insurance. Fortunately, a long history of research using expert review of symptom patterns does allow us to reliably make a diagnosis, which points us to an algorithm for starting treatments.[30] In short, as psychiatrists, we love to look at the brain—but we're not going to put you through the time, cost, and risks of brain imaging unless there's evidence that it is likely to benefit you.

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Insomnia: A Current Review

by Sowjanya Naha, MD, Manjamalai Sivaraman, MD & Pradeep Sahota, MD

Insomnia is a widely prevalent disorder with pervasive effects on quality of life.



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Abstract

Insomnia is a prevalent sleep disorder with pervasive effects on quality of life. The deleterious effects of insomnia are largely preventable with appropriate therapeutic interventions. Pharmacotherapy should be initiated in patients with inadequate response to CBT-I and tailored to comorbidities. Referral to a sleep medicine specialist should be considered in patients with a suboptimal response.

Introduction

Insomnia is a prevalent sleep disorder that is frequently underdiagnosed or undertreated. It is clinically characterized by subjective difficulty falling asleep or staying asleep which must be present for at least three days a week for three months to meet ICSD-3 diagnostic criteria.[1] Importantly insomnia occurs despite adequate opportunities to sleep and is accompanied by daytime symptoms. Similar criteria have been proposed and established by the DSM-5 and ICD-10.[2,3]

In adults, daytime effects can range from fatigue, trouble focusing, reduced motivation, and irritability to memory impairment. Affected individuals may report dissatisfaction or anxiety about the quality of their sleep. In children, insomnia is typically reported by parents or caregivers as resistance to going to bed and poor academic performance.

Types of insomnia

Insomnia is classified based on the duration of symptoms. Chronic insomnia is defined by symptoms occurring at least three times a week for at least three months. Short-term insomnia is distinguished by symptoms that last less than three months. It is often seen in association with acute stressors and disappears with resolution of the stressor but can evolve into chronic insomnia when perpetuating factors are present.

Epidemiology and Pathophysiology

Estimates of the prevalence of insomnia in the adult population vary from 10% to as high as 40%.[4] This uncertainty stems from lack of awareness and the complexity of diagnostic criteria required to make a definite diagnosis.[5] Contributing factors for insomnia are defined by Spielman's three-factor model which classifies them as predisposing, precipitating, and perpetuating factors.[6]

Predisposing factors include advanced age, female gender, depressed mood, increased levels of perceived stress, hypnotic use, substance abuse, and a positive family history of insomnia.[7] Lower socioeconomic status has been associated with insomnia, although racial and ethnic minorities are less likely to report it possibly because of perceived implications for employment.[8,9] Insomnia has been linked with many chronic

medical conditions including heart disease, cancer, neurologic disease, chronic urinary and gastrointestinal disorders, and chronic pain.[10-12] Up to 40% of affected individuals are diagnosed with psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder.[12]

Precipitating factors include stressful life events, medical or psychiatric illness, and medications like steroids that can cause insomnia.

Perpetuating factors include maladaptive responses such as daytime napping and increasing anxiety that sustain this process, eventually culminating in chronic insomnia.

Aside from its biological effects, insomnia has economic implications for society. Insomnia can cause chronic absenteeism with a propensity to self-medicate with over-the-counter medications and alcohol. Indirect cost to the economy is estimated at over $60 billion per year, excluding direct healthcare costs.[13] These costs are largely preventable by timely diagnosis and institution of appropriate therapeutic interventions.

Treatment of Insomnia

Treatment of insomnia is broadly grouped into non-pharmacologic and pharmacologic interventions.

Non-pharmacologic Interventions

These interventions constitute the cornerstone of management and should be applied before attempting pharmacotherapy. Moreover, they should be continued while the patient receives pharmacotherapy for effective treatment with the lowest possible medication. This minimizes the risk of medication side-effects and improves sustainability of the therapeutic strategy.[14]

Cognitive Behavioral Therapy (CBT)

CBT is a psychotherapeutic technique focusing on identifying and eliminating intrusive thoughts with negative effects on behavior and emotion.[15] CBT for insomnia (CBT-I) is specifically tailored to insomnia and combines educational and behavioral interventions with cognitive techniques. Educational intervention is centered around sleep hygiene, which includes maintaining a regular sleep schedule, avoiding screen time 30 minutes prior to bedtime, maintaining a cool and dark sleeping environment, avoidance of caffeine after lunch, and minimizing daytime naps. Behavioral interventions include stimulus control, sleep restriction, and relaxation techniques. Cognitive interventions include thought-stopping, constructive worry exercise, cognitive restructuring, cognitive defusion, and paradoxical intention.[14,16,17] While best delivered by psychologists, online versions are available.

Pharmacologic Interventions

Available interventions include numerous FDA-regulated agents spanning prescription medications approved for insomnia, prescription medications used off-label for insomnia, and over-the-counter drugs. Additionally, we will review unregulated supplements and recreational agents like alcohol that are frequently used for self-medication by persons suffering from insomnia as they have implications for pharmacotherapy of insomnia.

FDA-Approved Pharmacotherapy for Insomnia

Several pharmacotherapeutic agents are approved by the FDA for use in insomnia. These agents can exert their effects through the $GABA_A$ receptor (benzodiazepines, and non-benzodiazepine Z drugs), orexin receptor (DORAs), or melatonin receptor (ramelteon).

Drugs Acting Via the $GABA_A$ Teceptor

They include benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists (BZRAs) also known as 'Z' drugs. They have a rapid onset of action and increased total sleep time making them effective in sleep-onset and sleep maintenance insomnia.[18]

- ***Benzodiazepines***

Benzodiazepines (BZDs) are positive allosteric modulators of the $GABA_A$ receptor complex. Gamma amino butyric acid (GABA) is a sleep-promoting neurotransmitter in the central nervous system. BZDs exert their effect by increasing GABA binding to the $GABA_A$ receptor resulting

Table 1. Summary of available benzodiazepines including indication, dosing and half-lives.

BZD	Sleep-onset insomnia	Sleep maintenance insomnia	Dosing in adults<65 yr	Dosing in adults ≥65 yr	Half-life (hrs)
Estazolam	+	+	1-2 mg	0.5-1 mg	10-24
Flurazepam	+	+	15-30 mg	15 mg	48-120
Quazepam	+	+	7.5-15 mg	7.5 mg	48-120
Temazepam	+	+	7.5-30 mg	7.5 mg	8-22
Triazolam	+	-	0.125-0.5 mg	0.125-0.25 mg	2-4

in increased intracellular chloride, membrane hyperpolarization, and signal inhibition. This is accomplished by binding of BZD to the alpha subunit of the receptor complex. There are six subtypes of the alpha subunit that determine the downstream effects of GABA including muscle relaxation, anxiolysis, and sedation.[19] BZDs bind to subtypes 1, 2, 3, and 5.

The rapid onset of action of BZDs requires that they be dosed at bedtime and their long half-life necessitates that adequate time be allowed in bed and hazardous activities avoided after drug administration. Special precautions should be taken when prescribing these agents to older people and individuals with liver impairment.

Although generally well tolerated, BZDs can have side-effects ranging from daytime somnolence, dizziness, ataxia, and headaches to more serious conditions like anterograde amnesia and complex sleep behaviors like somnambulism.[19] They are also associated with rebound insomnia and withdrawal symptoms like anxiety and seizures when abruptly discontinued after prolonged use. Patients who receive these agents should be educated about the potential for such complications. Individual drugs are summarized. (Table 1).

- ***Non-benzodiazepine BZRAs (Z Drugs)***

These agents are pharmacodynamically similar to BZDs and also act on the alpha subunit of the $GABA_A$ receptor complex to enhance GABA binding. However, unlike BZDs, these drugs bind specifically to the alpha-1 subunit which mediates the sedative action of GABA. As a result, they have fewer "off-target" effects seen with BZDs and are better tolerated.[20] The majority of these drugs are long-acting; except zaleplon, which is short-acting and not associated with daytime somnolence. They carry the potential for excessive sedation in older and hepatically-impaired individuals. Additionally, zolpidem requires dose modification in women because of slower metabolism.[21] Z drugs have been linked with complex sleep behaviors that can lead to potentially fatal situations. Reports of such incidents led the FDA to issue a black box warning for these agents in April 2019.[22] Individual drugs in this category are summarized (Table 2).

- ***Dual Orexin Receptor Antagonists***

Dual orexin receptor antagonists (DORAs) act by blocking receptors to orexin peptides A and B. The orexin pathway promotes wakefulness and arousal.[23] Suvorexant, lemborexant, and daridorexant are currently approved in this class. They are effective in both sleep-onset and sleep-maintenance insomnia. They are long-acting and can cause daytime somnolence. These drugs have better safety profile in the elderly.[24] Despite a favorable benefit-risk profile, DORAs are not preferred over other FDA-approved drugs due to significant cost. The pharmacokinetic properties of these agents are summarized (Table 3).

Ramelteon

This is a synthetic analog of melatonin, which acts selectively on the MT1 receptors in

Table 2. Summary of available non-benzodiazepine BZRAs including indication, dosing and half-lives.

Non-BZD	Sleep-onset insomnia	Sleep maintenance insomnia	Dosing in adults <65 yr	Dosing in adults ≥65 yr	Half-life (hrs)
Zaleplon	+	-	5-20 mg	5 mg	1
Zolpidem IR	+	+	5-10 mg*	5 mg	1.4 – 4.5
Zolpidem oral liquid	+	+	5-10 mg* (5 mg/ spray)	5 mg	1.4 – 4.5
Zolpidem ER	+	+	6.25-12.5 mg†	6.25 mg	1.6 – 4
Zolpidem sublingual	-	+	3.5 mg‡	1.75 mg	1.4 – 4.5
Eszopiclone	+	+	1-3 mg	1-2 mg	6

*5 mg in females due to slow metabolism
†6.25 mg in females due to slow metabolism
‡1.75 mg in females due to slow metabolism

the suprachiasmatic nucleus to attenuate the circadian alerting signal and shorten sleep-onset latency. It is suitable for sleep-onset insomnia such as individuals with delayed circadian rhythm/sleep cycle. Ramelteon is not helpful for individuals with difficulty staying asleep. The clinical efficacy of ramelteon is relatively minor, but studies have reported subjective benefits extending up to a year.[25] Ramelteon dose is 8 mg once daily within 30 minutes of bedtime. It is a relatively safe drug, does not cause daytime sedation or withdrawal effects after cessation, and does not have abuse liability.

Doxepin (Low Dose)

Doxepin is a selective histamine receptor antagonist. At low doses of 3-6 mg, it acts selectively on H1 receptors and is effective for sleep maintenance because of its relatively long half-life. Although it can cause daytime somnolence, it has no abuse liability and there is no limitation on duration of use.

Off-Label Use of Prescription Medications (FDA-Approved But Not for Insomnia)

Many medications produce sedation—including antidepressants, anticonvulsants, mood-stabilizing agents, and antipsychotics. Their sleep-promoting effects are mediated by suppression of wake-promoting neurotransmitters such as acetylcholine, dopamine, norepinephrine, serotonin, and histamine. These agents are typically not recommended as stand-alone therapy for insomnia. However, in patients with insomnia and concurrent psychiatric disorders requiring pharmacotherapy, the sedating properties of these drugs can be useful in alleviating insomnia.[26]

Antidepressants

Examples include trazodone and mirtazapine. Trazodone has a rapid onset of action that makes it helpful for sleep-onset disorders but a long half-life that can cause excessive daytime sedation. Additionally, trazodone is associated with serotonergic adverse effects including hypotension, sweating, arrhythmias, and serotonin syndrome. Because of these adverse effects, trazodone is not recommended as a standalone therapy for insomnia.[27] However, one review article suggests that trazodone may be used in low doses (25-100 mg) for insomnia.[28] Mirtazapine has similar sleep-promoting properties and is associated with

Table 3. Summary of available DORAs including dosing, half-lives and adverse effects.

DORA	Dose	Onset (mins)	Half-life (hrs)	Adverse effects (class effects)
Suvorexant	10-20 mg	30	12	• Daytime somnolence • Significant drug interaction (CYP3A4 dependent metabolism) • Sleep paralysis • Hypnagogic and hypnopompic hallucination • Cataplexy-like symptoms • Contraindicated in narcolepsy
Lemborexant	5-10 mg	15-20	17-19	
Daridorexant	25-50 mg	60	8	

anticholinergic adverse effects but does not cause cardiac and sexual dysfunction, unlike trazodone. Mirtazapine and trazodone are best considered in patients with comorbid depression with insomnia.[29]

Anticonvulsants

Gabapentin and pregabalin may be considered in patients with comorbid pain, seizure disorder, and alcohol use disorders. There are no randomized controlled data to support the use of these agents for insomnia in the absence of such conditions.[30]

Antipsychotics

They are considered in patients with comorbid psychosis and insomnia unresponsive to standard therapies: examples include quetiapine and olanzapine. Olanzapine has a prolonged half-life that can cause marked daytime sedation. They may be associated with significant toxicity and should not be used for insomnia in the absence of comorbid psychiatric indications.[31] Quetiapine for instance carries a black box warning for suicidal thoughts and both agents carry warnings about increased mortality in older individuals.[32]

Over-the-Counter Medications

Antihistamines

These medications do not require prescription and include agents like doxylamine and diphenhydramine. Despite their widespread use, accounting for an estimated 60% of all medications used for insomnia,[33] there is little to no high-quality evidence to support their use for this indication. They exert their sleep-promoting effects via postsynaptic histamine receptor blockade. They can cause anticholinergic side-effects like dry mouth, blurry vision, confusion, and urinary retention, as well as prolonged sedation and daytime sleepiness. These effects are magnified in older individuals and patients receiving other anticholinergic medications.[34] Given the potent anticholinergic effects of diphenhydramine (also available in combination with acetaminophen), its use is not recommended for insomnia. Moreover, the use of these agents is typically associated with rapid development of tolerance, which renders them ineffective for chronic insomnia.

Unregulated Supplements and Recreational Substances

Unregulated Supplements

Safety concerns apply to over-the-counter medicines and supplements. Examples include ashwagandha, chamomile flower extract, magnesium supplements, glycine, L-theanine, and valerian root with limited data to support their efficacy, safety, and quality control.[35] They

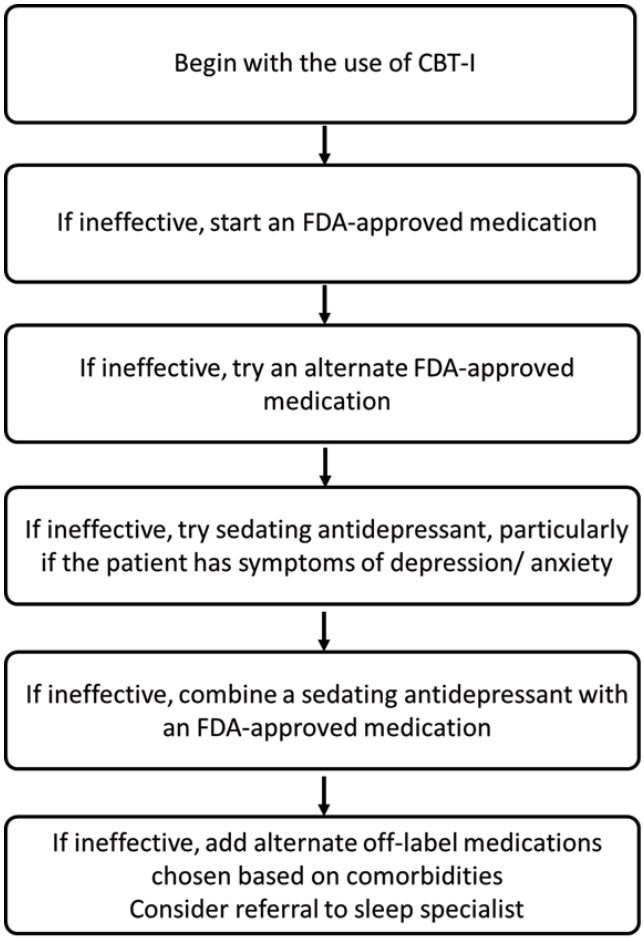


Figure 1. Simplified algorithm for initiating and/or combining pharmacological therapy.

are not regulated by the FDA, do not require a prescription, and their use is not supported by the American Academy of Sleep Medicine.[27]

Melatonin

Melatonin is a hormone secreted by the pineal gland. Melatonin levels are suppressed during the day, rise towards nightfall, plateau overnight, and then fall back to daytime concentrations by dawn.[36] The sleep-enhancing effects of melatonin are mediated by MT1 and MT2 receptors.[37] The circadian reinforcing effect of melatonin makes it suitable for patients with sleep-onset disorders.[38] Melatonin has been used in patients with Delayed Sleep Phase syndrome, who go to sleep later and may present as sleep-onset insomnia. This agent may be used in appropriate settings under the supervision of a clinician.

Recreational Substances

Acute ingestion of alcohol reduces sleep latency and improves quality and quantity of non-REM sleep during the first half of the night. However, there is disruption of sleep architecture in the second half.[39] Thus, alcohol use leads to diminished sleep quality, sleep disruption, and worsening insomnia. Insomnia is a prominent symptom of alcohol withdrawal leading to a vicious cycle of relapsing alcoholism as withdrawing patients use alcohol to control symptoms.[40] There is also a significant risk of extreme sedation if patients prescribed medications for insomnia consume alcohol. Therefore, it is imperative to obtain a careful history before starting pharmacotherapy for insomnia.[41]

Principles of Pharmacologic Therapy in Insomnia

When used appropriately, pharmacotherapy is effective in managing insomnia and produces quick symptom relief. However, pharmacotherapy can produce significant side-effects that potentially offset its benefits and it is important to use good judgment when prescribing such medications. These drugs should be used at the lowest effective dose to minimize risk of adverse effects and the maximum recommended dose should not be exceeded. They should be supplemented with CBT-I wherever possible to maximize benefit. In fact, CBT-I should always be the first line of treatment. Efforts should also be made to taper the dose with improvement in symptoms. The duration of pharmacotherapy for insomnia is not well established and should be individualized. For reference, it must be remembered that most clinical trials did not extend beyond 12 months of therapy. Limiting the use of these agents to a shorter duration reduces risk of dependence. However, such a strategy may not be feasible in patients with chronic comorbidities who require prolonged therapy.

Patients on these agents should be educated about the goals of treatment and potential safety issues including the risk of withdrawal and drug interactions with alcohol and other CNS

depressants. Patients must be regularly evaluated while on therapy to assess efficacy, ongoing needs, adverse effects, and new symptoms. Pharmacotherapy is not recommended in individuals below 18 years. On the other hand, although effective in older patients, these drugs must be used with caution and at lower doses to mitigate the risk of adverse events.

With a wide range of pharmacologic agents available, determining which medication is most likely safe and effective in an individual requires careful consideration of several factors including the pattern of symptoms (sleep-onset, sleep maintenance, or both), the effectiveness and tolerability of past treatment, access to non-pharmacologic therapy, medical comorbidities, side-effect profile of the medication being considered, potential interactions with the patient's other medications, cost of therapy and patient preference. Further complicating this process is the fact that some patients might not respond to single-agent therapy and thus require combination therapy. A simplified algorithm for initiating and/or combining pharmacological therapy is outlined (Figure 1).

Conclusion

Insomnia is a widely prevalent disorder with pervasive effects on quality of life. Effective management should begin with non-pharmacologic interventions such as CBT-I. Pharmacotherapy should be initiated in patients with inadequate response to CBT-I and tailored to comorbidities to maximize benefits and minimize side-effects. Combination therapy with two or more classes of medication may be needed in some individuals but should only be attempted under close medical supervision. Referral to a sleep medicine specialist should be considered in patients with suboptimal response to standard pharmacotherapy approaches outlined in this article.

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Disclosure

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Syncope in Athletes: A Prelude to Sudden Cardiac Death?

by Deepa Baswaraj, MBBS & Greg Flaker, MD

Syncope in an athlete is challenging to manage and it requires understanding of normal physiological changes that occur with physical training.



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Abstract

Athletes are generally healthy but might have certain cardiac disorders which might, during athletic participation or training, result in cardiac symptoms including syncope. Vasovagal syncope is probably the most common cause of syncope in athletes, but syncope in the context of these cardiac disorders might be a warning of sudden death.

Introduction

Sudden cardiac death in an athlete is a rare, tragic, and seemingly unpredictable event. However, many patients who have survived sudden cardiac arrest recall warning symptoms, including syncope, in the weeks prior to event.[1] In addition, in patients with implantable defibrillators (ICD) who have experienced an appropriate shock, ventricular ectopy often occurs in the 30 days prior to ICD discharge.[2] These data suggest that sudden cardiac death might be heralded by cardiac symptoms, including syncope.

Consequently, the evaluation of syncope assumes extreme importance, particularly if these underlying cardiac conditions are present.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an important cause of sudden death in athletes, accounting for approximately 20% of cases.[3] HCM is characterized by marked left ventricular hypertrophy, usually in an asymmetric pattern, and often involving the basal interventricular septum. The asymmetric hypertrophy results in left ventricular outflow obstruction in about one-third of cases with a characteristic systolic murmur along the lower left sternal border. Another third of patients have what is called a provokable gradient detected after the administration of an inotropic agent. Some forms of HCM are not associated with obstruction which may limit the sensitivity of physical examination in diagnosing HCM.

More than 11 causative genes have been identified which encode a variety of sarcomere proteins in HCM. Abnormal sarcomere development results in disordered alignment of myocardial fibers, interstitial collagen deposition and eventual cardiac fibrosis, thought to be related to coronary microvascular-mediated flow dysfunction and ischemia. This abnormal cardiac architecture is a substrate for ventricular arrhythmias.

Approximately 60% of patients with HCM have a familial component, usually inherited in an autosomal dominant fashion. Consequently, a family history of sudden death in a first degree relative assumes importance in the

evaluation of the athlete. Most patients with inherited HCM demonstrate left ventricular hypertrophy by early adulthood.[4] However, some individuals have a delayed phenotypic expression. Hence, a normal physical examination and echocardiogram cannot rule out the possibility of developing HCM in the future.[5]

Physiological changes in an athlete's heart include left ventricular hypertrophy that can be confused with pathological changes in HCM. Asymmetric increase in left ventricular wall thickness more than 12mm, decreased LV cavity, diastolic filling patterns, and cardiac MRI demonstrating delayed gadolinium enhancement are features less characteristic of athletic training and more likely to represent HCM.[6]

Syncope in an athlete with HCM might be due to vasovagal syncope or due to left ventricular outflow tract (LVOT) obstruction. However, in HCM neither vasovagal syncope nor a basal LVOT gradient (≥30mmHg) is associated with sudden death.[8] Although the presence of a left ventricular gradient is not considered to be a major risk factor for sudden cardiac death, it might be a target for pharmacologic modulation. Similarly, the development of hypotension during exercise might provide important clues for therapy in the athlete who experiences syncope with exertion.

A second cause of syncope in the athlete with HCM is atrial arrhythmias. Because of diastolic stiffness due to ventricular hypertrophy, patients with HCM rely on the atrial contribution to ventricular filling and atrial arrhythmias can be associated with syncope in HCM.[9] Asystole and heart block have also been reported with HCM,[10] but would be less likely in a young athlete.

Finally, syncope in a patient with HCM might be due to ventricular arrhythmias which could be a precursor to sudden death. A risk factor for sudden death in HCM include multiple and prolonged episodes of ventricular tachycardia on ECG monitoring. Other major risk factors include extreme septal thickness, or HCM-related sudden death in a first degree relative. Newer risk factors include the presence of a left ventricular apical aneurysm or extensive fibrosis seen with late gadolinium enhancement on MRI. In the presence of these risk factors, an implantable defibrillator (ICD) may be placed in the athlete with HCM which has implications for the athlete's continued participation in sports.

The previous guidelines restricted competitive sports for persons with HCM to low intensity sports such as golf and bowling.[11] There were concerns that most sudden death in young athletes occurred with exertion[12] and were likely due to ventricular arrhythmias. If an ICD was implanted, shouldn't the ICD eliminate concerns about sudden death?

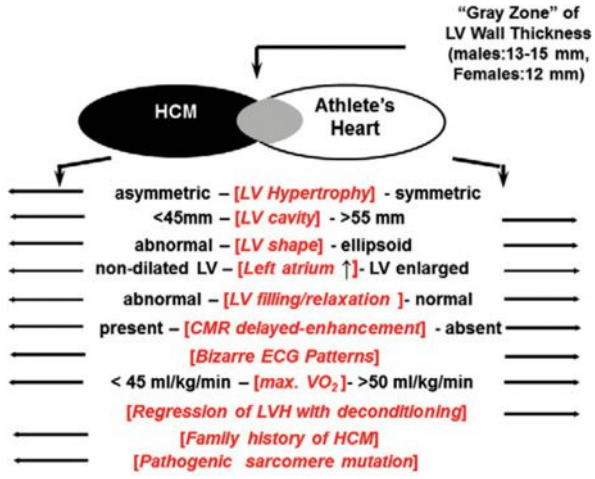


Figure 1. Criteria used to distinguish HCM from athlete's heart.
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Previous guidelines discouraged the implantation of an ICD in an athlete with HCM for the sole purpose of permitting high intensity sports participation.[11] There were several reasons for this. ICDs were implanted and tested for efficacy during the resting state. Would ICDs successfully defibrillate athletes during athletic participation with high catecholamine levels and other physiologic changes? Could there be injury as a result of a ventricular arrhythmia occurring during sports participation? There were also concerns about inappropriate shocks. Finally, could there be damage to the ICD during the physical contact of sports?

An International Registry of athletes with implantable defibrillators has revisited the question of athletic participation in patients with ICDs for HCM as well as other cardiac conditions. The Registry sampled athletes with ICDs who participated in high intensity sports. No deaths, no resuscitated arrests, and no shock-related injuries were noted in a median follow-up of 44 months.[13] In part because of this data, many clinicians are allowing athletes with ICDs to participate in competitive athletics. A few medical and legal issues have been raised, trying to balance the desire of the athlete with the medical teams who want safety in sports participation.[14]

An important aspect of the use of ICD in athletes is appropriate programming. ICDs are programmed to

provide protective shocks if a certain rate is achieved. Athletes often achieve extremely high heart rates which might result in an inappropriate shock. Programming ICD to higher rates to specifically detect ventricular arrhythmias, is one way to avoid inappropriate shocks. In addition, exercise often results in T wave changes which might be "double counted" by the device which results in an inappropriate shock. Adjustment of sensing algorithms can be effective in eliminating inappropriate shocks.

Myocarditis

Myocarditis is an inflammatory disease of the myocardium characterized by inflammatory infiltrates with necrosis of nearby myocytes.[15] The types of cellular infiltrates seen (lymphocytes vs eosinophils) might suggest a particular etiology and help guide management.

The incidence of myocarditis has been reported to be 1-10/100,000. However, since the COVID pandemic, with the recognition of COVID-associated myocarditis, the incidence of myocarditis has increased to 20-64/100,000.[16]

Myocarditis can lead to cardiac arrhythmias and is associated with sudden cardiac death. In autopsy studies in young persons (<35 years) who died suddenly, myocarditis was reported to be found in 10% of the sample size.[17] In athletes, the Expert Panel from the National Center for Catastrophic Injury Research reported the incidence of myocarditis in athletes to be 4%.[18] The first manifestation of myocarditis might be sudden cardiac death which is often related to activity.

The gold standard for diagnosis of myocarditis has been an endomyocardial biopsy.[19] However, it is an invasive procedure with significant risks. Further, there is a need for expertise in performing and interpreting the biopsy. Hence, the frequency with which this test is performed varies between institutions.

Advances in cardiac imaging have changed the standard of care in diagnosing myocarditis. Cardiac MRI, with the use of gadolinium enhancement, is a valuable tool to detect areas of cardiac dysfunction, hyperemia and edema, and excess extracellular volume. With updated criteria,[20] the sensitivity and specificity for the diagnosis of myocarditis has been reported to be 88% and 96% respectively.[21] A cardiac MRI has the highest sensitivity if performed two to three weeks after initial presentation and can be repeated in six to 12 months to determine the presence of myocardial scar—an important predictor of cardiac mortality.[22] However, some MRI-detected scars in athletes might be a normal finding[23] and careful interpretation of imaging studies along with good clinical judgement is required for accurate diagnosis.

Early in the COVID pandemic there were reports linking COVID with myocarditis. Because of this association, major collegiate conferences mandated that all athletes who contracted COVID be screened with high sensitivity troponin, ECG, and echocardiography. As it turns out, the frequency of myocarditis with COVID is low. Professional and collegiate registries showed the prevalence of myocarditis in athletes with COVID to range from 0.4% to 2%.[24] Importantly, no adverse cardiac effects were noted in these registries.

With these data, the evaluation of the athlete who contacts COVID has evolved. After a period of self-isolation, an asymptomatic patient with a new diagnosis of COVID may resume training after three days of rest. Those with mild to moderate cardiac symptoms should refrain from exercise until resolution of symptoms. Athletes with a remote history of infection (>3 months) and who are asymptomatic can exercise. For patients with acute COVID infections who have severe cardiovascular symptoms or who are hospitalized, especially those with troponin elevation, an abnormal ECG, or an abnormal echo, a cardiac MRI is recommended. Those with confirmed myocarditis should not return to competition for three to six months and then should have a gradual return to exercise.[24]

The management and return to play recommendations for athletes who have recovered from COVID with mild symptoms, but have persistently elevated high sensitivity troponin, a low normal function on echo, or persistent scar or edema on follow-up MRI, is not clear.[25] These athletes might be at higher risk for sudden death; hence, accelerated monitoring or periodic exercise ECGs seems to be the reasonable thing to do as we wait for more long-term data on such individuals.

Arrhythmogenic Right Ventricular Dysplastic Syndrome

Arrhythmogenic Right Ventricular Dysplastic Syndrome (ARVD) is an inherited cardiomyopathy, characterized by ventricular arrhythmias and an increased risk of sudden cardiac death. In the general population, the prevalence of ARVD is 1 per 1000 to 1 per 10,000 persons, with a high prevalence in Italy.[26] An autopsy study from Italy described the condition to be present in as high as 20% of deaths in young people, often occurring with exertion,[27] while a subsequent study in the

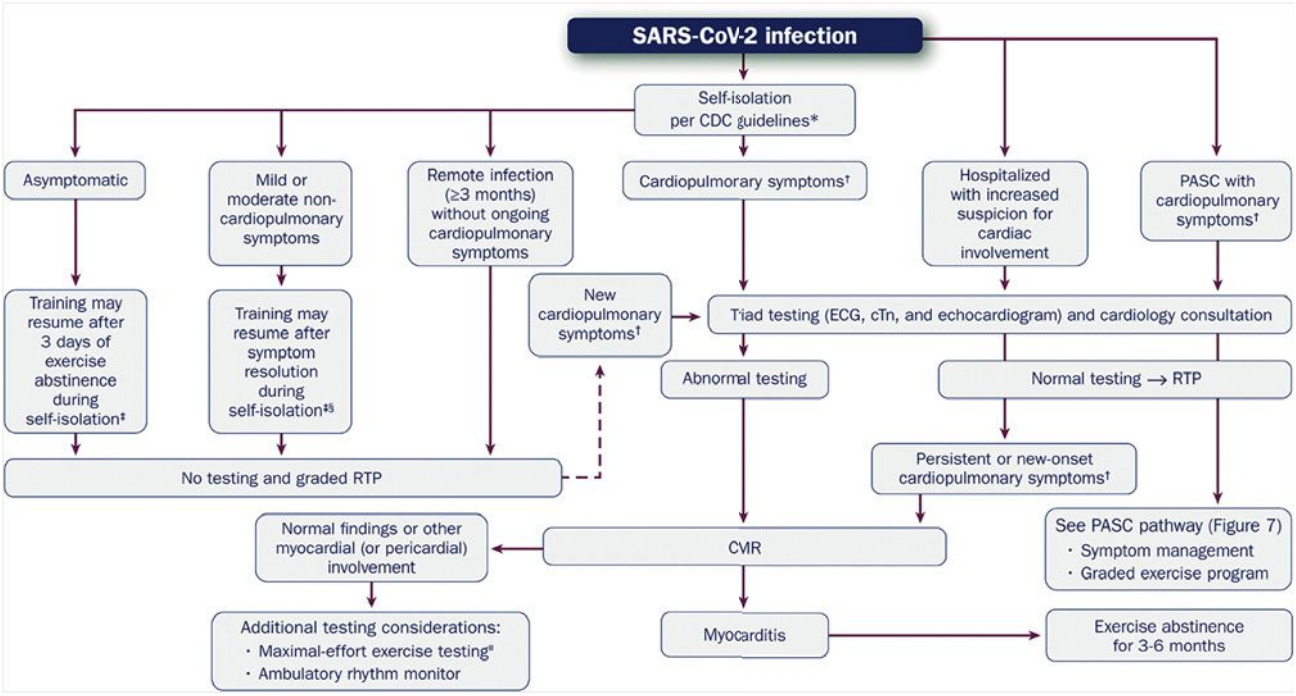


Figure 2. Evaluation of the athlete recovering from SARS-CoV-2 infection and guidance on return to play.
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United States showed fewer sudden cardiac death due to ARVD in competitive athletes[28]. Current estimates suggest that ARVD accounts for about 6% of sudden deaths in athletes.[29]

ARVD is due to mutations in genes which encode for desmosomal proteins which play an important role in adhesion between cells. After premature cell death, fatty deposits replace myocardial cells, and eventually fibrosis occurs. This remodeling is thought to potentially cause fatal arrhythmias, which can be aggravated by increasing pressure, afterload conditions and wall stress as in physical exertion. Hence, ARVD can present at an earlier age in a young athlete. About half the cases of ARVD are familial, inherited with an autosomal recessive pattern.

ARVD first manifests itself in the right ventricle although with advanced disease, involvement of the left ventricle is not uncommon.[30] Because the RV is involved early, athletes who have syncope and who have ECG findings of RV abnormalities such as diffuse T wave inversion in the anterior precordium, or terminal QRS notching in ECG lead V1, or who have PVCs or ventricular tachycardia with a left bundle configuration, might have ARVD. The sensitivity and specificity of standard screening tests including ECG and echo are relatively low and other imaging modalities are often required to make the diagnosis. Cardiac MRI is currently the preferred method. It can identify fibrofatty myocardial scarring in the RV free wall using late gadolinium enhancement. Other conditions that need to be differentiated from ARVD include sarcoidosis and congenital disease causing right ventricular volume overload.[30]

Exercise is associated with sustained ventricular arrhythmias[32,33] and may lead to premature cardiac dysfunction in ARVD. For patients with borderline or definitive diagnosis of ARVD, AHA/ACC guidelines from 2015 recommend restriction from competitive sports.[11] More recent studies have suggested that some physical activity in patients with ARVD is acceptable. Patients with ARVD can exercise at up to two to four times the AHA recommendation for healthy adults without excess risk for cardiac arrhythmias.[34] A prior history of sudden cardiac arrest, sustained VT or syncope appear to be most important prognostic factors and are indications for ICD placement.[30]

Coronary Artery Anomalies

Coronary artery anomalies refer to a heterogenous group of conditions that include an abnormal origin or

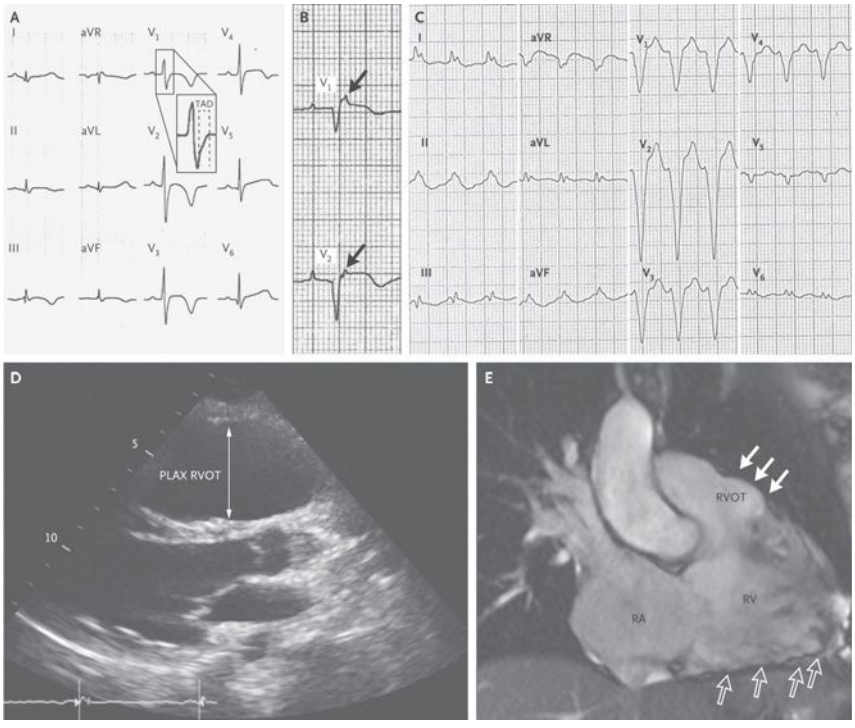


Figure 3. ECG and imaging features of ARVD.
(A) Negative T waves in leads V1 to V4.
(B) Epsilon waves which are small amplitude distinct potentials between the end of QTS complex and beginning of the T waves.
(C) Ventricular tachycardia with a left bundle-branch block pattern.
(D) Parasternal long axis view in the echocardiogram demonstrated dilatation of the right ventricular outflow tract.
(E) Cardiac MRI shows an aneurysm of the right ventricular outflow tract (solid arrows) and multiple sacculations of the inferior and apical regions (open arrows)
Reprinted with permission from - Arrhythmogenic Right Ventricular cardiomyopathy; N Engl J Med 2017;376:61-7231

course of any of the three epicardial coronary arteries. The prevalence of coronary anomalies is 1% to 8%.[35–38] It is the second most common cause of sudden cardiac death noted in athletes after HCM[39] accounting for 12-14% of cases.[29,39]

Many coronary anomalies have a benign course. However, when the course of a coronary artery is between the aorta and pulmonary artery, compression of the coronary artery occurs and increases the risk of sudden death. Other high-risk features include fish mouth or slit like shaped orifice, acute angle take off, intramural course or proximal narrowing. The origin of a coronary artery from the pulmonary artery (ALCAPA) is another form of congenital disorder that is associated with high mortality.[37]

Unfortunately, conventional cardiac testing is often insensitive in detecting these congenital abnormalities. While the transthoracic echo can view the origin and proximal course of coronary arteries, this requires good expertise on the part of the sonographer and seems to be of more value in children than adults. In a review of 27 sudden deaths in young athletes who were found to have an abnormal origin of either the left or right coronary artery, 15 had no cardiovascular manifestations or testing prior to the event. However, 12 had syncope or chest pain prior to death. All cardiac tests including ECG, stress test, and echo were normal.[40] Hence, special vigilance is required in the type of testing for the athlete with syncope. Coronary CTA has become the first-line imaging modality to visualize the origin and full course of coronary arteries, including the relationship with other major blood vessels. Younger athletes with high- risk features are often restricted from high intensity athletic competition without surgical correction.[41] Asymptomatic athletes with low- risk features and no evidence of ischemia can return to athletic competition, with close surveillance.[41]

Other coronary artery anomalies include myocardial bridges and coronary artery aneurysms such as those seen with Kawasaki disease.

Long QT Syndrome

Long QT syndrome (LQTS) is an inherited cardiac channelopathy that is associated with sudden cardiac death. The prevalence of LQTS in the general population is about one in 2000[42] although LQTS accounts for 5.3% of sudden deaths in athletes.[29]

At least 700 mutations have been identified in 13 genes which encode proteins which are essential in the formation of the cardiac action potential. There are at least 16 clinical forms of LQTS with unique clinical and electrocardiographic features. For example, LQTS-1 patients typically have symptoms which occur with exercise, particularly swimming. The ECG shows a broad- based T wave. Patients with LQTS-2 often have symptoms related to auditory

stimulation with notched T waves. LQTS-3 patients usually have symptoms at rest or sleep with a late appearing T wave often with a very long QT interval. Major genes that have been identified and the types of LQTS are KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3), accounting for ≈90% of all genotype-positive cases of LQTS.[43]

In an athlete with syncope, careful attention should be made to analysis of the QT interval. The QT interval is often provided by computer interpreted ECG, but should be measured manually. The QT interval should be corrected for rate (QTc). 99% of males have a QTc interval of < 470ms and 99% of females have a QTc of < 480ms. However, some genetically proven patients with LQTS have relatively normal QTc intervals. In these patients, exercise may, paradoxically, prolong the QTc interval, establishing the diagnosis, especially in LQTS-1. Scoring systems which incorporate the QTc interval as well as clinical and genetic factors can help diagnose LQTS in borderline cases.[44] Of note, a QTc interval of >500ms correlates with an increased risk of torsade des pointes.

All prescription and over-the-counter medications should be reviewed in athletes with LQTS with strict avoidance of QT prolonging drugs. CredibleMeds is an online resource that maintains and updated list of drugs that have a risk of QT prolongation. Registration to this website is free and this can serve as a great resource for physicians and patients to check medications that may be safe to prescribe in patients with LQTS.

In the past, sports participation for athletes with LQTS, especially those with syncope, was discouraged. Specific recommendations have specified that athletes with LQTS-1 syndrome should not engage in sports that require diving into cold water since this activity was associated with increased cardiac arrhythmias.[41] However, with full consent of the athlete and involvement of coaches and trainers as well as availability of personal external defibrillators, more LQTS athletes are safely returning to play. A 2021 study showed a low rate of non-lethal events in athletes with LQTS over a 20-year follow-up. The minority of these patients (11%) had an ICD.[45] There are some athletes with syncope and LQTS who might be eligible for an ICD.[46]

Beta blockers are standard therapy in most patients with LQTS. However, beta blockers impair exercise performance. Beta blockers are also banned, with some exceptions, by the World Doping Agency which governs sporting competition around the world. Consequently, beta blocker therapy can be met with resistance from the athlete and a discussion of the risk and benefits of the therapy must be made between the health care provider and the athlete.

Pre-Excitation Syndrome

Athletes with syncope may have evidence of ventricular pre-excitation on ECG, characterized by a short PR interval and a delta wave in the initial portion of the QRS complex. The ECG abnormality is due to a group of electrical fibers joining the atrium and ventricle, often time capable of extremely rapid conduction. It was first described in 1930 and it was 40 years later that risk of sudden cardiac death from rapid conduction through the accessory pathway was recognized. WPW accounts for about 4% of sudden cardiac arrest in athletes, although it is thought to be underrepresented as it is difficult to diagnose ventricular pre-excitation in postmortem cases with sudden cardiac arrest being the initial presentation.[29] The risk of sudden cardiac arrest seems to be highest in males and those younger than 18 years.[47] Some of the patients experienced sudden cardiac arrest during exercise. Many patients typically have warning symptoms prior to malignant arrhythmia.[48]

Athletes who present with syncope and who have ECG evidence of WPW often undergo electrophysiologic studies with ablation, a highly successful form of therapy.[48]

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a very rare inherited channelopathy characterized by ventricular tachycardia which occurs during exercise or strong emotion. Patients typically have normal resting ECG, a structurally normal heart and a reproducible bidirectional or polymorphic ventricular arrythmia which occurs during stress testing or with emotional stress. There is often a family history of syncope or sudden cardiac death. Mutation in genes encoding for RYR2 or CASQ2 is known to cause CPVT. Therapy includes beta blockers, calcium channel blockers, or flecainide and often an ICD placement or other surgical therapies.[49] The 2015 AHA guidelines recommend restriction from competitive sports for previously symptomatic CPVT or asymptomatic CPVT,[50] even though recent smaller studies show no difference in event rates with or without sports participation.[51]

Brugada Syndrome

The Brugada syndrome is a rare condition originally described in eight patients with recurrent episodes of sudden death, all with a RBBB and persistent ST segment elevation.[52] Abnormalities in sodium channels in the right ventricular outflow tract have been identified, hence the typical ECG findings in the right precordial leads. The ECG finding can sometimes be found by moving ECG leads V1 and V2 up one interspace. A genetic form associated with the SCN5A gene has been described with an autosomal dominant pattern of inheritance, but other genes have been identified with Brugada syndrome and their association with cardiac events remain to be determined. Some cases seem to be acquired. Known factors which magnify the ECG abnormality are certain drugs and fever. The annual incidence of cardiac arrest is estimated to be 0.5% in patients without an ICD.

Most individuals with Brugada syndrome remain asymptomatic throughout their lives and the majority of events occur at rest, sleep or during fever. Sports participation in asymptomatic patients with Brugada syndrome could be allowed after full discussion with the patient and physician. The exception might be those sports associated with an increase in core temperature, like endurance sports under hot conditions.[41]

Coronary Artery Disease

Coronary artery disease should also be in the differential diagnosis in athletes presenting with syncope, especially syncope with exertion, and especially if above the age of 40 years or in athletes with a family history of premature CAD or familial hypercholesterolemia. Other risk factors include history of smoking, male sex and hypercholesterolemia. An important part of the evaluation of exertional syncope includes exercise stress testing, typically with imaging to improve on the detection of cardiac ischemia. Other causes for exertional syncope might include cardiac arrhythmias or a drop in blood pressure which might indicate cardiac dysfunction. CCTA also plays an important role in diagnosis and if needed coronary angiography. If inducible myocardial ischemia is identified, coronary angiography and PCI if indicated should be considered. Sports restriction post PCI or after acute coronary syndrome is recommended at least for the first three months. During this time graduated exercise schedule in the setting of structured cardiac rehabilitation program plays an important role in safe return to previous levels of exercise. After three months, consideration of exercise stress test prior to returning to high intensity sports competitions is advised. Close monitoring for symptoms during exercise, periodic assessment with imaging is needed to prevent any further events in addition to compliance with medications. For patients post PCI on dual anti-platelet, restriction of contact sports may be needed to prevent any major bleeding.[53]

Conclusion

Syncope in an athlete is challenging to manage and it requires understanding of normal physiological changes that occur with physical training. Even though vaso-vagal syncope is the most common cause of syncope in this population, other cardiac abnormalities that can present with syncope need to be ruled out.

Timely identification and management of exertional syncope due to cardiac conditions plays a vital role in prevention of sudden cardiac arrest in athletes. Often, primary providers are the first physician contact for evaluation of syncope and they play an important role in risk stratifying and sending cardiology referral if needed.

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Home Sleep Apnea Testing for Obstructive Sleep Apnea

by Omar Hussein, MD, Aseel Alkhader, MD, Ashraf Gohar, MD & Abid Bhat, MD

The increasing prevalence and awareness of OSA in the last few decades have created an overwhelming demand for more accessible and efficient diagnostic testing.



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Abstract

Obstructive Sleep Apnea (OSA) is a major public health problem affecting almost one billion individuals worldwide. Ninety percent of patients with OSA are still undiagnosed. Although an attended polysomnography (PSG) testing is the gold standard to diagnose OSA, it is time-consuming and is associated with higher costs. The Home Sleep Apnea Testing (HSAT) is now available to diagnose OSA. Understanding the indications and limitations of HSAT is important to avoid misdiagnosis and improve patient outcomes.

Introduction

Obstructive Sleep Apnea (OSA) is a disorder characterized by recurrent collapse of the upper airway during sleep.[1] This repetitive process, over time, can result in a wide range of physiologic consequences involving the cardiovascular, pulmonary, and neurocognitive systems. Existing evidence also indicates that appropriate treatment of OSA reduces the risk of these consequences.[2] The increased prevalence of obesity and overall survival, which have accompanied advancements in healthcare, have contributed to the rise in OSA prevalence. The prevalence of OSA varies according to the severity cutoff used for diagnosis and the age of the population studied. Some reports have estimated that at least 20.2% of men and 10.0% of women are affected with moderate-severe OSA.[3]

Evaluation of OSA starts with exploring clinical symptoms, physical signs, and completion of validated questionnaires to help identify patients who may benefit from testing to confirm the diagnosis.[1] Overnight polysomnography (PSG) is still considered the gold standard test for confirming a diagnosis of OSA and other Sleep Disordered Breathing (SDB).[4] Despite being the gold diagnostic test, a PSG may have limitations related to cost, long wait times, and lack of access. For this reason, several new technologies have been developed to assess for sleep apnea out-side of the sleep lab to accommodate demand and increase access to patients.[4,5]

Basics of Obstructive Sleep Apnea Diagnostic Tests

A standard PSG involves data collection from seven or more channels including a limited Electroencephalogram (EEG), Electrooculography (EOG), Electromyogram (EMG), one lead Electrocardiogram (ECG), air flow channels (nasal pressure transducer

Box 1: Obstructive Sleep Apnea (OSA) severity based on Apnea/Hypopnea Index (AHI).

OSA Severity	AHI (events/hour)
Normal	<5
Mild	5 to <15
Moderate	15 to <30
Severe	≥30

Ref: Malhotra A, Ayappa I, Ayas N, et al. Metrics of sleep apnea severity: beyond the apneahypopnea index. Sleep. Vol 44, Issue 7. March 2021

Table 1 American Academy of Sleep Medicine classification of sleep apnea diagnostic modalities

Test level	Description	Personnel	Parameters Measured
Type 1	Standard PSG performed in a sleep lab	Attended	EEG, EOG, chin EMG, ECG, airflow, respiratory effort and oxygen saturation
Type 2	Portable PSG	Unattended	Same as type 1
Type 3	Cardiorespiratory polygraphy	Unattended	4–6 signals, (two respiratory variables, oxygen saturation, and pulse or heart rate)
Type 4	1–2 signals	Unattended	Typically includes oxygen saturation or airflow

PSG: polysomnography; **EEG**: electroencephalography; **EOG**: electro-oculography; **EMG**: electromyography.

Reference: Portable Recording in the Assessment of Obstructive Sleep Apnea. Ferber R, Millman R, Coppola M et al. Sleep, Volume 17, Issue 4, June 1994, Pages 378-392.

and oronasal thermal flow sensor), respiratory effort (respiratory inductance plethysmography belts), and pulse oximeter.[6]

Using the respiratory derived data from different sensors, an Apnea-Hypopnea Index (AHI) can be calculated, which is the result of the total respiratory events (Apneas and Hypopneas) divided by Total Sleep Time (TST)[1] (Box 1). An apnea is scored when a reduction in respiratory flow signal equals or exceeds 90% of pre-event baseline and lasts more than 10 seconds. A hypopnea is scored when a 30% or more reduction in respiratory air flow lasts more than 10 seconds and is associated with a reduction in oxygen saturation of 3% (or 4% based on CMS criteria) from pre-event baseline and/or associated with an arousal.[7] The AHI serves as a way to classify severity of OSA with AHI <5/hour being normal for adults, 5–15/hour indicating mild OSA, 15–30/hour for moderate OSA; while an AHI ≥30/hour reflecting severe disease.[8]

The calculation of AHI requires an accurate assessment of Total Sleep Time (TST), rather than total time in bed, which is derived from the EEG signal obtained in a polysomnogram. The quantification of TST is usually limited in most Home Sleep Apnea Tests as EEG signals are often not measured. For this reason, Monitoring Time (MT) is usually reported instead, which is usually obtained by subtracting periods of artifacts and wakefulness as determined by actigraphy, respiratory pattern, body position sensor or patient diary, from the Total Recording Time (TRT). When a HSAT is performed, OSA severity is sometimes expressed using the Respiratory Event Index (REI) which is the result of dividing the number of respiratory events (Apneas and Hypopneas) by the MT.[8] Since EEG is not used to accurately estimate sleep time when MT is measured, it is usually longer than the TST and this can result in underestimation of OSA severity especially when the HSAT is performed on patients with low pre-test probability for the disease. When HSAT is considered for evaluation of OSA, a careful patient selection is crucial to improve the utility of the test and reduce the rate of false negative results.[10] A more detailed description of the suggested criteria for the use of HSAT will be discussed later in this review.

Classifications of Obstructive Sleep Apnea Testing

The first classification system for sleep apnea testing was introduced by the American Sleep Disorders Association, now the American Academy of Sleep Medicine (AASM) in 1994.[9] This system suggested four types of sleep apnea testing as listed in Table 1.

Type 1 study includes the standard attended PSG, while the remaining types 2,3 and 4 include the portable techniques for testing. Type 2 sleep study uses the same equipment used in a standard PSG but without the supervision of a trained sleep technician. Although type 2 testing has been used experimentally in some clinical trials, many other studies have questioned the validity and reliability of the data collected by this home based PSGs, especially when a sophisticated device is being used by patients without supervision.[10] Type 3 and type 4 studies represent the

majority of home sleep apnea testing in clinical practice.

With the advancements in technology and innovations in home sleep apnea testing, it was noted that many new devices did not fit into these categories and hence the need for a more comprehensive categorization system. In 2011, the AASM issued a classification system based on sleep physiologic parameters measured during sleep. The proposed system relayed on the Sleep, Cardiovascular, Oximetry, Position, Effort, and Respiratory (SCOPER) parameters collected during testing.[1] In this classification, the ability to determine sleep and wakefulness in addition to sleep staging, has classified these devices to ones that use three or less EEG channels for sleep measurement and staging, to devices that uses sleep surrogates, like actigraphy, for sleep quantification. For cardiovascular monitoring, there are devices that used either the cardiac signal (one or more ECG leads) or vascular signal (peripheral arterial tonometry) to derive a respiratory event. Measurement of oxygen with a pulse oximetry was a requirement for the device to be included in this classification system. Ability to determine sleep position during sleep was used to define devices that used visual versus nonvisual measurement. For respiratory effort assessment, devices were graded from ones that used two Respiratory Inductance Plethysmography (RIP) belts (gold standard) versus one belt or other effort measures (including piezo belts). Lastly, for respiratory flow measurement, there were devices that used either nasal pressure or thermal sensors to detect flow, a combination of these sensors or used end-tidal CO2 as an indirect way to detect respiration.[13,2]

There are currently many commercially available devices for home sleep apnea testing that use different combinations of sensors for detecting sleep apnea.

A direct comparison between these devices can be challenging due to the variability in the methods used in their validation studies and differences in the populations that were tested.



Figure 1. HSAT device utilizing respiratory parameters (airflow and effort) for sleep apnea testing. Thoraco-abdominal RIP belts are used for respiratory effort detection. A nasal pressure transducer through a nasal cannula and oronasal thermal sensors are used for airflow detection. Pulse oximetry through a finger probe is used for oxygen saturation measurement and pulse wave generation.
Source: https://www.wsj.com/articles/SB10001424127887324715704578480883962087110

HSAT Utilizing Respiratory Flow and/or Effort Parameters

The most well established and studied method of HSAT includes the portable monitors of respiratory parameters that records a minimum of four signals. These usually consist of measurement of respiratory air flow, respiratory effort, oximetry, and pulse or heart rate.[3] Respiratory airflow is usually measured using a nasal pressure transducer or an oronasal thermal airflow sensor. Quantification of airflow is possible with the nasal pressure sensors making it more reliable in detecting partial reduction in airflow as in the case of hypopneas. Thermal airflow sensors can detect apneas by using the difference of temperature between the inhaled and exhaled air in a respiratory cycle.[4] Respiratory effort is measured by using Respiratory Inductance Plethysmography (RIP) which provides an estimate of changes in tidal volumes through a recording band around the chest and abdomen. RIP bands have an electrical wire that is arranged as a coil, changes in circumference during respiration results in changes in inductance or resistance which is used to estimate lung volumes. Dual RIP belts is also recommended by the AASM scoring manual for measurement of respiratory effort.[5]

Monitoring of heart rhythm can be derived from pulse oximetry. A more precise method for rhythm detection is through a signal lead ECG. Body position during sleep is sometimes determined by a 3D accelerometer sensor which can also provide an estimate of the sleep-wake state in some HSAT devices (Figure 1).



Figure 2. HSAT device with PAT measurement technology. A finger probe for PAT signal detection incorporates pulse oximetry and heart rate monitoring. An additional body position and snore sensor can be placed on the upper chest.
Source: https://sleeprightmckinney.com/comfortable-sleep-apnea-testing-option/

Peripheral Arterial Tonometry devices relay on detecting changes in blood volume in the peripheral arteries. It is well known that various respiratory events, apneas, and hypopneas, are associated with sympathetic activation during sleep. This activation results in vasoconstriction mediated by alpha receptors of vascular smooth muscles leading to reduction of blood flow in peripheral arteries.[1] A finger probe with a pneumo-optical sensor is used to continuously measure the digital arterial pulse wave volume. A pulse oximeter is integrated to the device system which also allows for oxygen saturation and heart rate measurements. A combination of a reduction in oxygen saturation, a decrease in PAT signal and an increase in heart rate help to identify reparatory events. Recent devices now also include an actigraphy which, along with PAT signal, has been used to determine sleep and wake time in addition to estimation of various stages of sleep, mainly non–rapid eye movement (NREM) sleep, and REM sleep, due to differences in sympathetic tone in each of these stages. A body position sensor and a microphone for snore detection has also been integrated in some devices allowing for more accurate evaluation of respiratory events[8] (Figure 2).

HSAT Utilizing Minimal Contact or Contactless Methods for Assessment of Respiration

Newer methods for assessing sleep-related breathing disorders by contactless techniques include recording and analysis of respiratory sounds (breathing, snoring, choking, gasping). A combined sensor that contains a microphone and a pressure transducer can be applied to the suprasternal notch that is used to calculate the respiratory flow, respiratory effort and snoring. Studies that compared this method to PSG have shown that this approach has high sensitivity and specificity for detecting apneas and hypopneas and can differentiate central from obstructive sleep apnea.[14,1]

Recently, built-in-mobile microphones and sound analyzer applications have been used to detect sleep related breathing disorders, but these devices are still under research development and have not been approved yet as commercial devices in clinical practice.[2] Movement analysis is another approach that uses non-contact methods to detect sleep related breathing disorders. The movement of the chest and abdomen during respiration can be assessed with a biomotion sensor that uses a low-power radio frequency transceiver to detect respiratory events. One validation study for this method reported a sensitivity of 89% and a specificity of 92% for detecting clinically significant SDB (AHI>15).[3] Although promising, many of these methods are still under development and further validation studies are still needed to be approved as medical devices.

Understanding Indications and Limitations of Home Sleep Apnea Tests

In 2017, the American Academy of Sleep Medicine (AASM) issued a position statement to address the acceptable clinical use of a home sleep apnea tests (HSAT).[4] This statement highlighted the importance of using HSAT as a part of a more comprehensive sleep evaluation rather than a standalone test. With the current availability of numerous commercial HSAT devices, the statement emphasized that only a physician should make the decision that HSAT is appropriate for a patient based on history and examination findings. Diagnosis and treatment decisions should not rely completely on automaticity scored HSAT data and interpretation of raw data should be performed by a board-certified sleep medicine physician (Box 2).

The most recent practice guideline by AASM for the diagnostic testing of OSA outlined the appropriate indications of HSAT. The guideline specified that a technically adequate HSAT device may be used for evaluation of OSA in medically uncomplicated patients with history and clinical findings suggesting at least moderate to high pre-test probability of the disease. Based on this, and to avoid false negative results, HSAT should not be used for routine testing or screening of general

Box 2: Advantages and disadvantages of HSAT

Advantages:

- Possible improved sleep in a patient preferred sleep environment in addition to less monitor leads.
- An alternative testing method if PSG is difficult to perform (limited access, patient's immobility)
- Reduced study to study cost compared to PSG.
- Number of tests performed are not limited by the capacity of the sleep lab as in PSG.
- Reduce wait times for establishing diagnosis and initiating treatment.

Disadvantages/limitations:

- Increased number of technically inadequate studies given the unattended nature of the study.
- Possible underestimation of AHI and severity of OSA as accurate sleep time is not quantified in most HSAT.
- Limited evaluation of non-obstructive sleep disordered breathing (central sleep apnea, significant hypoxemia or hypoventilation).
- Not recommended for sleep apnea evaluation in patients with neuromuscular disease and respiratory muscle weakness, significant cardiopulmonary diseases, chronic opioid use and history of stroke.
- Not recommended for patients who may require evaluation for comorbid non-respiratory sleep disorders (sleep related movements disorders, REM behavior disorder, parasomnias).
- Negative or inadequate study with high clinical suspicion for OSA requires repeat testing

Ref: Uses and Limitations of Portable Monitoring for Diagnosis and Management of Obstructive Sleep Apnea, Berry, Richard B. Sleep Medicine Clinics, Volume 6, Issue 3, 309 - 333

population or asymptomatic individuals.

In general, an attended polysomnography (PSG) rather than HSAT should be used for diagnosis of sleep disorders in patients with the following conditions:

1. Patients at increased risk of non-obstructive sleep disordered breathing including central sleep apnea, significant hypoxemia or hypoventilation. This also includes patients suspected of having obesity hypoventilation syndrome.
2. Patients presenting with symptoms of non-respiratory sleep disorders that require attended sleep evaluation like parasomnia and sleep related movements disorders.
3. Patients with medical conditions that may interfere with the accuracy of HSAT results (severe insomnia), or any environmental or personal factors (physical disability) that could affect the accuracy of HSAT data collection and interpretation.
4. Patients with Super Obesity (BMI > 40 or 50).

Specific medical conditions of important relevance that may predispose patients to non-obstructive sleep disordered breathing include significant cardiopulmonary diseases, neuromuscular disease resulting in respiratory muscle weakness, chronic opioid use and history of stroke. In certain cases of high clinical suspicion for OSA despite a negative or inconclusive HSAT result, a repeat testing with a full night polysomnogram (PSG) should be performed. [5] Figure 3 demonstrates a summary of the 2017 AASM guideline for the diagnostic testing of OSA in adults.

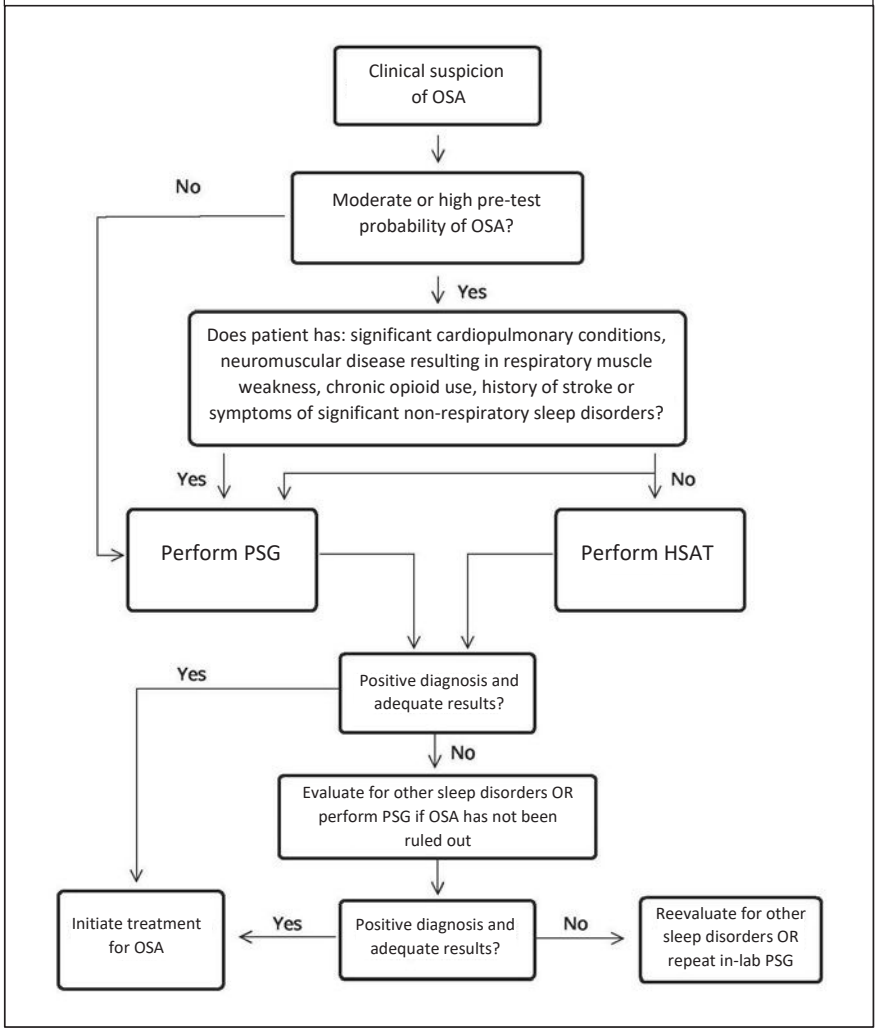
Conclusion

The increasing prevalence and awareness of OSA in the last few decades have created an overwhelming demand for more accessible and efficient diagnostic testing. HSAT has offered an alternative for the long waiting times and limited availability of in lab polysomnograms. In order to make the most benefit of this technological advancement in diagnostic testing, clinicians should be aware of the limitations and common pitfalls when it comes to ordering and interpreting the results of these tests to avoid misdiagnosis and ultimately patient harm.

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Figure 3: The American Academy of Sleep Medicine clinical algorithm for the use of Home Sleep Apnea Tests in evaluation of obstructive sleep apnea.



Adapted from Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine. Vol 13, Issue 3, March 2017, Pages 479–504.

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Disclosure

None reported. Artificial intelligence was not used in the study, research, preparation, or writing of this manuscript. **MM**

KCU Sharpens Focus on Population Health and Equity Through New Center of Excellence

by Marc B. Hahn, DO

KCU has a unique opportunity to address our communities' urgent needs—particularly those who are vulnerable, underserved, economically disadvantaged or lack access to health care—while also preparing the next generation of professionals.

For over 107 years, Kansas City University has remained true to its mission of "improving the well-being of the communities we serve," which is reflected in a strong commitment to diverse and underserved populations. Today, our efforts continue to focus sharply on population health, seeking to improve the health outcomes of groups of individuals in our community, with a priority on reducing health inequities due to the social and structural determinants of health—the factors (social, environmental, cultural, and physical) that have a measurable impact on people's ability to thrive and maintain optimal health.

A critical underpinning for further achieving our goals will be the development of KCU's Center for Population Health and Equity (CPHE), made possible by congressionally directed spending in fiscal years 2022 and 2023 totaling more than $11 million, with a commitment of more than $12 million from KCU and philanthropic support.

The CPHE will compare and contrast the needs of the two distinct communities we serve—our rural campus in Joplin (opened in 2017) and our original urban-core campus in Kansas City—and inform strategies that integrate the Center's four pillars of education, research, clinical service and community outreach. The goal is to establish a seamless approach that will contribute to long-term societal benefits and greater health equity.

Specifically, the Center will:

1. Develop future medical, dental, behavioral health, and health care leaders who will serve as population/public health strategists through an interprofessional education (IPE) framework with the goal of improving patient outcomes.
2. Research, analyze, and disseminate data to identify and improve the health and well-being of the Kansas City and Joplin, Missouri, communities. This will include the yearly publication of an Annual Heartland Health Report, which will be a meta-analysis that identifies the factors (including race, socioeconomic, geographic, and others) that



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have a direct impact on the health of urban and rural populations throughout the state; and an assessment of the equity of care delivered.
3. Increase clinical services anchored in interprofessional practice, which incorporates the integration of service learning from multiple health professions.
4. Enhance community engagement to advance community education related to improving health and expanding health care services.

With nearly 2,000 health professional graduate students and a focus on IPE, which includes degree programs in osteopathic medicine, dentistry, clinical psychology, and biomedical research, KCU has a unique opportunity to address our communities' urgent needs—particularly those who are vulnerable, underserved, economically disadvantaged or lack access to health care—while also preparing the next generation of professionals.

Goal of Reversing Our Country's Declining Health

The US ranks 46th in the world for life expectancy and is projected to rank 64th by 2040.[1] Since 1990, Missouri has fallen from 24th to 39th among states in health outcomes and is considerably below the US average.[2,3]

The urban and rural factors that influence health are not only medical; they include factors such as housing, food security, health literacy, voter access, adverse childhood experiences, transportation and access to health insurance and health care. Despite this fact, health professions education has traditionally focused on the diagnosis and treatment of disease, rather than on the prevention of disease by addressing these other determinants.

To stop this downward spiral and improve our population's life expectancy and overall health outcomes, it is necessary to build healthy systems and increase the support structures needed before critical medical interventions are required.

Desired Program Outcomes

We look for this program to build momentum around understanding and addressing the variables that affect a population's health. Only recently have researchers begun looking more closely at the specific impacts of IPE beyond classroom and learning outcomes to include health and health systems outcomes. Although more research is needed to evaluate the full impact of IPE and strengthen the evidence base, the current literature confirms the ability to link the IPE learning process with outcomes in population health, as well as patient safety, quality of care, provider and patient satisfaction and cost of care.[4]

Therefore, near-term interventions include developing and refining innovative interprofessional population health curricula that will educate students about community-based strategies that promote health. By educating students and conducting research to better understand the social determinants of health, the Center can hopefully effect systemic change to improve population health and equitable health outcomes for the urban and rural populations in Missouri and the region. These efforts will foster a new generation of physicians, dentists, psychologists, scientists and other health professionals to promote health equity for the entire community.

Kansas City University is proud of our growing recognition as a change leader in health professions education and our efforts to create conditions in which all people have the opportunity to thrive, flourish and attain their full health potential. KCU's new CPHE is a key strategy to further achieve these goals and a demonstration of our enduring commitment to improve the health and well-being of our communities. We appreciate the congressional funding support that made this effort possible.

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The Neurochemistry of Depression: The Good, The Bad and The Ugly

by Kami Pearson, MS, Kimberley Beier, BS, Thornton Mardis, MA, Bryan Munoz, MS & Asma Zaidi, PhD

Kansas City University

This article reviews the various metabolites generated in the competing pathways of tryptophan metabolism including the kynurenine pathway.



Kami Pearson, MS, is a Research Associate, **Kimberley Beier, BS,** Thornton Mardis, MA, and Bryan Munoz, MS, are medical students, and Asma Zaidi, PhD, (pictured), is a Professor of Biochemistry. All are at Kansas City University, Kansas City, Missouri.

Abstract

A large constellation of experimental evidence suggests that neuroinflammation is involved in the onset of depression and neurodegenerative disorders. Many studies have shown impairments in tryptophan metabolism, the major pathway for the synthesis of serotonin, the mood regulating neurotransmitter. This article reviews the various metabolites generated in the competing pathways of tryptophan metabolism including the kynurenine pathway. Increased synthesis of the neurotoxic compound quinolinic acid occurs at the expense of the synthesis of the neuroprotective metabolite kynurenic acid. This shift in equilibrium plays a critical role in the induction of oxidative stress, neuroinflammation, and neurotoxicity. Sufficient protein intake with adequate amounts of tryptophan along with dietary antioxidants and flavonoids may offer protection against major depressive and neurodegenerative disorders.

Depression

Depression, aka major depressive disorder (MDD), is recognized as a leading cause of disability worldwide, with 350 million people affected as of 2019, an increase of 18% over the last decade.[1] Approximately one in five individuals will experience a major depressive episode during their lifetime. Women are affected by depression at rates nearly twice that of men.[2] The economic burden of MDD, estimated at $236 billion in 2010, showed a steep 40% increase to $326 billion in 2018.[3] Depression occurs on a spectrum and is a complex disorder with a wide array of symptoms and clinical features that may require unique treatments. Clinical presentations include depressed mood, anhedonia, insomnia, appetite or weight changes, anergia, psychomotor or neurocognitive dysfunction, and most notably, suicidal ideation.[2] Over the last decade, major advancements have been made in elucidating the etiology of depression. The role of serotonin continues to be studied, and inflammation is now understood as a major player in the development of depression. It is clear that depression is a heterogeneous disease, with distinct biochemical features underlying each subtype. Emerging new evidence challenges existing assumptions of the key players that contribute to the development of depression and the severity of symptoms.

Tryptophan Metabolism

Tryptophan, an essential amino acid, is critical in the synthesis of multiple bioactive metabolites including serotonin, kynurenine, melatonin, and vitamin B3.[4] It is important in both gastrointestinal and central nervous system (CNS) function and can be metabolized through multiple pathways.[5] In recent studies, the gut microbiota have shown significant effects on tryptophan metabolism.[6] Modulation of the gut-brain-axis is implicated in intestinal and neuropsychiatric disorders such as irritable bowel syndrome and depression.[7] Of the essential amino acids, tryptophan possesses the lowest reserve, making it vulnerable to deficiency.[8] Understanding the role of tryptophan metabolism in MDD may help uncover potential alternative therapeutic approaches for the treatment of depression. This review focuses primarily on the intricate components of tryptophan metabolism in relation to the CNS and depressive disorders, including the serotonin and kynurenine pathways. Through an analysis of novel evidence, the role of tryptophan metabolism in the biochemistry of depression can be better understood.

The Serotonin Pathway

The monoamine theory has been the leading theory of depression since the 1950s. Interestingly, a recent systematic review of serotonin's role in depression concluded that there is no consistent evidence of a direct association between depression and the famous neurotransmitter.[9] Furthermore, no evidence supports depression stemming from decreased activity or concentration of serotonin. The monoamine theory has still persisted in part due to the effectiveness of selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) in treating depression, which are effective in 70% of MDD patients. The partial effectiveness of anti-depressant medications in treating depression may indicate that serotonin does play a role, although not directly as previously believed. The monoamine theory alone is not enough to explain the heterogeneity of clinical symptoms in patients, or why symptoms can vary so much, even for a given patient.[2]

Serotonin (5-hydroxytryptamine, or 5-HT) is a well-known neurotransmitter, but still relatively poorly understood. It is a product of tryptophan metabolism, with 5-10% of tryptophan contributing to serotonin production.[10] The rate limiting enzymes in this pathway are tryptophan hydroxylase 1 (TPH1) and tryptophan hydroxylase 2 (TPH2) with the latter being found exclusively in the CNS. TPH1 and TPH2 function to convert tryptophan into 5-hydroxytryptophan which undergoes an enzymatic decarboxylation to form serotonin. Serotonin can be further metabolized to either melatonin or be converted to 5-hydroxyindoleacetic acid via the action of the enzyme monoamine oxidase (MAO), a target for monoamine oxidase inhibitors (MAOIs), therapeutic agents used to treat depression.[5]

Although serotonin is involved in many peripheral processes such as peristalsis, mucus production, blood vessel dilation, etc., its role in the CNS has been the focus of most studies. In particular, its involvement in depression and schizophrenia are the subject of intense research.[11] The major functions of serotonin include involvement in movement, mood, learning and memory, sleep and circadian rhythm, anxiety, aggressiveness, and social status.[12] The vast diversity of effects induced by serotonin is due to simultaneous effects on multiple neuronal targets and the large number of receptors expressed on a variety of cells, with differing locations, affinities, and downstream signaling pathways. 5-HT neurons in the CNS are localized to the raphe nuclei in the midbrain. These are known as the B1-B9 cell groups and provide descending serotonergic innervation to the spinal cord and medulla.[12] 5-HT neurons terminate in several major CNS regions, including the cortex, limbic system, midbrain, and hindbrain.[13] However, the enterochromaffin cells of the enteric nervous system account for approximately 90% of serotonin production.[14]

After serotonin is released from a neuron, it binds to the serotonin receptors (5-HTR). There are seven 5-HTR classes, with various subgroups, based on their structures and functions. 5-HTR_{1A} and 5-HTR_{1B} are of particular interest because of their noted involvement in the pathophysiology of MDD, bipolar disorder, schizophrenia, and anxiety disorders.[15] Once in the neuronal synapse, serotonin is taken back up by the presynaptic neuron to terminate signaling. The serotonin transporter (SERT) drives the reuptake of 5-HT

from the synaptic cleft back into presynaptic neurons via utilization of sodium and chloride gradients. The SERT is the target of many widely used medications including SSRIs and SNRIs.[16] which target serotonin and norepinephrine. The proposed mechanism of action of SSRIs is inhibition of SERT, resulting in increased extracellular serotonin levels present in the synapse.[17] SNRIs achieve faster antidepressant effects by elevating concentrations of dopamine in the forebrain.[18] As mentioned before, there is insufficient evidence supporting a direct correlation between decreased serotonin levels and depression[9,15] suggesting that the observed beneficial effects of antidepressants may include other mechanisms.

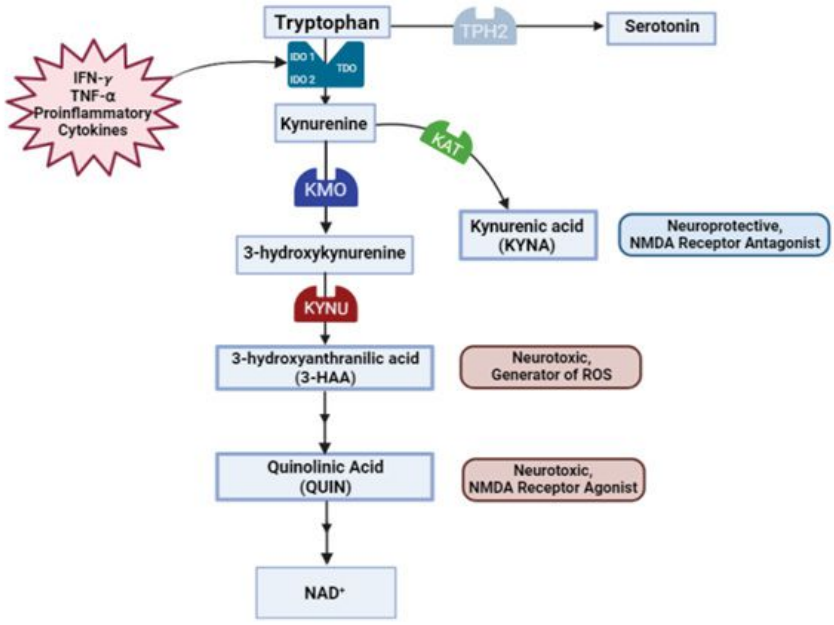


Figure 1. The Kynurenine Pathway.
The presence of pro-inflammatory cytokines results in the activation of the kynurenine pathway through the activation of tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase 1 and 2 (IDO 1 and 2). Kynurenine aminotransferase (KAT) catalyzes the synthesis of kynurenic acid (KYNA) from kynurenine. Kynurenic acid is a neuroprotective agent and is an antagonist of NMDA receptors. This pathway is inhibited by IL-1β, TNF-α and IFN-γ. An alternative pathway utilizes the enzyme kynurenine 3-monooxygenase (KMO) to synthesize the intermediate 3-hydroxykynurenine. Kynureninase (KYNU) acts on 3-hydroxykynurenine to produce 3-hydroxyanthranilic acid (3-HAA), which promotes the production of hydroxyl radicals, directly causing oxidative stress. Quinolinic acid (QUIN) acts as an agonist of the NMDA receptor (NMDAR), activation of which leads to an influx of Ca^{2+} and Na^{+}. 3-HAA and QUIN are considered neurotoxic because they create excitotoxicity and induce apoptosis while decreasing synaptic plasticity.[21,22,35,41,69]
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The Kynurenine Pathway

The predominant catabolic pathway for tryptophan in most tissues is the kynurenine pathway (KP), accounting for 90-95% of tryptophan metabolism.[5,7] Several metabolites are formed through the KP, including kynurenic acid (KYNA), quinolinic acid (QUIN), and 3-hydroxyanthranilic acid (3-HAA) (Figure 1). These molecules are the focus of ongoing research in our laboratory. The prevalence of this pathway is largely observed in the liver, brain, and in immune cells. The activation of KP is tightly regulated and dependent on tissue specific enzymes. In the liver, the prominent rate determining enzyme is tryptophan dioxygenase (TDO). While, in the brain and immune cells, the enzymes indoleamine 2-3-dioxygenase 1 (IDO1) and 2 (IDO2) are both utilized in the formation of kynurenine, the first important product in the metabolism of tryptophan.[19] Kynurenine can be further metabolized to form 3-hydroxykynurenine, anthranilic acid, or kynurenic acid through interactions with the enzymes kynurenine-3-monooxygenase (KMO), kynureninase (KYNU), and kynurenine aminotransferase (KAT), respectively. Of the possible fates of kynurenine, 3-hydroxykynurenine is the favored product. Further downstream, 3-HAA is formed from 3-hydroxykynurenine through interactions with KYNU. This product is then catabolized into QUIN, a known neurotoxin, and consequently into nicotinamide adenine dinucleotide (NAD^{+}), a molecule important for cellular energy and redox reactions.[20-22]

Inflammation

Inflammation is a biological process that allows the immune system to fight sources of infection and repair damaged tissues.[23] This is true especially in the case of chronic inflammation, where peripheral cytokines induce an array of depressive symptoms referred to as sickness behaviors.[24] The connection between chronic stress and the pathophysiology of many psychiatric disorders, including MDD, have been well documented. Clinical studies have discovered alterations in stress hormone levels, namely glucocorticoids, in depressed patients. Consequently, glucocorticoids and their receptors have been investigated as primary targets in depressive disorders.[25] Individuals diagnosed with MDD exhibit increased peripheral inflammatory biomarkers as measured in blood plasma or cerebrospinal fluid compared to healthy controls. One example of this is the positive correlation between elevated levels of a well-known multifactorial and non-specific pro-inflammatory marker, C-reactive protein (CRP) and suicide attempts in depressed patients.[26] Elevated CRP has also been shown to correlate with the severity of the depressive symptoms.[26,27] Additionally, there is a correlation between CRP and known central inflammatory biomarkers, including tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6.[26,28-30] Pro-inflammatory cytokines including TNF-α and IL-1β are known to induce neuronal serotonin reuptake.[31] Glutamate neurotransmission is greatly affected by inflammation. Glutamate secretion is increased under stress, with high levels inducing excitotoxicity; this can be exacerbated by synergistic activity between glutamate and QUIN, one of the metabolites generated in the KP.[10] This information suggests that during inflammatory states, inflammatory signaling can potentiate a depressive episode, via depleted serotonin levels and enhanced QUIN/glutamate induced excitotoxicity. Increased CRP has been associated with increased glutamate in the brain and is hypothesized to be connected to alterations in reward processing and dopamine neurotransmission. Inflammatory biomarkers mentioned above have the ability to cross the blood-brain barrier and are believed to contribute to oxidative stress, neurotoxicity, and dysregulation of glutamate levels within the brain.[30,32,33] Additionally, evidence exists that these depressive symptoms further promote the production of pro-inflammatory molecules, creating a cyclic feedback loop exacerbating symptom severity.[29]

The neuro-inflammatory hypothesis of depression emphasizes that elevated levels of inflammatory cytokines in the CNS resulting from stress-induced immune system changes contribute to depressive symptoms via neurotoxic effects and oxidative stress.[34] This newly proposed hypothesis, while still being investigated, shows promise in the field of depression research. Tissue injuries resulting from inflammation are often mediated by oxidative damage of cellular components. While reactive oxygen species (ROS) cause DNA and protein damage, antioxidants act as ROS scavengers and prevent this damage from occurring. One such compound capable of ROS scavenging is L-kynurenine. This compound not only scavenges the highly damaging hydroxyl free radicals and peroxynitrite, but also prevents DNA and protein degradation induced by oxidative stress.[35] This finding identifies the antioxidant properties of L-kynurenine as a potential target for the treatment of MDD symptoms. Conversely, studies have shown that other KP metabolites, such as 3-HAA, facilitate the formation of peroxyl free radicals which cause tissue damage. Another intermediate of this pathway, 3-hydroxykynurenine, has been shown to induce neuronal apoptosis in certain regions of the brain. It is unclear if these findings are representative of the effects of endogenous tryptophan metabolism in the pathophysiology of MDD. Several studies have shown that antidepressant medications reduce overall inflammation throughout the body. Additionally, behavioral interventions such as psychotherapy also appear to decrease inflammatory signaling.[10] While other non-pharmacological approaches, such as diet and exercise, have been recommended for years to treat symptoms of depression, the anti-inflammatory effects of such treatments are just now being understood.[36]

Kynurenines and their Clinical Relevance

Under multiple pathological states, tryptophan is catalyzed at a higher rate due to increased activation of the KP.[37] Multiple signaling molecules and pro-inflammatory cytokines activate the IDO enzymes in the brain. The major KP metabolites (kynurenic acid (KYNA), QUIN, and 3-HAA)

show a wide variety of effects on neuronal cells ranging from neuroprotective to neurotoxic. Over the last decade thanks to exciting advances in our understanding of tryptophan metabolism, numerous promising therapeutic avenues have been discovered for a wide array of pathologies including Parkinson's, Alzheimer's, tissue damage caused by ROS, MDD, HIV-related cognitive decline, and schizophrenia.[8,38,39]

Of the three compounds, KYNA and QUIN are the most widely studied and have been shown to exhibit an interesting dichotomy through direct and indirect neuroprotective and neurotoxic effects, respectively. Here we will explore the various mechanisms of action of KYNA, QUIN and 3-HAA, while discussing possible therapeutic avenues.

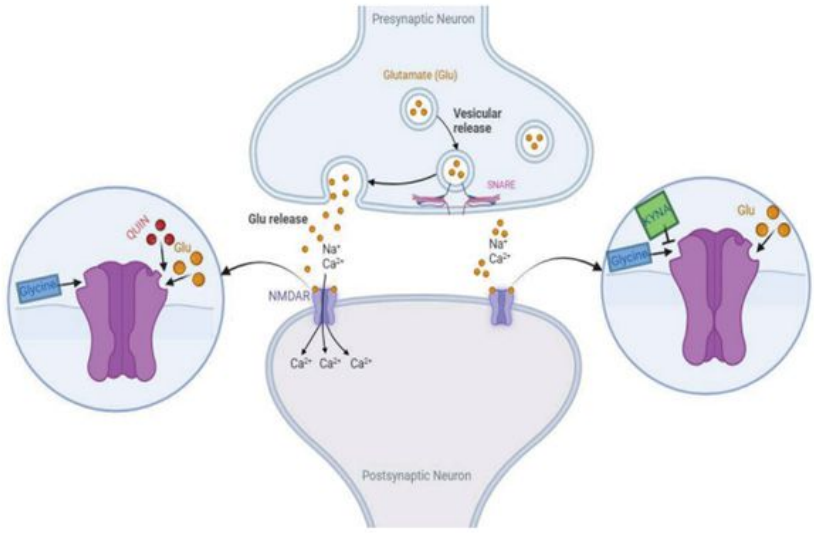


Figure 2. NMDA Receptor Activation and Inhibition by Kynurenic Acid and Quinolinic Acid.
Activation of the presynaptic neuron causes vesicular release of glutamate. Glutamate binds to the NMDA receptor (NMDAR) on a postsynaptic neuron. NMDARs are an ionotropic glutamate receptor, activation of which is responsible for an influx of Ca^{2+} and Na^{+}. Quinolinic acid (QUIN) is an NMDAR agonist and activates the receptor by binding directly to the glutamate binding site. Kynurenic acid (KYNA), an NMDAR antagonist, inhibits NMDA receptor activation by binding to the glycine-binding site. [8,39-45,49,61,64]
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Kynurenic Acid

Kynurenic acid (KYNA) interacts with multiple neuronal targets: the ionotropic glutamate receptors N-methyl-D-aspartate (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR), kainate receptors (KAR), the α7 nicotinic acetylcholine receptor, the orphan G protein-coupled receptor GPR35, and the lesser known G protein-coupled receptor HCAR3.[40-43] As early as the 1980's, KYNA was discovered to act as a broad-spectrum competitive antagonist at the glutamate and glycine co-agonist binding sites on the NMDAR[44] (Figure 2). NMDARs are a ubiquitous ionotropic glutamate receptor present in all tissues but are exceptionally important in neuronal cells as they are a key player in calcium signaling. Dysregulation of the NMDA receptors result in excitotoxic effects on neurons, which has been a mechanism of cell injury implicated in many neurodegenerative diseases.[8,39,45]

KYNA also exhibits similar competitive antagonistic effects on the AMPAR, present in both pre– and post– synaptic plasma membranes and play a key role in neuronal plasticity and pathology.[46] KYNA exhibits a biphasic effect on AMPA receptors *in vitro*: low micromolar concentrations act as a positive modulator to increase AMPA activity, whereas higher millimolar concentrations exhibit antagonistic effects. Low micromolar concentration of KYNA has been proven to increase excitatory synaptic transmission, thereby providing a potential therapeutic target for learning and memory formation.[47] Less is known about the exact function of KAR but it is thought to play a role in pre– and post–synaptic signaling and plasticity.[48] More research needs to be conducted to elucidate the direct effects of KYNA–mediated antagonism of KAR.

Though these interactions are substantial, it appears the protective actions of KYNA are multifactorial, as inhibition of NMDAR and interaction with other bona fide KYNA receptors alone do not explain the metabolite's ability to protect against complex neurodegenerative and psychiatric diseases and ischemic injury.

Recent studies have shed light on many more protective effects of kynurenic acid, including a meta-analysis measuring peripheral KYNA, L-kynurenine, and QUIN levels in patients diagnosed with depression. The results revealed a statistically significant decrease in both KYNA and L-kynurenine, whereas QUIN remained stable in patients that were on antidepressants. It is still unknown whether this imbalance of the ratio between KYNA and QUIN is a causative or correlative nature of the disease. Further research is needed to determine the exact mechanism involved in the complex pathogenesis of depression.[49]

KYNA is also a potent antioxidant in the brain where it scavenges ROS that are generated in neonatal hypoxia-ischemia (HI), an unfortunate occurrence seen in approximately two to four in 1,000 live births in the US.[50] One study highlighted the possible therapeutic routes regarding this mechanism. The results of this research showed that treatment of rats with KYNA one hour post-HI significantly reduced ROS, glutathione (GSH) level, and antioxidant enzyme activity.[50] Not only is KYNA a direct antioxidant but it also acts indirectly via activation of GPR35, which in turn prevents ATP loss in post-ischemic attack via the remodeling of the mitochondrial ATP-synthase enzyme.[51]

Quinolinic Acid

Quinolinic acid (QUIN) is a biologically active intermediate of the KP, which ultimately serves as a precursor for the initiation of the NAD cycle and nicotinamide catabolism, producing niacin and NAD^+.[20,52] Interestingly, when compared with KYNA, QUIN exhibits opposite effects on cells; these effects become apparent in states of chronic inflammation. Most of the QUIN present in the CNS is produced by activated resident microglia and macrophages in response to an inflammatory extracellular environment.[53] Shifts in tryptophan metabolism leaning towards high QUIN:KYNA ratio has been correlated with many neurodegenerative and psychiatric diseases found in the US population[54].

One proposed mechanism for this is the metabolite's known effect as an NDMAR agonist (Figure 2), which has the potential to lead to increased intracellular calcium levels resulting in downstream damage of astrocytes and neurons with subsequent disruption of metabolism and induction of apoptosis.[55,56] Increased QUIN levels have also been linked to increased oxidative stress leading to lipid peroxidation. This membrane damage is modulated by interaction of QUIN with Fe^{2+} to form QUIN-Fe^{2+} complexes that mediate ROS generation.[57] Overall, it is clear that increased levels of QUIN production correlate to pathologic states. Whether this observation is completely correlative or if there is a causative effect is an exciting area of future investigation.

Disruption of tryptophan metabolism with increased activity of the KP and production of QUIN may result in deficiencies in tryptophan and the derived neurotransmitters. With the activation of microglia and macrophages in response to inflammation in the brain, QUIN may reach neurotoxic levels, which can lead to neuronal dysfunction, lipid peroxidation and cytoskeletal destabilization.[58,59] The toxicity of QUIN specifically affects neurons located in the hippocampus, striatum, and neocortex, due to the selectivity of QUIN toward NMDA receptors residing in these locations.[60]

3-Hydroxyanthranilic Acid (3-HAA)

3-Hydroxyanthranilic acid (3-HAA), a transient intermediate that contributes to the production of QUIN, has been generally overlooked when compared to other key players in the KP. Nevertheless, its acute cytotoxicity has been well documented. 3-HAA spontaneously oxidizes to form cinnabarinic acid, an unstable side product that reacts with GSH under physiologic conditions. Cinnabarinic acid is also a known agonist of both metabotropic glutamate receptor and the aryl hydrocarbon receptor.[61] 3-HAA itself has been directly implicated in apoptosis, likely due to decreased mitochondrial membrane potential and increased production of ROS.[62]

3-HAA plays a prominent role in the liver, kidneys, and brain.[20] In adolescents diagnosed with MDD, elevated levels of 3-HAA and striatal choline have been found in plasma, thus correlating neurobiological differences with clinical presentation.[63] Total striatal choline is a biomarker for cell membrane turnover, indicative of cell

death. 3-HAA has been proposed to contribute to the development of depressive symptoms via the overstimulation of NMDA receptors.[64] Additionally, neuronal atrophy resulting from free radical generation further promotes depressive symptoms. Studies have also shown that under pathological conditions, 3-HAA can induce apoptosis in neuronal cells in specific brain regions.[23] This is due to 3-HAA's ability to directly cause oxidative damage through the metabolism of 3-HAA to cinnabarinic acid and the resultant production of free radicals. Additionally, 3-HAA has been shown to decrease intracellular NAD^+ levels in human neurons and astrocytes.[65]

Conclusion

This review has summarized key aspects of the neuro-inflammatory hypothesis of depression and has highlighted the myriad of roles played by kynurenic acid (KYNA), quinolinic acid (QUIN) and 3-hydroxyanthranilic acid (3-HAA), metabolites generated in the kynurenine pathway (KP). The diverse effects of these compounds in the central nervous system, ranging from neuroprotective to neurotoxic, is indicative of a new direction in understanding the etiology of depression and identification and development of novel targets for its treatment.

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Disclosure

None reported. Artificial intelligence was not used in the study, research, preparation, or writing of this manuscript. **MM**

Integration of Osteopathic Manipulative Treatment for Patients with Chronic Pain

by Sharon Gustowski, DO, Turner Slicho, DO & D'Angeleau Newsome

The Five Models of Osteopathic Medicine offers guidance on creating a treatment plan that includes osteopathic manipulative treatment for patients with chronic pain.



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Abstract

The Five Models of Osteopathic Medicine offers guidance on creating a treatment plan that includes OMT for patients with chronic pain. Using OMT on one body region or system has numerous downstream effects and can influence multiple models. This paper describes this therapeutic modality.

Introduction

During 2021, "an estimated 20.9% of US adults (51.6 million persons) experienced chronic pain, and 6.9% (17.1 million persons) experienced high-impact chronic pain"[1] which by extrapolating from 2023 census figures,[2,3] translates into over 958,000 Missourians living with chronic pain. The implications of chronic pain reach far beyond the individual and estimated costs in 2010, were "$560 billion to $635 billion per year, composed of direct health care costs ($261 billion to $300 billion), days of work missed ($11.6 billion to $12.7 billion), hours of work missed ($95.2 billion to $96.5 billion), and lower wages ($190.6 billion to $226.3 billion)".[4]

The treatment of patients with chronic pain presents significant challenges for the modern-day medical practitioner. The chronic pain state occurs when physiologic process shifts away from an acute healing phase and the sympathetic nervous system, endocrine, immune, and central nervous system regions are activated.[5] Because so many systems are involved in the generation of a chronic pain state, including emotional and psychological systems, identifying one therapy that is curative is challenging. Research continues to emerge that demonstrates the efficacy of multidisciplinary team approach to chronic pain management. Typically, these programs consist of physicians, psychologists, counselors, physical therapists, case managers, occupational therapists, and other health professionals, e.g. psychiatrists, nursing staff, etc.[6] A treatment plan also requires individualization that must take into account access to care, patient resources, community resources, and patient buy-in. Osteopathic manipulative treatment (OMT) offers a first line or adjunct treatment modality that can be incorporated into the management patients with various presentations and etiologies of chronic pain.

Integrating OMT into Chronic Pain Management

When indicated, OMT can be used as a primary treatment or adjunct treatment in a multidisciplinary approach to the chronic pain patient. OMT is manual treatment for somatic dysfunction, which is: "the impaired or altered function of related components of the body framework system: skeletal, arthrodial, and myofascial structures, and their related vascular, lymphatic, and neural elements".[7] As a primary treatment, OMT will sometimes resolve the patient's pain and is most often effective in cases of minor acute injuries that cause somatic dysfunction, such as strains or low-grade sprains. As an adjunct treatment, OMT may not fully resolve the patient's pain directly, but may enhance healing by improving musculoskeletal range of motion, decreasing pain, and lowering allostatic load. A metanalysis by Franke et al. indicated that OMT was effective in patients with low back pain, including those who were pregnant, post-partum, or had non-specific acute and chronic pain.[8] Bagagiolo, et al. found that OMT is possibly effective in patients with conditions such as chronic neck pain, chronic low back pain and chronic non-cancer pain.[9] There are a wide variety of OMT techniques that can be used and detailed knowledge of which technique is applicable for which conditions and/or patients is part of the educational process for osteopathic medical students.

There is sufficient literature pointing to efficacy, safety, cost effectiveness, as well as guidelines which indicate that various manual therapies including OMT, are appropriate to use in clinical practice in a variety of musculoskeletal conditions.[10,11] OMT is generally safe to perform on patients of any age and any condition, including performing around stable artificial joints and internally fixated hardware.[12]

Five Models of Osteopathic Medicine

A tool called the Five Models of Osteopathic Medicine is a framework for creating a holistic treatment plan for patients with chronic pain, which may or may not include osteopathic manipulative treatment (OMT). The Five Models of Osteopathic medicine are five different components from which to approach health and disease: Biomechanical, Respiratory-Circulatory, Neurologic, Metabolic-Energy and Behavioral. The models are described below and include various chronic pain conditions where OMT can be integrated.

Biomechanical Model & Context

The biomechanical model is a framework for looking at how body structures, including joints, fascia, and musculature, are affected by a condition. Optimal body structural integrity allows for optimal function. Prioritizing body function for ambulation and activities of daily living can improve quality of life not only through decreased pain but also through greater autonomy to care for oneself.

Example: Patients with Chronic, Non-Specific Neck Pain & OMT Integration

OMT is a comparatively safe and efficient approach for patients with chronic neck pain, as reported in a meta-analysis and systematic review of moderate quality.[13] A study by Cholewicki et al. indicated that OMT can lessen pain and disability while improving sleep, fatigue, and depression in individuals with chronic neck pain.[14] Some osteopathic techniques can also improve neck muscle strength.[15] A randomized clinical trial of OMT for patients with chronic neck pain after whiplash injury demonstrated a positive effect on quality of life.[16] For patients with chronic neck pain, a reasonable biomechanical approach is to examine and perform OMT to the occipito-atlantal joint, cervical vertebrae, trapezius and suboccipital musculature, the thoracic outlet and first ribs. Gentle OMT techniques such as counterstrain, muscle energy, and myofascial release are all appropriate to use. While not contraindicated, using direct joint mobilization techniques such as high-velocity low amplitude should be used cautiously. OMT combined with other therapies for patients with chronic neck pain have demonstrated effectiveness, such as using OMT with dry needling[17] and exercises.[18]

Respiratory/Circulatory Model & Context

The respiratory/circulatory model recognizes the interconnection between breathing (respiration) and circulation of fluids within arterial, venous, capillary,

and lymph vessels. Efficient gas exchange and circulation of fluids ensures delivery of oxygen, nutrients, and medications, as well as the removal of inflammatory waste products and inflammatory mediators. Studies have been performed that assess the effects of OMT on circulating cytokines and their influences on the immune system.[19] Many positive effects were noted, namely a decrease in levels, suggesting that OMT can directly decrease inflammation.[19]

Examples: Post-Mastectomy Lymphedema, Chronic Lymphedema Due to Venous Insufficiency, Post-Operative Cardiac Surgery Patients & OMT Integration

One study demonstrated that osteopathic lymphatic pump techniques significantly increase thoracic and intestinal duct lymph flow,[20] as well as increases the lymphatic flux of cytokines, chemokines, as enzymes involved in defense of oxidative stress, in both the thoracic duct and intestinal duct.[21] The osteopathic pedal pump technique also showed statistically significant change in lower limb volumes of healthy individuals.[22] While these effects are transient, they can be incorporated into a treatment plan coupled with exercises, breathing techniques, and stretches to augment their treatment effect.[23,24] Improvements in pain management, respiratory capacity and hospital length of stay have also been demonstrated in the post-operative cardiac surgical patient.[25] To address the lymphatic system, perform OMT on the thoracic outlet and other areas prone to lymphatic congestion, such as the thoracoabdominal and pelvic diaphragms, as well as the thoracic spine and ribcage to help restore respiratory mechanics.

Neurologic Model & Context

The neurologic model focuses attention on the nervous system, including peripheral and central structures as well as the motor, sensory, and autonomic innervations. Attention to the area generating nociceptive input is important, however, it is also important to identify any areas of possible somatic dysfunction along the nerve pathway from peripheral to the spinal cord that could be affecting nerve function.

Example: Patients with Chronic, Non-Specific Low Back Pain, Radicular, and Non-Radicular & OMT Integration

National guidelines support the use of OMT as effective in decreasing low back pain and increasing function, for up to a year.[26] In addition, there is evidence that OMT improves low back pain functioning in pregnant patients.[27] Interestingly, OMT performed to the internal organs via fascial connections, called visceral manipulation, is showing promising results for patients with low back pain.[28,29] OMT can be performed safely on patients with radicular pain with potential for positive outcomes, including less sciatic nerve symptoms.[30] Utilizing OMT in patient with chronic low back pain includes examining the os coxae (innominates), sacrum, sacroiliac joint, lumbar vertebrae, and numerous muscles, including the piriformis, iliopsoas, pelvic floor, and quadratus lumborum for somatic dysfunction.

Assessment of postural alignment including foot position and spinal curvatures, particularly for patients who are ambulatory, is also warranted.[30,32]

Metabolic-Energy & Context

Optimal cellular metabolic needs are different for individuals with chronic pain who must accommodate for physical impairments such as lack of movement and inflammation. Restoring optimal body function can decrease pro-inflammatory mediators, pain and decrease the work or energetic needs required for movement.

Example: Myofascial Pain Syndrome & OMT Integration

There is an inflammatory component to myofascial pain syndrome, mediated by various interlukins, cytokines, and neuropeptides. Some of these biomarkers, namely IL-6, substance P and beta-endorphin, and TNF-alpha have been shown to be decreased with the use of various osteopathic techniques, including myofascial release, counterstrain, as well as stretching.[33] In one study of OMT in patients with chronic low back pain, circulatory pain biomarkers including beta-endorphin (a neuropeptide with morphine like effects) and palmitoylethanolamide (reduces

swelling and inflammation) were increased immediately posttreatment, as well as 24 hours post-treatment, with the effects being greater in the chronic subjects compared to the control group.[34] The techniques resulted in a physiologic response of the target tissues with a positive anti-inflammatory and analgesic effect. Any OMT can be used on any region in patients with myofascial pain syndrome, but gentle ones such as myofascial release, indirect, balanced ligamentous tension and lymphatic techniques are recommended.

Behavioral Model & Context

Behavioral health interventions provide coping mechanisms, emotional support opportunities and sometimes significantly alleviate or even resolve chronic pain. Over time, psychosocial factors become increasingly important in the maintenance of chronic pain. The negative impact on multiple life areas frequently leads to a perception of a lack of control or self-efficacy in managing pain.[35]

When resolution of the chronic pain state is not feasible, treatment goals must therefore be one of adaptation and functional optimization, building off the patient-doctor relationship, coupled with OMT and other disciplines when warranted to empower the patient to be an active participant in realizing their health and wellness. Setting expectations with regular follow-up to hold the patient accountable for buy-in further builds on the strength of the relationship established with the patient.

Example: Any Patient with Chronic Pain & OMT Integration

Preliminary studies indicate that OMT could have a direct effect on anxiety and depression. For example, in a pilot study, Abraham et al. investigated the use of OMT as an intervention to reduce stress, anxiety, and depression in first responders. The OMT treatment group showed a short-term downward trend of serum biomarkers associated with stress, anxiety, and depression when compared to the sham OMT group.[36] While this study did not measure symptom improvement, it suggests the possibility of such correlation between serum biomarkers and stress symptoms. Additionally, research has shown that OMT intervention can lessen the physiological response to stress situations, reducing cortisol levels as well as promoting a "faster recovery of heart rate and sympathovagal balance after an acute mental stressor by substantially dampening parasympathetic withdrawal and sympathetic prevalence."[37] Treatment of structural somatic dysfunctions to improve optimal physiological functioning in whatever state of health the patient may present allows the patient to achieve better balance between mental and physical health in the face of the psychosocial stressors that chronic illness or pain presents.

Conclusion

The management of chronic pain patients is complex, and an individualized plan is usually warranted. The Five Models of Osteopathic Medicine offers guidance on creating a treatment plan that includes OMT for patients with chronic pain. Using OMT on one body region or system has numerous downstream effects and can influence multiple models. For example, OMT to the iliopsoas musculature reduces tension and improves hip and low back motion which decreases pain. OMT can also affect diaphragmatic function and therefore oxygenation and lymph flow. When OMT is not available, other manual and conservative therapies such as exercises, physical therapy, chiropractic, and myofascial trigger point therapy, can be substituted and/or used in conjunction with other interventions including pharmaceuticals and surgery.

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Opioid Use Disorder in Missouri: An Evidence-Based, Public Health-Oriented Approach

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To reduce opioid use disorder associated morbidity and mortality, we need to meet people wherever they are and provide them holistic, non–judgmental, non–stigmatizing care.



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Abstract

Opioid use disorder (OUD) represents a growing public health crisis in Missouri and nationwide. Reversing the trend of rising OUD-associated morbidity and mortality will require implementing evidence-based approaches grounded in public health principles. Key evidence-based interventions include medications for opioid use disorder, naloxone distribution, overdose education, and syringe services programs. The increasing presence of fentanyl and xylazine in the drug supply represent new challenges to the OUD crisis in Missouri. Optimal implementation of evidence-based interventions will require action at the individual physician, community, and state policy level.

Introduction

Opioid use disorder and its associated morbidity and mortality represent a growing public health crisis, both in Missouri and nationally. In Missouri in 2022, 2,178 individuals lost their lives to a drug overdose. Among those overdose deaths, 72% involved opioids and 67% specifically involved fentanyl. The number of deaths from opioid overdose has climbed each of the last 4 years in the state.[1] At a national level, annual opioid overdose deaths now far exceed annual deaths from HIV at the peak of the AIDS epidemic in the mid-1990s.[2,3]

Opioid use disorder is a pattern of opioid use that leads to physical, mental, social and legal problems. It is a treatable chronic medical condition characterized by episodes of remission and recurrence.[4,5] The recent history of the opioid epidemic in the United States can be described in four major phases, or waves. The first wave in the 1990s was largely driven by availability of prescription opioid medications in response to a push to increase prescribing of these medications for chronic pain. The dynamic of the epidemic shifted around 2010 at which time there were increasing rates of overdose from heroin. The third wave started soon thereafter in the mid 2010s, and was characterized by rising

mortality from fentanyl, a highly potent synthetic opioid that has increasingly become part of the illicit heroin supply in the United States. We are now in the fourth wave of the epidemic. This most recent wave is characterized by increasing mortality from fentanyl, rising rates of polysubstance use including methamphetamine, and the addition of other constituents to the fentanyl supply including xylazine.[6]

An Evidence-Based, Public Health-Oriented Approach to Opioid Use Disorder

Reversing the trend of escalating morbidity and mortality related to OUD in Missouri will require optimal implementation of evidence-based approaches that have shown empirical success in reducing harm from opioid use. This includes medications for opioid use disorder (MOUD) like methadone and buprenorphine, along with harm reduction approaches such as naloxone and syringe services programs. This focus on evidence-based approaches with strong outcomes data should be combined with analysis of the problem through a public health lens. A public health approach to addressing the OUD crisis considers not only individual biomedical and psychosocial treatment approaches, but also what is needed to address this health challenge at a community and population level. Such an approach requires consideration of the broader socio-economic factors and policy landscape that may either accelerate or impede progress in addressing the OUD crisis.

Role of Medications for Opioid Use Disorder

The standard of care for treatment of patients with opioid use disorder is medication therapy. There are currently three FDA-approved medications to treat opioid use disorder: methadone, buprenorphine, and naltrexone. These medications have been shown to increase retention in treatment, reduce ongoing opioid use, and reduce the harms associated with opioid use disorder.[7] Methadone and buprenorphine are considered first-line and have been associated with reductions in both all-cause and cause-specific mortality. A meta-analysis of 138,716 people treated for OUD with methadone or buprenorphine demonstrated reductions of all-cause mortality from 36.1 to 11.3 per 1,000 person/years with methadone and a reduction from 9.5 to 4.3 per 1,000 person/years with buprenorphine, compared with individuals with OUD not receiving these medications.[8] In fact, the data to support medication treatment for opioid use disorder is as strong or stronger than many medications routinely prescribed in outpatient primary care. A recent cohort study showed that the number needed to treat (NNT) with buprenorphine to prevent one death in the year after an overdose was 52.6.[9] By comparison, the NNT for statins used as primary prevention to prevent a composite of adverse cardiovascular outcomes in asymptomatic patients is 78.[10]

The goals of medication treatment for opioid use disorder include managing symptoms of withdrawal (sometimes referred to as "detoxification"), preventing complications of OUD, and helping people maintain long-term recovery from OUD.[4] Given that OUD is a chronic medical condition characterized by periods of remission and recurrence, MOUD is intended to be utilized as an ongoing treatment aimed at reducing opioid use and its associated harms. Despite strong evidence supporting medication treatment beyond the period of opioid withdrawal, many addiction treatment facilities provide medications only during the period of opioid withdrawal ("detoxification"), or provide psychosocial treatments only. Studies of medications for opioid withdrawal management not followed by ongoing pharmacotherapy have shown that more than 80% of patients return to illicit or non-prescribed opioid use.[7]

Behavioral treatments such as counseling and peer support can be valuable adjuncts to medication therapy; however, these treatments have not demonstrated effectiveness as standalone treatments for OUD. A large comparative effectiveness study comparing six treatment pathways for OUD (no treatment, inpatient detoxification, intensive behavioral health, non-intensive behavioral health, buprenorphine or methadone, and naltrexone) showed that only methadone and buprenorphine were significantly

associated with reductions in overdose and opioid-related acute care.[11]

Methadone is a long-acting full opioid agonist that reduces opioid withdrawal symptoms and cravings. Patients in opioid withdrawal can begin methadone immediately without any washout period.[4] In the US, methadone can only be prescribed for OUD through federally-regulated opioid treatment programs (OTPs). These highly structured treatment programs require patients to present in-person up to six days a week for medication administration.[12] Although this treatment structure may benefit some patients, it may present a barrier to care for others with OUD who are unable to access in-person care at this frequency. Furthermore, the requirement that methadone only be administered for OUD treatment at federally regulated OTPs may inequitably limit access in rural areas,[13] a challenge that may significantly affect access in Missouri.

Buprenorphine is a partial mu-opioid receptor agonist that reduces opioid withdrawal symptoms and reduces cravings for opioids. As a partial agonist, it has a lower overdose risk given that its maximal effect is lower than full agonists like methadone. A unique feature of buprenorphine is that it may cause precipitated withdrawal from opioids, due to its strong affinity for the mu opioid receptor. For this reason, patients need to be in mild to moderate withdrawal at the time of buprenorphine initiation.[4,6] One advantage of buprenorphine for patients with opioid use disorder has been its availability in office-based settings outside of highly structured OTPs. Until 2023, office-based buprenorphine treatment was limited by the Drug Addiction Treatment Act (DATA 2000), requiring physicians to obtain a special "X waiver" to their DEA license to prescribe buprenorphine outside of an OTP. The X waiver included a requirement for physicians to complete eight hours of training, additional documentation requirements for patients on buprenorphine, along with caps on the number of patients a prescriber could simultaneously treat with buprenorphine. Recent federal legislation eliminated the X waiver effective January 12, 2023, removing one important barrier to outpatient MOUD. With this change, any prescriber with a general DEA license to prescribe schedule III controlled substances can now also prescribe buprenorphine.[14] This legislative change presents a valuable opportunity to increase patient access to MOUD in Missouri.

Role of Harm Reduction

Patients with opioid use disorder may present to health care settings at varied levels of readiness to make behavioral changes. For some, abstinence from all non-prescribed substances may be a realistic and attainable goal. For others, reducing use, preventing acquisition of HIV and/or Hepatitis C, and/or preventing fatal overdose may be the most appropriate immediate goals. This situation is similar with other chronic diseases like hypertension and diabetes. For example, although complete abstinence from all sugar-sweetened beverages be ideal for managing type 2 diabetes, this approach is not realistic for all patients. In spite of this reality, many addiction treatment programs continue to herald abstinence from all non-prescribed substances as the only appropriate treatment goal.[15] A myopic focus on abstinence excludes many individuals who would greatly benefit from tailored addiction treatment, but for whom abstinence is not the most appropriate treatment goal.

Harm reduction is one evidence-based approach to addiction care that can help physicians provide care tailored to the needs of each individual patient. Harm reduction "refers to interventions aimed at reducing the negative health effects of behaviors without necessarily extinguishing the problematic behaviors entirely."[16] Harm reduction is grounded in principles of patient-centeredness and respect for persons. A harm reduction approach involves meeting patients where they are at, discussing substance use in an open, non-judgmental manner, and using motivational interviewing techniques to help patients develop shared goals around managing their addiction.[16,17]

Naloxone—a rapid-acting opioid antagonist that can reverse opioid overdose—is one key evidence-based intervention grounded in principles of harm reduction. A Massachusetts–based study showed that community level opioid overdose education and naloxone distribution was associated with substantial reductions in mortality from

opioid overdose.[18] There are opportunities for expanding naloxone distribution at the individual clinic level as well as the community level. Physicians can set up their electronic medical records (EMRs) to automate prescribing of naloxone whenever MOUD is prescribed, or whenever full opioid agonists are prescribed for chronic pain. At the community level, local public health departments can explore opportunities for direct naloxone distribution, ideally targeted to areas where opioid overdose rates are highest.[15]

Syringe service programs (SSPs) are another important intervention based on harm reduction principles. SSPs were initially established with the goal of preventing HIV transmission through distribution of safe injection equipment. Their role has expanded to encompass other modalities of reducing harm associated with opioid use including testing for HIV and Hepatitis C, distribution of naloxone and fentanyl test strips to reduce risk of death from drug overdose, and linkage to medications for opioid use disorder.[19] SSPs meet people with opioid use disorder where they are at and create a low–barrier, non–stigmatizing environment for patients to connect with treatment when they are ready. There is strong data supporting the efficacy of syringe services programs. SSPs are associated with about a 50% decrease in HIV and HCV incidence. Furthermore, people who inject drugs who utilize SSPs are more than five times as likely to enter into addiction treatment and about three times as likely to report reducing or stopping injection as those who have never utilized SSPs.[20] In light of data supporting the effectiveness of SSPs, 31 states have legalized or reduced legal barriers to operating SSPs, including many southern, Midwestern and rural states who have changed these laws in the face of HIV/HCV outbreaks. Missouri law does not currently allow for the legal establishment of SSPs.[21]

Beyond naloxone distribution and SSPs, harm reduction strategies can be incorporated into other components of treatment for opioid use disorder, including medication treatment for OUD. Many treatment programs create high barriers to entry and continuation in treatment. Such barriers include long wait lists for treatment, requirements for intensive counseling to remain in treatment, as well as cessation of treatment in patients who continue to use illicit opioids and/or other substances. These barriers limit the number of patients who are able to benefit from treatment and leave many vulnerable to overdose and death from OUD. "Low-threshold" or "low barrier" buprenorphine treatment represents one promising approach to remove barriers to evidence–based OUD treatment and expand treatment access. These programs offer features like same–day treatment access, flexibility, and availability in places where people with opioid use disorder go. Early data on these approaches indicates that low barrier OUD treatment clinics fill gaps in the care continuum for patients with OUD, help patients initiate treatment in non-traditional settings, and help link patients to long-term care for OUD.[22,23]

Addressing Challenges Related to the Third and Fourth Waves of the OUD Epidemic

The shifting dynamics of the opioid epidemic—including rising mortality from fentanyl overdose and xylazine in the drug supply—will require innovative approaches to reduce morbidity and mortality from OUD in Missouri. In the last several years, illicitly manufactured fentanyl has overtaken heroin and prescription opioids as the most common drug involved in overdoses. Illicitly manufactured fentanyl is a highly potent synthetic opioid (up to 50 times more potent than heroin) often used as an additive by drug manufacturers to enhance the effect of other illicit substances. Powdered fentanyl is often mixed with drugs like heroin, cocaine and methamphetamine and manufactured into pills that look like other prescription opioids. People may be unaware that their drugs contain fentanyl. One valuable public health strategy to reduce harm from fentanyl in the drug supply is fentanyl test strips, which allow people who use drugs to determine if their drugs have been laced with fentanyl.[17,24] People who use opioids and other drugs can also be counseled to "never

use alone" and carry naloxone with them to reduce the risk of death due to unintentional overdose. Given the increased overdose risk with fentanyl–containing products, naloxone distribution and overdose education has taken on increased importance as part of a comprehensive public health strategy to reduce OUD–related morbidity and mortality. Lastly, medications for opioid use disorder remain a valuable strategy for treatment of people with OUD who use fentanyl; however, there is emerging evidence that the increased potency and lipophilicity of fentanyl may require modifications of usual protocols to buprenorphine induction to avoid the challenge of precipitated withdrawal.[25]

Xylazine is a rapidly emerging public health threat in the US that is also increasingly being found in illicitly manufactured fentanyl products. Xylazine is a centrally acting alpha-2 agonist approved by the FDA as a veterinary sedative that is not approved for use in humans. It is increasingly being found in the illicit drug supply as an additive to fentanyl and is thought to enhance the euphoria induced by fentanyl due to its longer duration of action. Xylazine intoxication can cause central nervous system depression, bradycardia, and hypotension. Although naloxone can reverse opioid–induced respiratory depression, it cannot reverse the effects of xylazine. Beyond its acute effects, xylazine has also been associated with severe necrotic skin ulcerations. More research is needed to develop a comprehensive medical and public health approach to addressing the presence of xylazine in the drug supply. Some initial steps that may prove helpful include accelerating development and distribution of point-of-care tests for xylazine. This should include biologic specimen testing that can be used by physicians as well as drug product testing that can be utilized by public health authorities as well as consumers.[26]

Future of Care for People with OUD in Missouri

Among the 2.4 million Americans with opioid use disorder, only about 20% receive any treatment for their disorder in a given year.[27] To reduce OUD–associated morbidity and mortality, we need to reach more people with OUD with health care tailored to their specific needs. This means meeting people with OUD wherever they are and providing them holistic, non–judgmental, non–stigmatizing care.

Improving our public health response to the OUD crisis will require action at the individual physician, community, and policy level. At the physician level, the removal of the X waiver for buprenorphine prescriber presents one valuable opportunity to increase MOUD access; however, more work is needed to increase access to MOUD for patients in Missouri. More physicians need training on opioid use disorder and MOUD, including trainees in medical schools, residencies and independent practice. Physicians need practice-level and institutional support to be able to provide effective OUD care, including adequate supports from administrative staff, nursing and behavioral health providers. Stigma is another major barrier to delivery of high quality, evidence-based OUD care at the physician level. Education for physicians and other health care providers should emphasize that opioid use disorder is a chronic medical illness characterized by periods of recurrence and remission, and is not a "moral failing." Training on OUD should also debunk the myth that MOUD is simply substituting one drug for another.[28]

At the community level, local health departments and community clinics should work to expand access to naloxone and overdose training, particularly in areas with a high prevalence of opioid overdose. Communities should also work to address the social determinants or drivers of health, in light of evidence that social challenges may exacerbate substance use disorders, and vice versa. Homelessness and substance use disorder often co-exist and may reinforce one another. "Housing first" models of addressing homelessness focus on addressing housing needs first, understanding that housing stability is necessary for individuals to effectively engage with substance use treatment programs.[28]

At the policy level, advocates should support city- and state-level policies that have demonstrated success in reducing opioid overdose morbidity

and mortality. Many Midwestern and rural states have reduced legal barriers to syringe services programs (SSP) in light of strong evidence that these programs can reduce infectious disease transmission and increase linkage to addiction treatment, yet SSPs are not legally permitted by Missouri state law.

Conclusion

By considering opioid use disorder from a public health perspective, Missouri physicians can work towards building a health care system that reduces OUD-associated morbidity and mortality and allows more patients with OUD to access high quality, evidence-based treatments. Key interventions include low barrier access to medications for opioid use disorder, increased availability of naloxone and overdose education, and access to syringe services programs. These interventions should be coupled with ongoing work to destigmatize substance use disorders and reframe OUD as a chronic medical condition —like hypertension or diabetes—that generalist physicians can effectively manage.

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Disclosure

None reported. Artificial intelligence was not used in the study, research, preparation, or writing of this manuscript. **MM**

Human Platelet Derived Mitochondrial OPA-1 Isoforms and Interaction With TDP-43 in Neurodegenerative Diseases

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Kansas City University

Studying the interaction between two proteins in healthy human subjects will help us to establish better understanding of TDP-43 protein in biology of mitochondria so that we will enhance our understating of the biology of Alzheimer's disease.



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Abstract

Optic atrophy 1(OPA1) is a GTPase protein that controls mitochondrial fusion, cristae integrity, and mtDNA maintenance. In neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), the mitochondrial network morphology is compromised. Studies on TAR-DNA binding protein 43 (TDP-43) has been the focus in our lab. OPA1 and TDP-43 interaction may shed a light on how aberrant TDP-43 interacts with OPA1, which will lead to mitochondrial dysfunction. The preliminary study tested the idea of whether OPA1 and TDP-43 are physically interacting in human platelet derived mitochondria obtained from healthy human subjects.

Intention of Study

Alzheimer's disease is the most common cause of dementia in the United States. An estimated 6.2 million people in the US over the age of 65 are currently living with Alzheimer's disease. Projections estimate this number could grow to 13.8 million by 2060, hence, it is crucial to discover a way to slow the progress or cure the disease.

Our lab had identified platelet TAR DNA-binding protein (TDP-43) as a potential blood-based biomarker. We have observed the presence of TDP-43 protein in mitochondria-enriched pellets obtained from human platelets. We studied the interaction between mitochondrial Optic Atrophy-1 (OPA-1) and TDP-43. OPA-1 is involved in many functions such as oxidative phosphorylation, mitochondrial DNA maintenance, mitochondria cristae integrity, and mitochondrial fusion. In Alzheimer's disease, TDP-43 is mislocalized from the nucleus and accumulates in the cytosol and possibly in mitochondria. Our overarching hypothesis is that TDP-43 may physically interact with OPA-1 in platelet-derived mitochondria obtained from Alzheimer's disease patients, which will interfere with OPA-1 homeostasis and mitochondrial integrity. Our preliminary data obtained from immunoblotting and High-Performance Immunoprecipitation indicate that there are not only multiple OPA-1 isoforms, but also a potential interaction between TDP-43 and OPA-1 in platelet-derived mitochondrial lysate. OPA-1 and TDP-43 are both related to the mitochondria and are affected in patients with Alzheimer's disease.

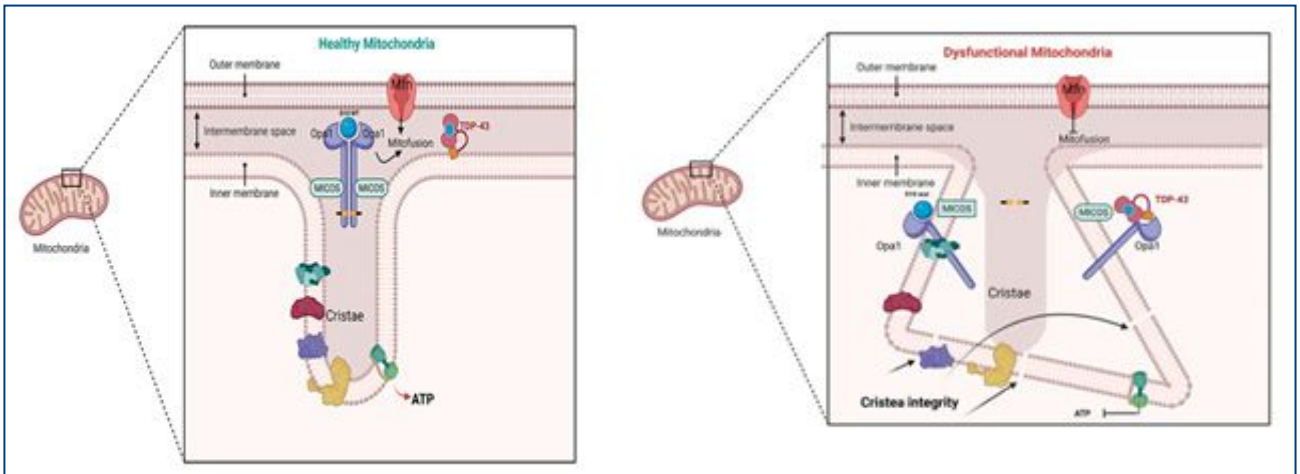


Figure 1. OPA-1 binding partners in health and disease condition. In healthy mitochondria OPA-1 protein is in homodimer (Left panel). In a disease states, TDP-43 interacts with OPA-1 protein and keeps them apart in dysfunctional mitochondria (right panel). Since OPA-1 lost its dimerization, mitochondrial cristae also lost integrity; hence mitochondria become dysfunctional organelle.
Figures created with Biorender.com

Thus, studying the interaction between these two proteins in healthy human subjects will help us to establish better understanding of TDP-43 protein in biology of mitochondria so that we will enhance our understating of the biology of Alzheimer's disease.

Introduction

Platelets are small mitochondria-containing anucleated cells 3-5 µm in size that patrol the vasculature to maintain the homeostasis by preventing blood loss and promoting wound repair.[1] Platelets possess five to eight functional mitochondria per cell,[2] making platelets a feasible venue to study mitochondria relevant research in neurodegenerative diseases. Platelets provide easy access to human tissue with a less invasive method of obtaining human samples (requires 8-10 mL of whole venous blood). We have shown that platelet TDP-43 protein reflects chemical changes in the central nervous system in neurodegenerative diseases.[3] OPA1 is critical for mitochondria fusion, cristae integrity, and mtDNA maintenance.[4-6] TDP-43 is a nuclear protein; however, this protein has the ability to shuttle back and forth between the nucleus and cytosol,[7] and it was detected in human platelets in our laboratory.[8] We have observed the presence of approximately 25 kDa truncated TDP-43 in mitochondria-enriched pellets obtained from human platelets.

Recent findings and knowledge of the mechanistic function of OPA1 protein and relevant isoforms offer a starting point for development of a more precise and defined therapeutic prospect for neurodegenerative disease.[9] In this preliminary study, we aim to identify the number of isoforms of human OPA1 that detectable in human blood-derived platelet lysate. The notion of TDP-43 induced disruption of the OPA1 homeostasis that leads to deficits in mitochondrial fusion signifies the role of TDP-43 in mitochondria in neurodegenerative diseases (Figure 1).

Our goal was to test the hypothesis that OPA-1 and TDP-43 physically interact in platelets obtained from healthy human subjects. Therefore, it is necessary to demonstrate the feasibility of protein-protein interaction in healthy human platelets and thereafter apply the same approach to platelets obtained from patients with neurodegenerative diseases. We will test this hypothesis with two experimental approaches:

1. To demonstrate OPA-1 presence and its isoforms in platelets obtained from healthy human subjects; and

2. to demonstrate the physical interaction between OPA-1 and TDP-43. OPA-1 and TDP-43 will be immunoprecipitated by their respective antibodies. Both immunoprecipitated proteins will be cross-immunoblotted with their respective antibodies (i.e. OPA-1 immunoprecipitate will be probed with anti-TDP-43 antibody. TDP-43 immunoprecipitate will be probed with anti-OPA-1 antibody).

Material and Methods

Platelet Cytosol Preparation

Human platelets were obtained from a local blood bank. We used about 50-100 mL of clinical grade platelets already isolated and stored in the facility of the Community Blood Bank of Kansas City. The platelet suspension was subjected to centrifugation at 1,200 x g for 15 minutes. The supernatant was removed and the pellet was resuspended in citrate wash buffer. At this stage some of the platelets pellets were kept at80oC for mitochondria isolation. Some of the platelet pellets were resuspended in citrate wash buffer (11 mM glucose,128 mM NaCl; 4.3 mM NaH2PO4; 7.5 mM Na2HPO4; 4.8 mM Na-Citrate; 2.4 mM citric acid, pH 6.5) for preparation of platelet lysate. The suspension was subjected to centrifugation at 1,200 x g for 15 minutes. The platelet pellet volume was about 3 mL. We resuspended the platelet pellet in 3 mL of lysate buffer (250mM sucrose; 1mM EDTA; 10mM Tris, pH 7.4) including 6 µL of protease inhibitor cocktails and 24 µL of phosphatase inhibitor cocktails. The platelet resuspension was incubated on an ice bucket for 20-25 minutes and the material was sonicated (setting 3, 20 seconds in continuous) in order to rupture the platelets. The platelet lysate was subjected to centrifugation at 20K x g for 30 minutes. Clear supernatant was saved for next phase of the experiment and membrane fragment containing pellet was discarded. Protein concentration was assessed by BCA assay. Platelet cytosol fractions were stored at -80oC until use.

Mitochondria Isolation from Frozen Human Platelets

An aliquoted platelet pellet (~ 3 mL) was gently resuspended in 3 mL of citrate wash buffer. The platelet suspension was subjected to centrifugation at 1,200 x g for 15 min at room temperature. The supernatant was decanted and the platelet pellet was resuspended in 25 mL of mitochondria isolation buffer, Mito-IB, (320mM sucrose; 10mM HEPES (free acid); 0.5mM EGTA, pH adjusted to 7.4 with KOH). We used 1 mL of Mito-IB for every 2X 109 platelets. We added about 195 µL of Proteinase K solution and gently inverted for five minutes at room temperature. The platelet suspension was gently homogenized by 30-40 passes in a Teflon pestle Potter- Elvehjem glass homogenizer placed in an ice-bucket without getting froth. We also added 1 µL of protease inhibitor cocktails (Calbiochem #539134) for every 2 mL of suspension. The platelet homogenate was subjected to centrifugation at 1,300 x g for 10 min at 4oC. The supernatant was saved and the resulting pellet was resuspended in 1 mL of Mito-IB and the suspension was subjected to centrifugation (1,300 x g for 10 min at 4oC). The supernatants were combined and the pellet was discarded. The poled supernatants were subjected to centrifugation at 13K x g for 10 min at 4oC to obtain a crude mitochondria pellet. The pellet was resuspended in 2.5 mL of Mito-IRB, pH 7.4. 250 µL of the resuspended crude mitochondria-enriched sample was layered on previously prepared 15% Percoll layer. We used 10 individual 15% Percoll density gradient for isolating a sufficient amount of mitochondria. All tubes were subjected to centrifugation at 21K x g for 8 minutes at 4oC without break so that Percoll gradient will not be disturbed at the end of the centrifugation. We harvested the mitochondria-enriched hazy band near the bottom of the tubes. Mitochondria- enriched fractions were combined and resuspended in 1 mL of Mito-IRB without EDTA, and re-centrifuged at 22K x g for 10 min at 4oC to remove the Percoll residue. The supernatant was removed, the pellet was washed one more time with 1 mL of Mito-IRB without EDTA, and final mitochondria–enriched pellet was obtained and stored in packed-ice at 4oC for subsequent immunoprecipitation process.

High Performance Immunoaffinity Chromatography

Ten µg of the primary antibodies (i.e. a-TDP-43 and a-OPA-1 antibodies) were chemically cross-linked in Protein-A coupled resin by disuccininilimidyl suberate (DSS) following the manufacturer's protocol (ThermoScience). We used tip-column manufactured by Phytips (Biotage # PTR-92-20-01) to cross-link the primary antibodies according to the manufacturer's protocol. 200 µL of tip-column was placed on a programmable electronic pipette (RAININ E4XLS) for performing the immunoprecipitation procedure. The program was fully driven by a software (PureSpeed) and pipetting error was minimized. The protocol flow-chart was illustrated in Figure 2.

The acidic eluate from the tip-column was

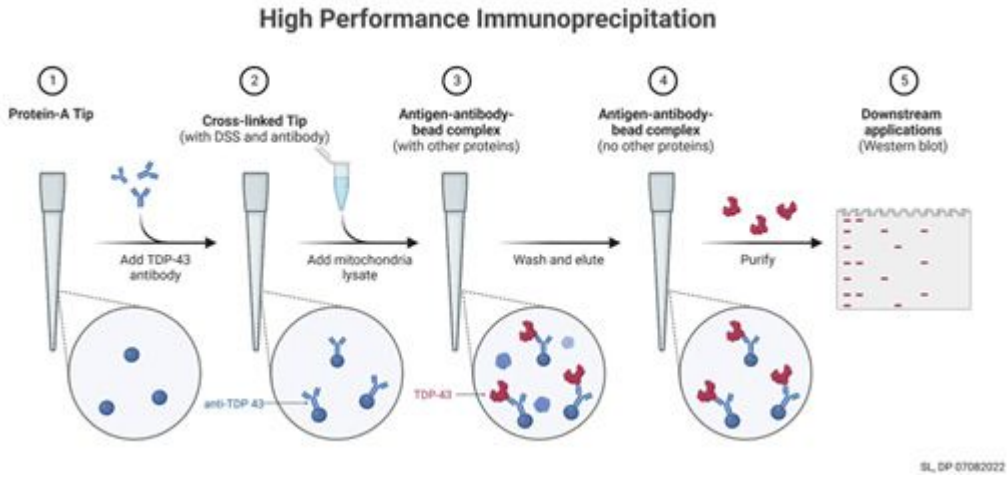


Figure 2. High performance immunoprecipitation flow-chart. Anti-OPA-1 and anti-TDP-43 antibodies were chemically cross-linked to Protein-A coupled resin. The immunoprecipitation procedure was fully automated. The eluate was analyzed by immunoprobing assay. *Figure created with BioRender.com*

automatically collected in a 1.5 mL microtube containing 5 µl of neutralizing buffer (1 M Tris-HCL, pH 9.5). The tube content was mixed well and stored in a -20oC freezer until use.

Immunoblotting

The eluates collected from High Performance Immunoaffinity Chromatography (HPIP) procedure were loaded on 4-20% gradient SDS/polyacrylamide gel and proteins were resolved by classical electrophoresis (100 V; 1h or until the dye-front reach to just above the bottom of the gel). The resolved proteins were transferred onto a PVDF membrane (75 V; 90 min without methanol). The membrane was stained for total protein to assess the transfer efficiency. The membrane was blocked in 50% fish serum blocking buffer (ThermoScientific # 37527) for one hour at room temperature (RT) and subsequently incubated in relevant primary antibody solution (1/500 a-OPA-1 antibody. 1/1000 a-TDP-43 antibody) for overnight at 4oC. The next day, the primary antibody solutions were removed, the membrane was washed 3 x 5 min and incubated with infrared dye-tagged secondary antibody solution for 1 hour at RT. The PVDF membrane was washed with a Tris Buffer Saline-Tween-20 (TBST) buffer 5 X 5 min and one final wash with TBS buffer excluding Tween-20 detergent to eliminate auto fluorescence caused by detergent. The PVDF membrane was imaged by LICOR-Odyssey system, and protein bands were analyzed by Image studio (v.5.2.)

Results

Both platelet cytosol and mitochondria lysates obtained from human platelets were resolved in 4-20% gradient SDS/PAGE. The resolved proteins were transferred onto PVDF membrane and proteins were immunoprobed by anti-OPA-1 antibody (1:1000 dilution). Figure 3A depicts the global OPA-1 profile of human platelet cytosol. Eight OPA-1 positive protein bands were identified (arrow). We have also included mouse brain cell lysate as a positive control for OPA-1 immunodetection. Figure 3B shows only two major protein bands in mitochondrial lysate isolated from human platelet. We have tested these proteins under reducing and non-reducing condition. The proteins did not resolve well and stayed on the top of the gel (~250 kDa) whereas at least two protein species were identified (79 and 55 kDa) under the reducing conditions.

To interrogate which of the OPA-1 positive proteins in mitochondrial lysate physically interact with TDP-43, we utilized a high-performance immunoprecipitation (HPIP) approach. We chemically cross-linked anti-TDP-43 antibodies and anti-OPA-1 antibodies in Protein-A conjugated tip-columns. Both TDP-43 and OPA-1 proteins were pull-down from mitochondrial lysates prepared from human platelets. The eluates were subjected to 4-20% gradient SDS/PAGE and subsequently immunoprobed with anti-TDP-43 and anti-OPA-1 antibodies. Figure-4 A shows immunoprobing of both TDP-43 and OPA-1 HPIP. A positive TDP-43 immunoblotting in OPA-1 HPIP was observed (right-hand side of the blot). TDP-43 HPIP

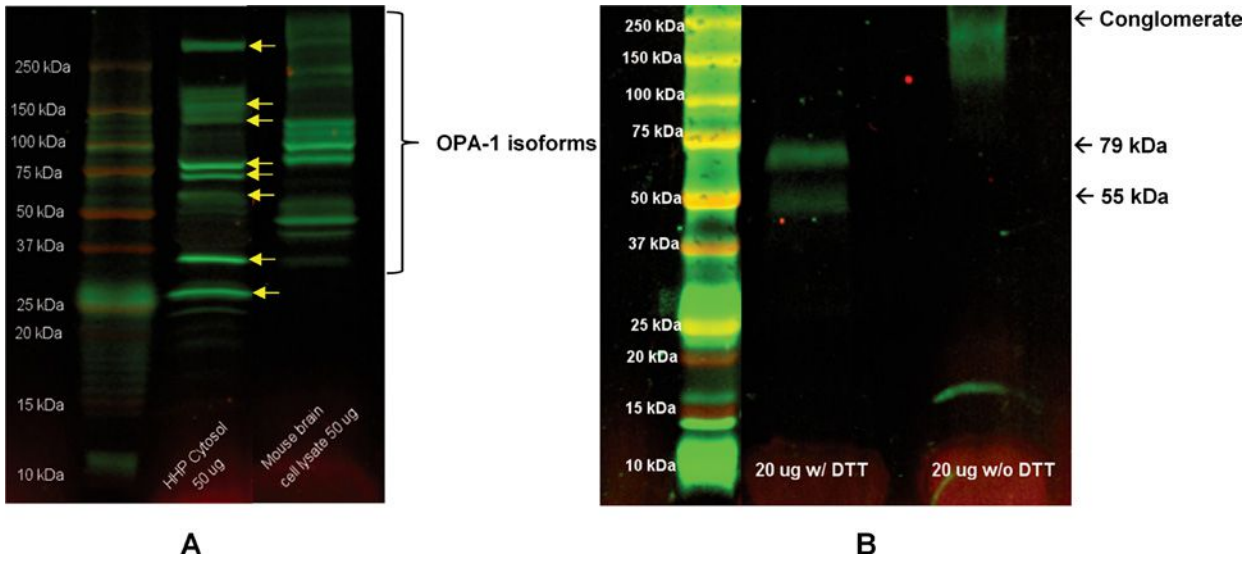


Figure 3. OPA-1 profile in human platelet cytosol and mitochondrial lysate. Human platelet cytosol and mitochondrial lysate obtained from human platelet lysate were analyzed by immunoblotting assay.
(A) Anti-OPA-1 pan antibody recognized 8 isoforms in human platelet cytosol in different protein levels (pointed with arrows). We include mouse brain lysate as positive control.
(B) Mitochondria-enriched pellet suspension was analyzed by an anti-OPA-1 pan antibody. Two isoforms were identified under reducing conditions. These proteins remained in conglomerate in the electrophoretic field (ask author) under non-reducing conditions.

(left hand side of the blot) eluate was also labeled by anti-TDP-43 antibody. Figure 4A showed that anti-OPA-1 antibody labeled about 25 kDa protein that pulldown by TDP-43 HPIP. There was an additional low molecular weight protein labeled by anti-OPA-1 Antibody at above 15 kDa marker. OPA-1 antibody did recognize two protein species that were pulldown by OPA-1 HPIP (arrow).

Discussion

We have made some interesting observations of the presence of ~25 kDa and ~ 17 kDa TDP-43 fragments pulldown by TDP-43-HPIP and immunolabeled by anti-OPA-1 antibody in mitochondria-enriched pellet prepared from human platelets. We are unclear as to the function of this fragmented TDP-43 in mitochondria-enriched pellets, as this fragment of TDP-43 is considered to be toxic to cells. Liu et al.[10] proposed a hypothesis that TDP-43 may interfere normal function of OPA1, which is maintaining cristae integrity and mitochondrial fusion. Demonstrating the interaction of OPA-1 and TDP-43 in human platelet-derived mitochondria is critical since this approach can be used for demonstrating the physical interaction that provides some explanation for our understanding how mitochondria integrity is compromised in neuro degenerative diseases.

In this preliminary study, we provided some evidence that there are several isoforms of OPA-1 in human blood serum. We were able to label them with a pan anti-OPA-1 antibody (Figure 3A). We were unable to identify isoform specific OPA-1; it is because the unavailability of specific antibodies for each isoform. Nevertheless, we attempted to demonstrate that OPA-1 proteins interact with TDP-43; but we do not know which specific isoform of OPA-1 interacts the best with TDP-43. More research is needed in this field.

Anti-TDP-43 antibody-HPIP and anti-OPA-1 antibody-HPIP methods yielded some interesting results. Anti-TDP-43 antibody labeled full size TDP-43 proteins as expected at ~48-50 kDa marker; however, anti-OPA-1 antibody did not label the full size of TDP-43, but it did label the fragmented TDP-43 at ~25 kDa marker (Figure 4B). This region is located in C-terminus of TDP-43 and highly rich in glycine, glutamine, and asparagine[11]. There was an additional distinct protein band at ~17 kDa marker in both TDP-43-HPIP and OPA-1-HPIP eluates. The same ~17 kDa protein band intensity was strong in flow through fractions. We do not know what these

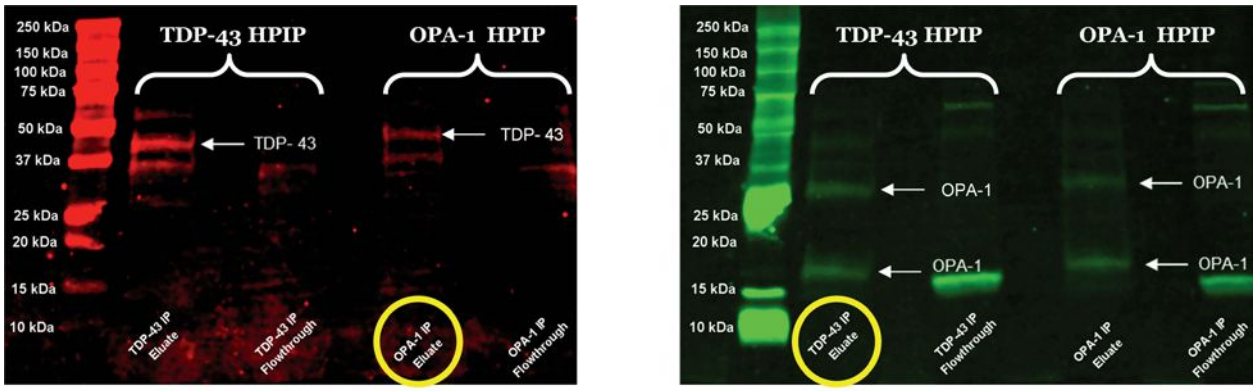


Figure 4. Co-immunoprecipitation profile of TDP-43 and OPA-1 in mitochondrial lysate.
(A) Both TDP-43 and OPA-1 HPIP eluates were resolved in 4-20% gradient SDS/PAGE under reducing conditions, and proteins were immunoblotted by anti-TDP-43 antibody. Both HPIP eluates were positively labeled with ant-TDP-43 antibody. It is important to note that OPA-1 and TDP-43 proteins were co-eluted.
(B) Both OPA-1 and TDP-43 HPIP eluates were resolved in 4-20% gradient SDS/PAGE under reducing conditions, and resolved proteins were immunoblotted with anti-OPA-1 antibody. Anti-OPA-1 antibody did not label its own protein immunoprecipitated by OPA-1 HPIP; instead, anti-OPA-1 antibody recognized two lower molecular weight proteins (25, kDa and ~ 17 kDa marker) in both HPIP eluates.

proteins are at present time. They don't seem to be fragmented TDP-43 since TDP-43 protein produces two major protein fragments, 35, and 25 kDa.[12] Anti-OPA-1 antibody did not perform well in terms of recognizing OPA-1 protein(s) pull down by OPA-1 HPIP (Figure 4B) whereas OPA-1 HPIP pulldown TDP-43 proteins (Figure 4A). We demonstrated that TDP-43 and OPA-1 physical interaction is possible under *in vitro* conditions; however, OPA-1 antibody did not label well the OPA-1 protein pulldown by OPA-1-HPIP. OPA-1 antibody, however, did recognize ~89 kDa protein in flow through fractions of both HPIP, indicating that OPA-1 is present in the sample, but not efficiently pulled down by HPIP (i.e. TDP-43 and OPA-1 HPIP). In addition, the mitochondrial lysate sample was not sufficient to perform effective HPIP. As a result, both TDP-43 and OPA-1 proteins are physically interacting in mitochondrial lysate obtained from human platelet. This interaction needs to be verified with a mammalian cell/tissue system where more mitochondria can be harvested.

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Disclosure

None reported. Artificial intelligence was not used in the study, research, preparation, or writing of this manuscript. **MM**

MSMA ANNUAL CONVENTION
2024 MSMA GENERAL SESSIONS



Friday, April 5 4:15 pm
Ballroom Level

Injections vs. Scalpels or Continuum of Care? Updates in Obesity Treatment

Speaker
Matthew B. Lindquist, DO, DABOM
Board Certified Obesity Medicince Specialist; Founder of University Health Weight Management, University of Missouri-Kansas City; UMKC Director of the Obesity and Nutrition Elective

Objectives
1. Explain treatment in context of chronic disease.
2. Recognize the patient's and physician's challenge with metabolic adaptation.
3. Describe treatment expectations.
4. Discuss current and future anti-obesity medications.
5. Identify who should be referred for surgery.
6. Compare outcomes with medications and surgery for obesity and diabetes.



Saturday, April 6 12:45 pm
Ballroom Level

Artificial Intelligence for Health Care

Speaker
Carl D. Dirks, MD
Assistant Professor, Department of Internal Medicine, University of Missouri - Kansas City

Objectives
1. Describe how to transform your health care organization and improve health outcomes using Artificial Intelligence (AI).
2. Discuss the fundamental concepts of AI for health care.



Saturday, April 6 2:00 pm
Ballroom Level

Managing Mental Health Disorders

Speaker
Erick Messias, MD, MPH, PhD
Chair, Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine

Objectives
1. Clarify the diagnoses of common psychiatric disorders.
2. Discuss first step in treating common psychiatric disorders.
3. Discuss the interplay between addiction and common mental health disorders.



Saturday, April 6 3:15 pm
Ballroom Level

Physician Employment Issues

Speaker
Richard Levenstein, Esq.
Attorney at Nason, Yeager, Gerson, Harris & Fumero, P.A., Palm Beach Gardens, Florida
Practice specialty: physician and medical staff representation and healthcare law
Adjunct Professor, Healthcare Law, Tulane University Law School, New Orleans, Louisiana

Objectives
1. Discuss current issues impacting physician employment.

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