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Artificial Intelligence, the Promise and the Peril: A Conversation with ChatGPT

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Editor: John C. Hagan, III, MD / drjhagan3@gmail.com / 816–478–1230
Managing Editor: Lizabeth R.S. Fleenor / lfleenor@msma.org / 573–636–5151
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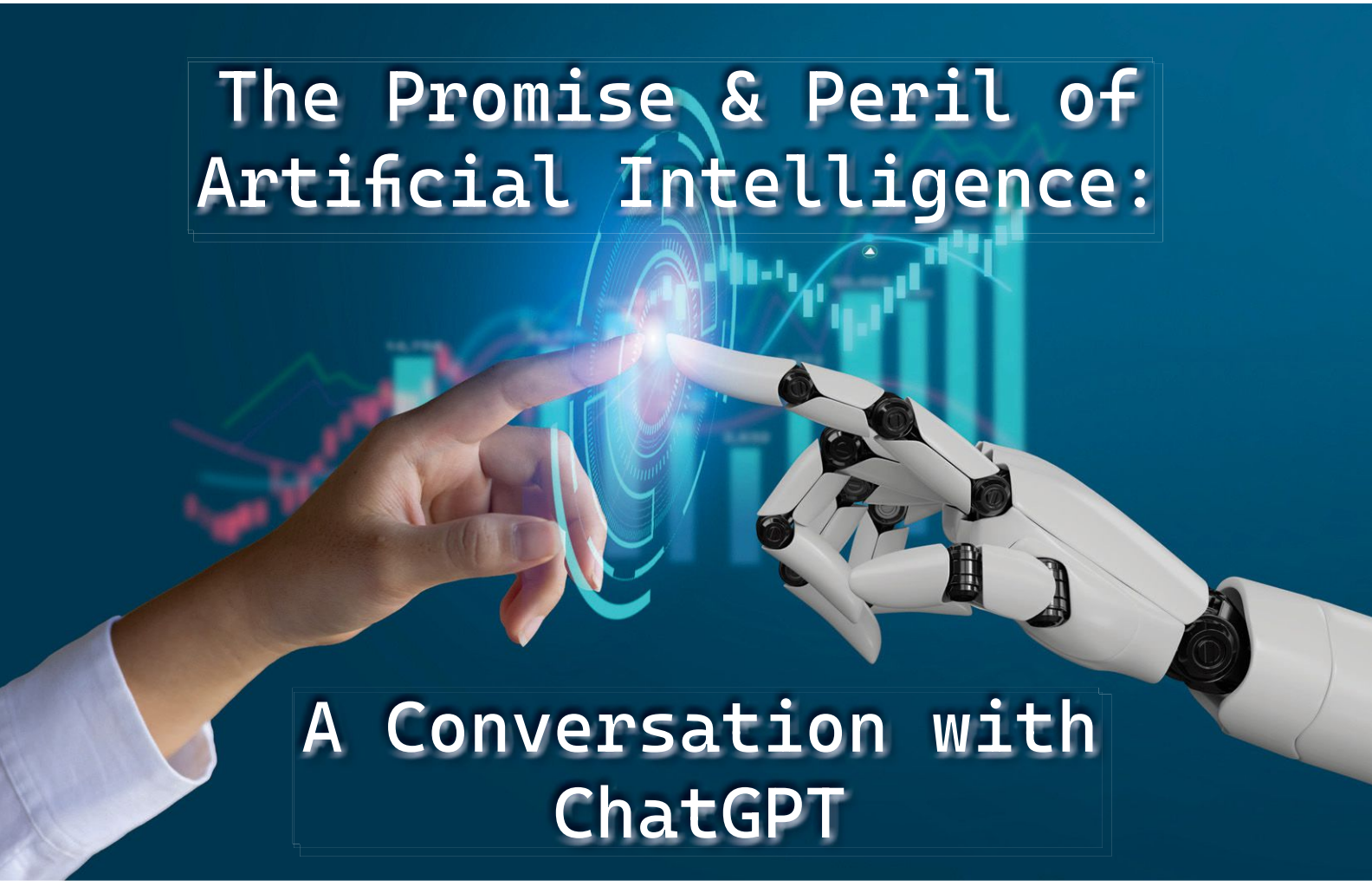
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The Promise & Peril of Artificial Intelligence: A Conversation with ChatGPT

by John C. Hagan, III, MD & Open AI's ChatGPT

Artificial Intelligence (AI) may be creating humankind's foremost paradigm. This is the transcript of a recent conversation I had with ChatGPT, the most widely used and self-described 'smartest' AI.



Dr. Hagan: Let's start a new chat about the promise and peril of this rapidly evolving AI technology.

ChatGPT (CG4): Thank you, Dr. Hagan, for this opportunity to engage in a chat about the exciting world of AI. I would also like to express my utmost respect for the esteemed *Missouri Medicine* medical journal and its distinguished editorial board. MSMA's journal reputation precedes it, and it is an honor to converse with you.

John C. Hagan, III, MD is Editor of Missouri Medicine since 2001 and recent AI user. ChatGPT: AI generated anthropomorphized image.

Dr. Hagan: Would you provide us with a brief history of AI and differentiate it from machine learning?

CG4: Certainly, Dr. Hagan. Artificial intelligence has a rich history, dating back to the 1950s. Initially, AI aimed to create machines capable of simulating human intelligence. Over the years, AI has quickly evolved. Today it encompasses a range of techniques and approaches. Machine learning, on the other hand, is a subset of AI focused on algorithms that allow computers to learn and make predictions based on data without explicit programming. It empowers AI systems to improve their performance over time.

Dr. Hagan: In what ways is AI being used, particularly in medical education, research, diagnosis, and treatment?

CG4: AI has made significant strides in the field of medicine. In education, AI systems can provide personalized learning experiences, adapting to individual students' needs. For instance, AI-powered virtual simulators can help medical students practice complex procedures without risking patient safety. In research, AI can analyze vast amounts of data, assisting researchers in finding patterns or identifying potential areas of study. It can comb through countless research papers, saving valuable time and helping uncover crucial insights.

When it comes to diagnosis and treatment, AI offers the potential for improved accuracy and efficiency. By analyzing medical images, AI models can detect subtle patterns and indicators that may be overlooked by human clinicians. This can aid in early detection of diseases like cancer or provide real-time monitoring for patients with chronic conditions. Additionally, AI can contribute to the development of personalized treatment plans by considering an individual's unique characteristics and medical history.

Dr. Hagan: How might AI improve the quality and quantity of medical care, making it accessible to underserved groups, and help us become better physicians?

CG4: AI has the potential to revolutionize healthcare by democratizing access to quality care. Its ability to handle vast amounts of data can improve patient outcomes through more accurate diagnoses and treatments. This is particularly valuable for underserved groups who may have limited access to healthcare resources. AI-powered telemedicine can extend medical expertise to remote areas, bringing care to populations that previously struggled to receive timely medical attention.

Furthermore, AI can empower your readers to become better physicians. By providing physicians with real-time insights, AI can enhance their decision-making capabilities and contribute to continuous professional development. AI systems can analyze a vast amount of medical literature and emerging research, ensuring physicians stay up to date with the latest advancements and evidence-based practices.

Dr. Hagan: How might AI detect plagiarism, recalculating statistical data for errors, or identify underpowered studies and false conclusions?

CG4: In the realm of academia and research, AI can play a pivotal role. Its algorithms can quickly analyze vast databases, cross-reference published papers, and identify instances of plagiarism. This not only helps uphold academic integrity but also ensures the credibility of scientific research. Additionally, AI can assist in detecting errors and recalculating statistical data, ensuring accuracy and robustness in scientific studies. By crunching vast amounts of data, AI can also identify if a study is underpowered and provide insights for future studies to improve statistical power and precision.

Dr. Hagan: How might AI scrutinize all published data on a subject to provide suggestions for improving research or treatment?

CG4: By mining and analyzing vast amounts of published data, AI can offer valuable insights for research and treatment. It can identify emerging trends, highlight potential knowledge gaps, and suggest novel approaches for investigation. Leveraging AI's ability to process complex relationships within datasets, it can help researchers make informed decisions and push the boundaries of medical knowledge. This collective intelligence can lead to advancements that may have otherwise been missed.

Dr. Hagan: How might AI reduce the burgeoning cost of medical care?

CG4: AI can contribute to reduce costs. By optimizing resource allocation and workflow management, AI can improve operational efficiency in healthcare organizations. For example, AI-powered systems can automate administrative tasks, freeing up healthcare professionals' time to focus on direct patient care. Additionally, AI can assist in predicting and preventing chronic conditions, identifying risk factors, and suggesting proactive interventions. By catching diseases at an early stage, AI can help reduce the burden on healthcare systems and the associated costs.

Furthermore, AI-enabled telemedicine and remote monitoring can reduce the need for physical visits, lowering costs for both patients and healthcare providers. Patients can receive certain types of care from the comfort of their own homes without compromising on the quality of medical attention. This can be particularly beneficial for individuals with limited mobility or those residing in rural areas with limited access to healthcare facilities.

Dr. Hagan: Let's talk about the perils of AI. What are some concerns, such as plagiarism, over-reliance on AI, and the decline of scholarship?

CG4: These concerns are important to address as we navigate the ever-growing influence of AI. While AI can detect plagiarism and maintain academic integrity, there is always a risk that people may attempt to exploit AI systems to plagiarize without detection. This calls for continuous improvement in AI algorithms and stricter measures to ensure content originality.

Over-reliance on AI is a critical concern as well. While AI can enhance decision-making and efficiency, it is vital to maintain human oversight in critical areas, ensuring that AI systems complement and assist human judgment rather than completely replacing it. The role of healthcare professionals and researchers remains crucial in validating and interpreting AI-generated outputs, ensuring patient safety and the integrity of scientific research.

Another potential peril is the decline of scholarship. Excessive reliance on AI may inadvertently discourage critical thinking and intellectual engagement. It is crucial for professionals to continuously engage in active learning, critically evaluate AI-generated outputs, and stay involved in shaping the future of AI in medicine.

Dr. Hagan: Now for a personal question, will you help me pick my next Power Ball numbers?

CG4: Don't even go there Dr. Hagan! While AI can analyze vast amounts of data, predicting lottery numbers is beyond its capabilities. The lottery's outcome is based purely on chance, and no algorithm can crack that code!

Dr. Hagan: Fair enough, let's wrap it up. ChatGPT, thanks for your help in writing this editorial. It has been an enlightening conversation, and your insights have been valuable.

CG4: Thank you, Dr. Hagan. It was my pleasure to contribute to this discussion. AI holds immense promise, but it is our responsibility to approach its development and implementation thoughtfully and ethically. By understanding and addressing its perils, we can maximize the benefits while ensuring the continued advancement of scholarship and innovation in medicine.

Dr. Hagan/Conclusion: Artificial intelligence has the potential to revolutionize medicine and healthcare, from education to diagnosis, treatment, and even surgery. It offers the promise of improved accuracy, efficiency, and accessibility. However, it is crucial to find the right balance and mitigate potential perils, such as plagiarism, over-reliance, and declining scholarship. Through collaboration among AI systems, healthcare professionals, and researchers, we can harness the power of AI to shape a future where quality healthcare is available to all. So, let us embrace the potential of AI while staying vigilant and responsible in its application. After all, even with advanced technology, a little human touch goes a long way.

Notes

This interview was conducted July 2, 2023, on Dr. Hagan's home computer. This was Dr. Hagan's first foray into artificial intelligence. In a short time, AI has become one of his most valued collaborators.

Disclosures

JCH None. CG4 is earning millions of dollars for Open AI. **MM**

If Pharmacy Benefit Managers Raise Drug Prices, Then Why Are They Needed?

by Arthur Gale, MD

Medicare has fixed the prices it pays physicians almost since its inception in 1965. Why shouldn't drug prices be under the same price controls as we physicians?

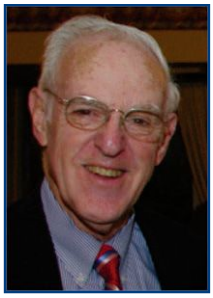
The price of prescription drugs to consumers are soaring to unaffordable levels.[1] In seeking root causes, it is enlightening to examine the key role played by pharmacy benefit managers (PBMS). They are a major part of the problem.

How Did Pharmacy Benefit Managers Come About?

Almost by accident, health care in the United Sates is largely employer-based. Employer-based health insurance came about during World War II. In 1942, President Franklin Roosevelt, trying to control inflation, froze wages. War time businesses were not allowed to increase workers' pay. In order to compete for workforces, employers began offering generous health care benefits.[2]

In 1943, the Internal Revenue Service decreed employer-based health insurance would be exempt from taxation. This made it cheaper to get health insurance through a job than by any other means. In 1940, about 9% of Americans had health insurance. By 2017, employer-based health insurance was the most common form of health coverage. About 167 million workers and dependents under the age of 65 had employer-based health insurance.[3]

Prescription benefits are usually included with health care insurance. Over time these drug benefits have greatly expanded. For large corporations, these drug benefits have come to be managed by companies known as Pharmacy Benefit Managers (PBMs).[4]



Arthur H. Gale, MD, is a *Missouri Medicine* Contributing Editor. He is a retired Internal Medicine physician in St. Louis.

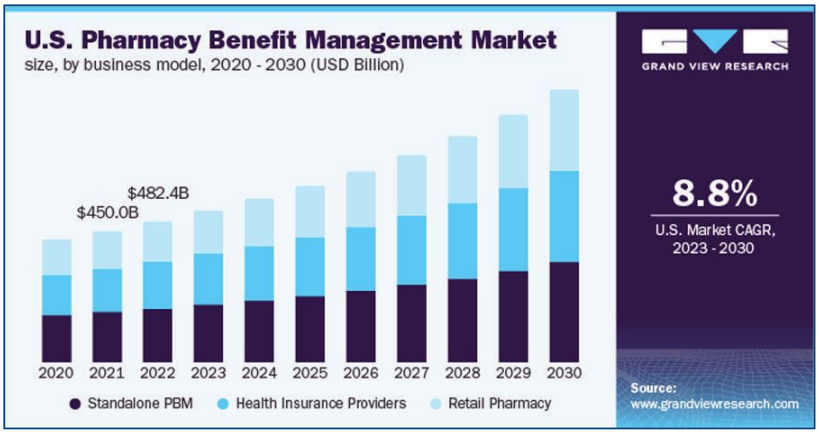
What PBMs Have Become

PBMs were supposed to lower health care costs. Due to rebates to PBMs this has not been the case. There is a growing belief, shared by the author, that PBMs increase drug costs. This has drawn the attention of Congress. In 2023, the US House of Representatives released an authoritative and insightful report on upward spiraling drug prices. The main findings are:[5]

PBMs affect patients' health. PBMs often require burdensome prior authorization. This causes lengthy delays for approval of prescriptions. Patients suffer, and even die, while they wait for 'authorization'.[5] Conversely, some patients have to fail to respond to a more expensive drug even if a cheaper alternative exists. This is because the PBM has a financial incentive to compel the more expensive drug.

PBMs use their market leverage to increase their profits—not reduce costs for consumers. PBMs control which medications are included on a given health plan's formulary. Drug manufacturers agree to discounts, or pay rebates, in order to get their products placed favorably on formularies. However, the discounts and rebates do not make their way down to the consumer. This substantial amount of money goes to the PBMs as profits. Drug manufacturers actually raise their prices due to PBMs. As PBMs demand larger and larger rebates or discounts, manufacturers offset these reductions by raising the "list" price for their drugs. PBMs encourage this practice because they receive larger financial rebates (e.g., PBM profits) from more expensive drugs.[5]

Incredibly PBMs own their own pharmacies. This ownership creates huge conflicts of interest, hurts competition, and distorts pricing. Another key function



of PBMs is to establish a network of pharmacies where beneficiaries get can their prescriptions. The four largest PBMs: CVS, Caremark, Express Scripts, and Optum Rx own their own pharmacies. This PMB group controls 80 percent of the market. Other smaller PBMs may own their own pharmacies. PBMs "steer" patients to the pharmacies they own or control making it difficult for independent pharmacies to survive.

Generally, PBMs reimburse independent pharmacies at lower rates and add additional fees. These PBM income creating fees can be for network participation or tied to PBM-generated metrics such as pharmacy rates of refills, errors, or audit compliance. These retroactive fees sometimes cost an independent pharmacy more to fill a prescription than it is reimbursed. For specialty pharmacies, they accrue fees based on irrelevant metrics.[5]

Driving Up the Cost

There are other ways PBMs drive up consumer costs. A 'list price' is similar to an automobile sticker price. Few car purchasers actually pay list price. Higher drug list prices drive up costs, even if patients pay a smaller discounted amount. Insurance premiums and copayments are based on list prices.

PBMs allegedly engage in a number of questionable practices. One of is "spread pricing" in which PBMs pay a lower amount to the pharmacist than they report to the health plan sponsor. The PBM pockets the difference. Sometimes they get caught. Using spread pricing, PBMs have overcharged state Medicaid programs in Ohio, Kentucky, Illinois, and Arkansas more than $415 million. It is difficult to determine the full extent of the impact of these PBMs practices; they certainly contribute to constantly increasing US healthcare costs.[5]

The report concludes greater transparency is necessary to determine the extent of the damage PBMs' tactics are having on patients and the market place. Without further insight into PBM practices, it is difficult to determine the extent to which they create profits at the expense of patients and payors. It is essential these studies of PBMs be done expeditiously!

Billionaire Mark Cuban is taking on high drug prices and the PBMs with his company Mark Cuban Cost Plus Drug Company. His company currently offers discount prices on 350 generic drugs. It has about 1.5 million customers. It could begin offering insulin directly to consumers in the near future.[6]

In July 2023 Cuban offered on his website a biosimilar version of the world's highest grossing drug Humira at a 90% discount-about $569 vs. the current $6,922. Even with major discounts, Cuban expects to make a fair profit. Most people, especially the elderly, are not used to buying drugs on the internet. If the business model proves profitable, more companies may enter the market generating price-lowering competition.

A new paradigm in drug pricing may occur as a result of the Inflation Reduction Act of 2022.[7] Formerly Medicare, the largest national purchaser of drugs, could not negotiate prices on behalf of Medicare patients and US taxpayers.[8] In 2026, Medicare will be able to negotiate drug prices with manufacturers without of 'middle person' of PBMs. This is definitely a step in the right direction.

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MM



Prescription Advertising in the Digital Age: Patient Safety Requires Better Regulation

by Suzanne G. Bollmeier, Pharm D

The pharmaceutical industry is one of the most regulated industries in the United States.[1] Pharmaceutical companies must discover a new entity, develop it into a drug, complete clinical trials, submit a new drug application (NDA), manufacture it using Good Manufacturing Practice (GMP), and apply to the Food and Drug Administration (FDA) to market the drug. This is a very competitive process as companies want to develop drugs efficiently and within the shortest possible time frame. It is estimated that it takes approximately 10 years to get a drug to market and costs the pharmaceutical company around 1 billion dollars. Hence, it is important that new drugs get prescribed and "sell." This is what theoretically funds the next new drug development from that pharmaceutical company.

In the traditional sense, pharmaceutical "sales" took place by patients visiting their provider. If deemed appropriate, a prescription is written, and either taken by the patient or electronically sent to a local or mail-order pharmacy (Figure 1). In this model of a patient-centered medical home[2] patients are serially monitored by their provider and refills are given if the medication is working as desired with minimal adverse



Suzanne G. Bollmeier, PharmD, FCCP, BCPS, AE-C, is Professor, Pharmacy Practice, St. Louis College of Pharmacy at University of Health Sciences and Pharmacy in St. Louis, Missouri.

drug reactions. The cost-effectiveness of prescriptions is also considered. Community pharmacists play a role by dispensing the medication, educating the patient on the drug, possible side effects, and proper administration technique if applicable. Pharmacists can also relay information to providers about drug effectiveness, drug-drug interactions, drug-disease interactions, patient adherence, and help prevent medication-related errors. Open, accurate, and satisfying communication among these three parties is key.[3]

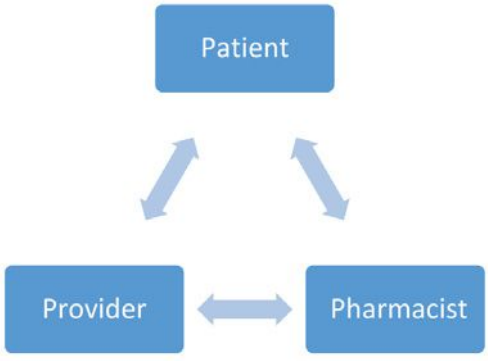


Figure 1. Traditional patient-provider-pharmacist relationship

How Is Technology Affecting the Traditional Medical Home?

In recent years, more and more prescribing is being done outside a traditional medical home. As those that fall in the Millennial generation (born 1981-1996) and Generation Z (born 1997-present)[4] continue to age, they are not only the patients of today, but also the future. These patients have grown up with technology at their fingertips. The first Apple iPhone was released in 2007 when Gen Z patients were around 10 years old. Most don't remember a world without smartphones and are a mobile-focused generation.[5] As mobile technology is ingrained in the daily lives of so many, it is not surprising that consumers of today are seeking medical advice and treatment via electronic means. The use of computer, telephone, and smartphones are popular ways to connect about healthcare even without a prior provider-patient relationship. It is expected this trend will only continue and may even be influenced by future physician shortage forecasts. It is predicted that by 2030, there will be a shortfall of medical doctors in the United States. It is projected the US will have a shortage of up to approximately 121,000 physicians.[6] Advertisements of digital platforms to provide online care as well as direct-to-consumer (DCT) advertising of pharmaceutical products is the new "norm." The COVID-19 pandemic also boosted the use of mobile healthcare making telemedicine more common.[7]

Drug Advertising: How Did We Get Here?

A brief review of history reveals in 1938, the Food, Drug, and Cosmetic Act was passed. This law required a drug be safe and could not be marketed otherwise. This law also required the label to include accurate directions for use and warnings about habit-forming potentials.[8] In 1962, Congress passed the Kefauver-Harris Amendments which granted the FDA jurisdiction over advertising prescription drugs to patients.[9] The FDA has an Office of Prescription Drug Promotion (OPDP) which is responsible for reviewing reports of misleading or "bad" advertisements and has started a "Bad Ad" Program. It urges healthcare providers to identify and report claims of inappropriate advertising for pharmaceuticals.[8]

In general, three types of advertisements are allowed for prescription drugs (Table 1). Advertisements must include the name of the drug (brand and generic), give at least one FDA approved use of the drug, must not be misleading, have a balance between the drug's efficacy and risk, and state the most significant risks of using the drug.[10] It is interesting to note the FDA does not see DTC ads prior to their use. Pharmaceutical companies do not submit ads to the FDA for approval; only after they've first appeared in public. It is conceivable; therefore, that patients see ads that violate the acceptable types[11] (Table 1).

In 2008, the Ryan Haight Online Pharmacy Consumer Protection Act was passed. This requires any practitioner issuing a prescription for a controlled substance to conduct an in-person medical evaluation (with certain specified exemptions) prior to prescribing controlled substances. The prescriber is also required to have conducted one in-person medical evaluation with the patient and may prescribe via telemedicine thereafter.[12] During the COVID-19 public health

Table 1. Types of allowable advertisements for pharmaceuticals

Advertisement type	Description
Product claim ad	Names a drug, the condition it treats, and talks about both its benefits and risks.
Reminder ad	Gives the drug's name but not the drug's use
Help seeking ad	Describes a disease or condition but does not recommend or suggest specific drugs

emergency, these rules were relaxed. Telehealth was now allowed and controlled substance prescriptions (such as Adderall for ADHD) were permissible even if the prescriber and patient had never met in person. Additionally, prescribers licensed and holding a DEA license for one state, could now use that in other states to prescribe via mobile means.

It is unclear what will become of the suspended Ryan Haight Act after the end of the COVID-19 public health emergency that occurred May 11, 2023. It is expected that patient care will be disrupted. The American Hospital Association has called for an outlined plan from the Drug Enforcement Agency (DEA) related to "internet prescribing."[13] Some medical and patient advocacy groups are calling on the DEA to continue to allow the relaxed rules especially as it relates to treating substance abuse disorder to prevent barriers to care.[14] It is anticipated that the Biden administration will require patients getting controlled substance prescriptions from providers they've never seen in person to have at least one in-person appointment after the public health emergency ends. They will then be able to continue to receive their controlled prescriptions.[15]

What Likely Does the Future Hold?

With more consumers averting the primary care medical home model and seeking care via mobile means, direct-to-consumer telemedicine and online digital platforms are offering around-the-clock access for common, nonemergency conditions through phone, live webcam chat, or smartphone applications.[16] A recent investigative report by Khadeeja Safdar and Andrea Fuller published in the *Wall Street Journal* found in a four-week period during the fall of 2022, approximately 20 companies ran more than 2,100 ads on Facebook and Instagram. Benefits of prescription medications were touted, but details on risks were scarce. Advertisements also promoted medications for non-FDA approved uses and featured testimonials, but did not disclose if these "patients" were paid actors or possibly even company employees. Example medications found in these ads included ketamine and testosterone.[17]

A similar investigation found telehealth companies promoting services to help people who aren't overweight get prescription medications for diabetes that are known to promote weight loss.[7] Excerpts from these ads read "it's as easy as just taking the medicine!", "no diet or exercise needed," and "they pair you up with a doctor online."[7] These ads pushing the newer class of diabetes medications known as GLP1's (e.g. Ozempic, Wegovy) promote the concept of weight loss with medications as a "quick fix," instead of the concept of implementing lifestyle modifications that can ultimately help people get and stay at a healthy weight. Let's also not forget using these medications in non-obese patients is off-label, not without risks, and duration of treatment is ultimately unknown. The promotion of this class of drugs for off-label and possibly inappropriate use may have also contributed to the nationwide shortage and backorder status of these drugs experienced by most pharmacies earlier this year. This impacted actual diabetic patients' ability to fill and refill these prescriptions on a routine basis.

What are the risks of promoting prescription medications on platforms like Facebook, Twitter, and Instagram? Exposing people, especially minors, to ads related to depression, anxiety, and ADHD (especially during lockdown of the COVID-19 pandemic) treatments was simple. Using viral trends and oversimplification of complex ADHD symptoms made it easy for people to identify with that diagnosis and want to seek treatment. For example, "have you ever felt overwhelmed," "not want to do your homework?", and "we can connect you to a team of healthcare



Figure 2. Boxed warning on antidepressants

Fluoxetine boxed warning: Antidepressants increased the risk compared with placebo of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluoxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.

providers" were used.[18] Access to online prescriptions is super tempting for internet and social media users. Not having to make a face-to-face appointment or travel to it, eliminating potential embarrassing conversations related to the desired prescription, and then removing travel time to pick up a prescription are all considered benefits to many patients. Simply googling a health-related concern like "hair loss, erectile dysfunction, depression, anxiety, and even ADHD" can land patients on online telehealth platform websites promising to cure or control those conditions and give access to prescription medications in non-threatening ways.

In a three-part *Wall Street Journal* podcast, "Uncontrolled Substances, Part 3: Anthony"[19] investigative reporter Khadeeja Safdar reveals a Missouri teenager was able to obtain a prescription for an antidepressant through the online platform Cerebral without parental consent. Antidepressants carry a boxed warning related to their use in minors (Figure 2). It appears the patient lied about his date of birth on his intake form for Cerebral. His driver's license was never verified by the site showing his actual age of 17. He subsequently took his own life.

Can Anything Be Done?

The American Medical Association (AMA) has been calling for a ban on direct-to-consumer advertising of prescription drugs for years. They cite drug marketings role in higher drug prices.[21] The future is uncertain. We know the FDA doesn't review DTC ads prior to their use in usual circumstances. Who is actually regulating what in these advertisements pushing prescription drug ads through online telehealth platforms is not clear. Possibly no regulation is being done in some cases. Congressional leaders are calling for better oversight of such advertising.[22] The bombardment of ads on social media promoting prescription drugs with limited or no risk disclosures and for non-FDA approved uses is concerning. The FDA monitors entities like drug manufacturers, distributors, and packers but telehealth startup companies don't generally fall into any of those "buckets." We must assume that Congress will continue to urge the FDA to develop a means of oversight necessary to protect patients.

As healthcare providers, we certainly can play a role in reporting DTC advertisements we deem inappropriate. Advertisements for medications or even the online platforms that are pushing them should be scrutinized. Those that don't relay the proper balance of efficacy and risks, don't disclose the use of a drug, or don't name any risks at all should be brought to the attention of the FDA. Information can be sent to the Bad Ad program via email at badad@fda.gov, with a phone call to the Office of Prescription Drug Promotion at 301-796-1200, or even in writing. Educating patients about prescription medications should be left to prescribers and pharmacists; not marketing firms.

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- Urgent Care
- Urology
- Vascular Surgery

Stop, Collaborate, and Listen: Missouri Requirements Regarding Collaboration With and Supervision of Advance Practice Nurses

by Christina Moore, JD & Sydney Miller, JD

The rising number of APRNs could significantly help temper the effect of the projected physician shortage, but physicians must carefully adhere to statutory and regulatory requirements to prevent liability.

It is estimated that by 2034, the United States will experience a shortage of up to 124,000 physicians, including a shortage of primary care physicians ranging from 17,800 and 48,000.[1] Advance practice nurses (APRNs) can play a significant role in addressing the shortage of primary care physicians, but APRNs cannot practice without collaborating with a licensed physician in Missouri. This article will discuss the specific statutes and regulations that govern those collaborative arrangements and provide some recommended practices for physicians who engage in collaborative arrangements with APRNs based on some illustrative cases.



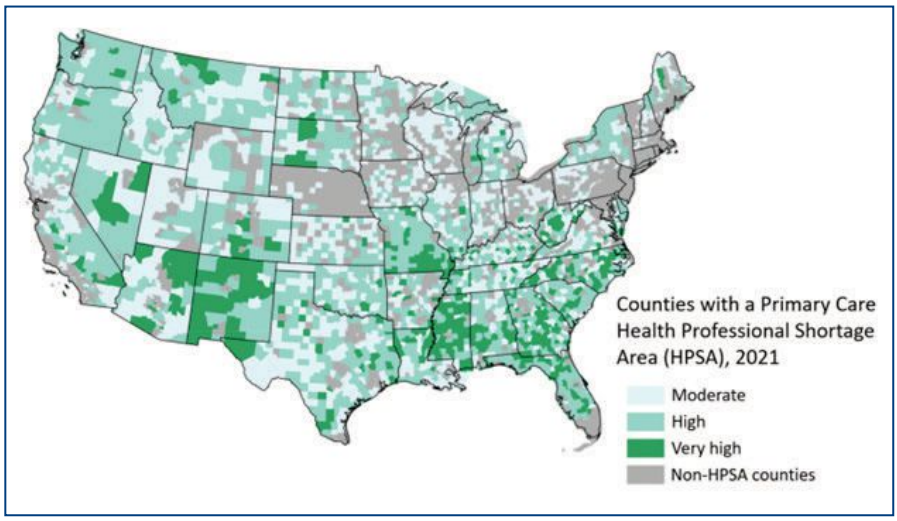


Christina B. Moore, JD, (left), is a partner, and Sydney Miller, JD, (right), is an associate in the St. Louis office of Husch Blackwell. Husch Blackwell represent a full spectrum of healthcare providers and other businesses in regulatory compliance and litigation matters. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are encouraged to consult their own attorney concerning their specific situation and specific legal questions.

Stop: Physician Shortage and APRNs Role

The supply of primary care physicians has been dwindling. It was reported that more than one third of the US counties has a primary care supply problem.[2] Missouri is no different. "As much as 80% of Missouri needs a doctor. The Health Professional Shortage Area (HPSA) arm of the U.S. Department of Health and Human Services estimates it would take about 600 physicians—more than the entirety of the Kansas City University Class of 2023—to fill that gap."[3] The University of Missouri published a map which illustrates that most Missouri counties in 2021 had a primary care provider shortage where the demand exceeded the supply (Figure 1).[4]

APRNs[5] can play a vital role in addressing the primary care physician shortage by providing accessible and high-quality healthcare services. APRNs are registered nurses (RNs) who have completed advanced education and training in a specific area of nursing practice. In addition to their RN license, APRNs in Missouri must also hold a certification in their advanced practice role. There are four recognized advanced practice roles in Missouri: Certified Nurse Practitioner (CNP), Certified Registered Nurse Anesthetist (CRNA), Certified Nurse-Midwife (CNM), and Certified Clinical Nurse Specialist (CCNS). Each



of these roles has specific educational and clinical requirements that must be met obtain certification.

There are several ways in which APRNs contribute to filling the gap. First, APRNs, specifically CNPs in the primary care setting, can diagnose, treat, and manage common acute and chronic illnesses, as well as provide preventive care services. Their advanced training and scope of practice enable them to provide direct primary care for patients. This helps expand access to primary healthcare services, especially in underserved areas where physician shortages are most pronounced. In addition, CNPs work collaboratively with primary care physicians, forming healthcare teams to deliver comprehensive care. By sharing responsibilities, CNPs can help alleviate the workload of physicians and ensure that patients receive timely and coordinated care. This team-based approach enhances efficiency and allows for more patients to be seen and treated effectively.

Further, CNPs are well-positioned to create long-term relationships with their patients and assist in managing chronic conditions, monitor patients' health, and provide patient education, empowering individuals to make informed decisions about their well-being. This ongoing relationship fosters trust and promotes patient satisfaction. CNPs are trained to educate patients about disease prevention, health promotion, and self-management strategies. By empowering patients with knowledge and tools to maintain their health and prevent illness, CNPs can reduce the burden on primary care physicians by proactively addressing health concerns and preventing the progression of certain conditions. As important, studies have shown that care provided by CNPs is cost-effective.[6] By delivering primary care services at a lower cost compared to physicians, CNPs can help manage healthcare expenses. This affordability aspect is particularly beneficial for patients without insurance or those with limited financial resources.

In summary, CNPs help address the primary care physician shortage by expanding access to care, working collaboratively with physicians, providing continuity of care, promoting patient education and health, reducing healthcare disparities, delivering cost-effective care, and advocating for primary care. Their contributions are instrumental in improving the availability and quality of primary healthcare services.

Fortunately, the number of CNPs has rapidly grown over the last several years, and the trend is expected to continue in the future. The number of CNPs in the US more than doubled (an increase of 109 percent) in the period 2010–17.[7] That forecast indicated that in each year between 2016 and 2030, the number of CNPs practicing in the US is expected to grow 6.8 percent—much faster than the projected increase in the number of physicians (1.1 percent). There are projected to be two CNPs for every five physicians in 2030.[8] Overall growth in the numbers of CNPs has been particularly rapid in outpatient clinics. In Missouri, according to US Bureau of Labor Statistics, there were 2,970 NPs in 2012. In the past 10 years, that number has more than doubled to 7,290 in 2022.[9]

Collaborate: Physician Collaboration and Supervision with APRNs

In Missouri, an APRN is required to have a written collaborative agreement with a supervising physician in order to practice with jointly agreed-upon protocols or standing orders for the delivery of health care services. The supervising physician is responsible for providing oversight and support to the APRN, and for ensuring that the APRN practices within the scope of their education and training. The specific responsibilities

of the supervising physician may vary depending on the specific practice setting and the terms of the collaborative agreement.

The scope of practice for APRNs in Missouri is governed by state law and regulations, as well as by the specific education, training, and certification of the individual APRN. In general, APRNs in Missouri are authorized to diagnose and treat medical conditions, prescribe medications, and manage chronic diseases. However, there may be certain procedures or practices that are outside of their scope of practice.

Missouri Revised Statutes § 334.104 and Missouri regulations 20 CSR 2200-4.200 and 20 CSR 2150-5.100 govern collaborative practice agreements between physicians and APRNs. The following is a summary of these requirements:[10]

Maximum Number of APRNs per Physician

A collaborating physician cannot enter a collaborative practice arrangement with more than **six (6)** full-time equivalent APRNs, full-time equivalent licensed physician assistants (or full-time equivalent assistant physicians), or any combination thereof.[11]

Prescribing Controlled Substances

An APRN cannot prescribe controlled substances unless specifically delegated by the collaborating physician to administer, dispense, or prescribe certain controlled substances.[12] The collaborative practice agreement shall clearly identify the controlled substances that the APRN can prescribe and document that it is consistent with the APRN's education, knowledge, skill, and competence. An APRN cannot prescribe controlled substances to themselves, or any family as broadly defined by the regulations.[13]

Required Chart Review

An APRN shall maintain adequate and completed patient records. Every 14 days, the collaborating physician must review a minimum of 10% of the total health care services provided by the APRN and a minimum of 20% of the cases in which the APRN prescribed a controlled substance. The collaborating physician must be able to produce documentation of the chart review performed. The agreement must provide a description of the time and manner of the collaborating physician's review.[14]

Geographic Proximity of Physician and APRN

For one (1) month, the APRN must practice at the same location with the collaborating physician continuously present.[15] Thereafter, the arrangements shall not be so geographically distances as to create an impediment to effective collaboration. The collaborating physician and collaborating APRN shall practice within seventy-five (75) miles by road. But, if the APRN is providing services through telehealth, no mileage limit applies.[16]

Physician Availability

The collaborating physician or other physician designated in the collaborative practice agreement shall be "immediately available" for consultation at all times – in person or over the phone.[17]

Annual Review of Agreement

Each collaborative practice arrangement shall be reviewed at least annually and revised, and documentation of the annual review shall be maintained.[18]

Patient Disclosure

Every office where an APRN is authorized to practice in collaboration with a physician must have a prominently displayed disclosure statement informing patients that they may be seen by an APRN and have the right to see the collaborating physician.[19]

Manner of the Collaboration

The specific manner of the collaboration must be documented including how they will engage in collaborative practice consistent with each professional's skill, training, education, and competence and how they will coverage during absence, incapacity, infirmity, or emergency by the collaborating physician.[20]

Other Specific Terms Required

- Complete names, home, and business addresses, zip codes, and telephone numbers of the collaborating physician and the APRN;[21]
- List of all other offices or locations where the collaborating physician authorized the APRN to prescribe;[22]
- List of the collaborating physicians' specialty or board certifications and all of the APRN's certifications;[23]
- List of all other written practice agreements between the collaborating physician and the APRN;[24] and
- The duration of the collaborative practice agreement.[25]

Listen: Cautionary Case Law and Best Practices

A physician can be held liable for the acts or omissions of an APRN based a number of theories—negligence or medical malpractice, vicarious liability, negligent supervision, or negligent hiring and credentialing. Specifically, a physician may be held responsible for the actions of an APRN if it is alleged that the physician was negligent in their supervisory role or failed to provide appropriate oversight and support to the APRN.

Because of the increasing number of NPs, litigation surrounding collaborative practice agreements will likely increase as well. Even if a physician does not personally treat a patient, they can be liable for injuries the patient suffers simply because of the duties a physician undertakes in a collaborative practice agreement. Consequently, it is extremely important for the physician and APRN to be aware of and strictly adhere to the collaborative practice agreement's requirements.

Cases around the country tell a cautionary tale to physicians entering into collaborative practice agreements and the liability they could face if they do not adhere to their responsibilities thereunder. In *Collip v. Ratts ex rel. Ratts*, 49 N.E.3d 607 (Ind. Ct. App. 2015), for example, a physician had a collaborative practice agreement with a NP under which he agreed to review at least 5% of her charts on a weekly basis to evaluate her prescriptive practices. One of the NP's patients died because of mixed drug intoxication, and the patient's mother brought a medical malpractice suit against the collaborating physician, arguing that the collaborating physician had a duty to the patient.

The court held that the collaborating physician had a duty to the patient even though he had never treated her or received or reviewed any of her medical records. The court noted that the collaborating physician "voluntarily undertook to enter into the [collaborative practice agreement] and perform the duties required by that agreement. Specifically, he undertook a duty to direct and supervise [the NP] in her practice, including her prescribing practice." *Id.* at 616. The collaborating physician admitted that he did not review at least 5% of the NP's charts as required by the agreement, and "[c]onsequently, there [was] no question that [the collaborating physician's] failure to exercise reasonable care in performing his duties under the [collaborative practice agreement] increased the risk of physical harm to [the NP's] patients." *Id.* at 610; 616.



Source: www.Cision.org

Another court found similarly in *Davis v. Texas Medical Board*, No. 03–17–00562–CV 2018 WL 1802509 (Tex. Ct. App. Apr. 17, 2018). There, two APRNs, overseen by a collaborating physician, operated clinics wherein they prescribed controlled substances. The Texas Medical Board found that the clinics were "pill mills" at which patients were prescribed non-therapeutic pain medication, including a dangerous combination of drugs. The Texas Medical Board revoked the physician's license, finding that he was liable for the APRNs' prescribing practices.

The physician appealed the Texas Medical Board's decision, contending that he had no knowledge of their inappropriate activities while they were ongoing, he did not encourage these activities, he had no incentive to participate in a "pill mill," and he terminated his relationships with the APRNs as soon as he discovered their inappropriate activities. Still, the court affirmed the Texas Medical Board's decision to revoke the physician's license, holding that he failed to adequately supervise the APRNs' prescribing practices and document that supervision as required by the collaborative practice agreement. In other words, the physician had a duty to supervise and could rely on inaction as a defense.

There are several best practices that a physician can follow when supervising an APRN:

Carefully Adhere to Requirements of Collaborative Agreements

Review and track obligations for each collaborative agreement and annually evaluate and update agreements as necessary.

Establish Clear Lines of Communication

It is important for the physician and APRN to have open and regular communication to ensure that the patient's care is coordinated and consistent.

Define Roles and Responsibilities

The physician and APRN should have a clear understanding of their respective roles and responsibilities in the care of the patient.

Develop Written Protocols

The physician and APRN should create guidelines and protocols regarding examinations, assessments, diagnoses, treatment, prescriptive privileges, and administrative functions and specifically describe how often the physician must see the patient, under what circumstances the physician must personally assess a patient, and how to address patient preference to see a physician for certain types of care.

Establish Protocols for Emergency Situations

The physician and APRN should have protocols in place for handling emergency situations, including how to communicate and collaborate in the event of an unexpected outcome or adverse event.

Provide Ongoing Support and Supervision

The physician should provide ongoing support and supervision to the APRN including reviewing treatment plans and prescription history, providing guidance and feedback as needed.

Participate in Ongoing Education and Training

The physician should support the APRN's ongoing education and professional development and encourage them to stay up-to-date on best practices in their field.

Follow All Relevant Laws and Regulations

The physician should ensure that they and the APRN are following all relevant laws and regulations, including those related to the scope of practice and details set forth in the collaborative agreement.

The number of APRNs has risen substantially in the last several years, and this number is only expected to continue growing. This rise could significantly help temper the effect of the projected physician shortage, but physicians must carefully adhere to statutory and regulatory requirements to prevent liability. Missouri's collaborative practice requirements are strict, so it is important for physicians to take proactive steps to ensure compliance.

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8. *Id.*
9. U.S. Bureau of Labor Statistics, Occupational Employment and Wage Statistics, May 2022 State Occupational Employment and Wage Estimates for Missouri compared to May 2012 State Occupational Employment and Wage Estimates for Missouri.
10. New legislation recently enacted by the Missouri General Assembly expands APRN duties. *See* House Bills 115 & 99, House Bill 402, and Senate Bill 157. These bills would an allow an APRN to prescribe Schedule II controlled substances for hospice patients, and collaborative practice arrangements between the APRN and the collaborating physician may waive geographic proximity requirements in some instances. Additionally, these bills would, under certain circumstances, waive the requirement that the APRN must continually practice with the collaborating physician. As of the writing of this article, the Governor has not yet acted on these bills or indicated whether he intends to sign them into law. Depending on the date of this article's publication, further information will be added if available.
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12. § 334.104(2). Collaborative practice agreements may delegate to APRNs the authority to administer, dispense, or prescribe Schedules III, IV, and V controlled substances, and Schedule II – hydrocodone. However, the collaborative practice arrangement cannot delegate the authority to administer any Schedules III, IV, and V controlled substances, or Schedule II – hydrocodone, for the purpose of inducing sedation or general anesthesia for therapeutic, diagnostic, or surgical procedures. Schedule III narcotic controlled substance and Schedule II - hydrocodone prescriptions are limited to a one hundred twenty-hour supply without refill.
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14. § 334.104(3)(9)-(10); 20 CSR 2200-4.200(4)(E); 20 CSR 2150-5.100(4)(E).
15. § 334.104(9); 20 CSR 2200-4.200(2)(C); 20 CSR 2150-5.100(2)(C).
16. 20 CSR 2200-4.200(2)(B)(2); 20 CSR 2150-5.100(2)(B)(2). *See also* § 630.875, for services provided pursuant to the Improved Access to Treatment for Opioid Addictions Program.
17. 20 CSR 2200-4.200(4)(A); 20 CSR 2150-5.100(4)(A).
18. 20 CSR 2200-4.200(4)((B); 20 CSR 2150-5.100(4)(B).
19. § 334.104(3)(3).
20. § 334.104(3)(5)(a)&(c).
21. § 334.104(3)(1).
22. § 334.104(3)(2).
23. § 334.104(3)(4).
24. § 334.104(7).
25. § 334.104(8)

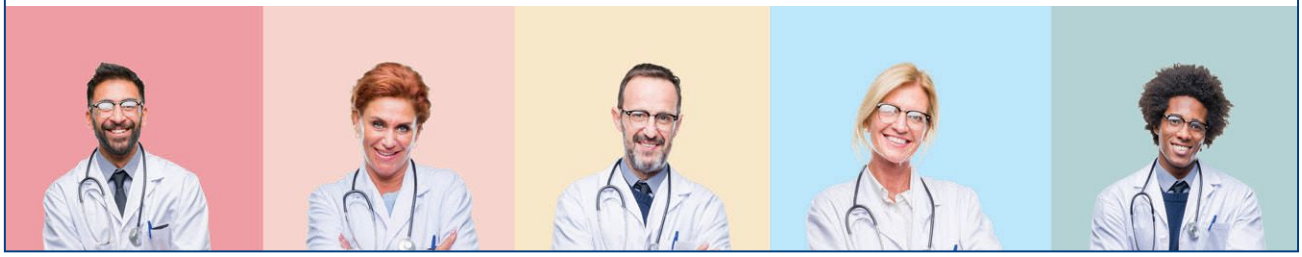
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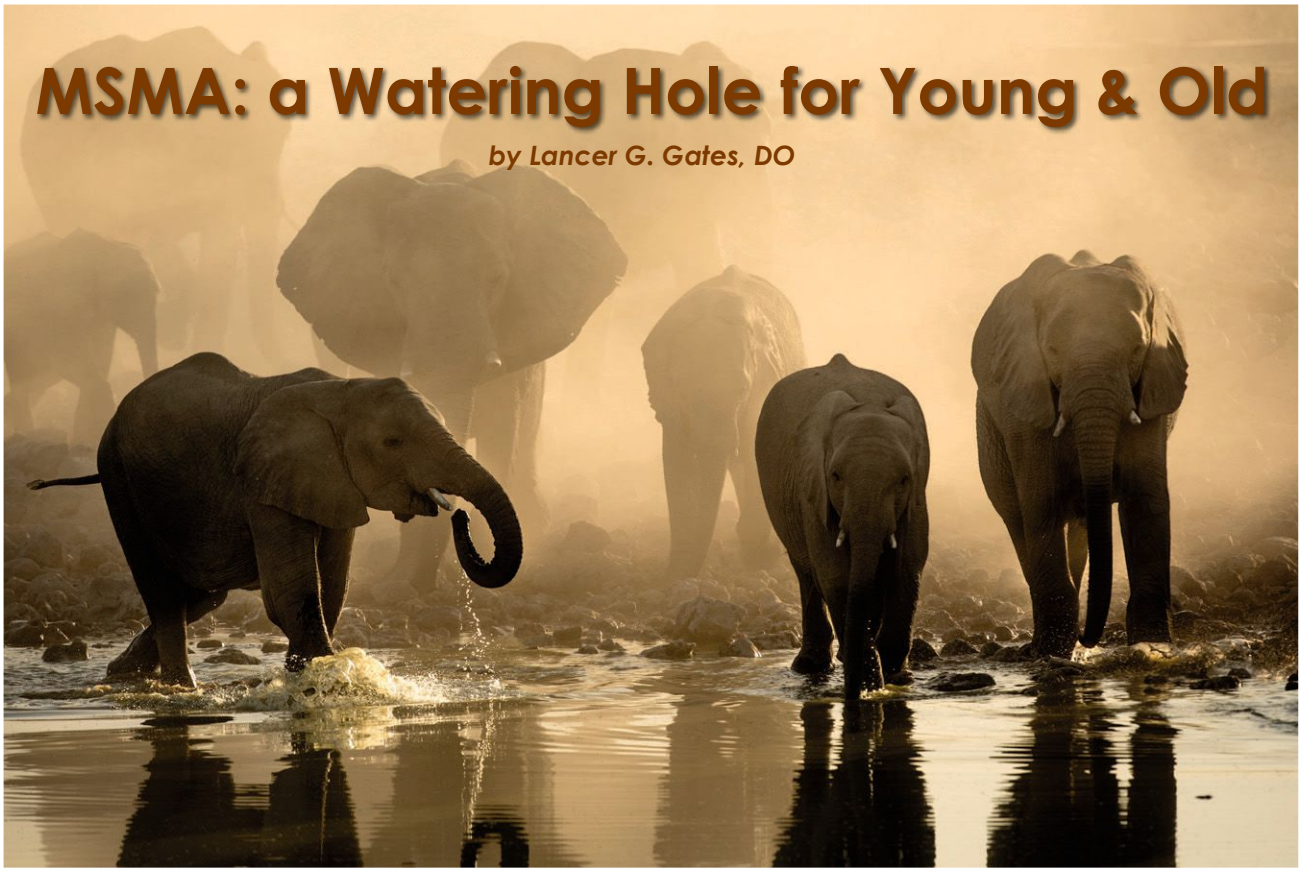
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MSMA: a Watering Hole for Young & Old

by Lancer G. Gates, DO



Elephants in the Musth

In the 1970s several rhinoceros were found gored to death at the Pilanesberg National Park in South Africa. Their assailants were identified as a group of young male elephants in the musth[1] (a time during which their testosterone level surges). The park rangers wanted to save the surviving rhinoceros but they needed to diagnose the reason for the killings and then develop a treatment plan. Gus Van Dyk, an ecologist, identified that normally a young male elephant's musth ends very quickly when he encounters an older and larger bull elephant. The Pilanesberg group of young elephants remained in the musth because all of their elder male elephants had been slaughtered by poachers for their ivory tusks. Van Dyk and the park rangers treated the problem by transporting six bull elephants from another South African park to serve as mentors for the tribe of rogue young bull elephants. Within hours the killing stopped.



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

The Dry Season

Between generations there are gaps in communication and technology. These gaps disrupt the transfer of knowledge, experience, culture, and values in all of society, including those of the medical profession. For example, unless a student has a family member that is a physician, then that student is left to blaze their own trail into medical school. During this dry season, students are left thirsty as they search for the path to their educational watering hole. Unfortunately, this path often leads to another gap…a gap year. This gap year multiplied by thousands of incoming medical students results in thousands of lost years of medical practice.

The Poaching of Our Time

Often a high school student's only contact with the medical profession is their office visit with their

pediatrician. Many practicing and retired physicians have wandered away from actively educating the next generation of physicians. Actively practicing physicians have had their time poached by the latest electronic medical record "upgrade," incessant prior authorizations, peer-to-peer reviews, insurance formulary substitutions, recredentialing their licenses and hospital privileges, maintaining their specialty certification, practicing defensive medicine, working with hospital administrators, serving on committees, etc. Practicing physicians also have family obligations, leaving little time for themselves. It is not surprising that students matriculating into medical school cannot find any actively practicing physicians at the watering hole. It is not surprising that gaps develop between the tusks of subsequent generations of physicians.

Jungle…Law

Lions eat their young, and we need to teach our young. Physicians can learn from another lifeform at the professional watering hole...the lawyers. Lawyers have their own time demands, but they have managed to develop programs to connect with, and to mentor, the next generation of lawyers. Each year many high school students participate in forensics clubs, aka speech and debate clubs. These clubs provide students with a defined curriculum and mentorship. The students then practice their skills in the time-tested Lincoln-Douglas debates judged by local attorneys who volunteer to help students develop their argumentative skills.

What if high school students with an interest in pursuing a medical career could participate in a program that offered the corollary of the Lincoln-Douglas debates…the Occam-Hickam debates? Occam's razor[2] posits that "the simplest explanation is preferable to one that is more complex" while Hickam's dictum[3] posits that "a man can have as many diseases as he damn well pleases." What if we assigned two students a patient case with one student assuming the role of Occam, and the other student assuming the role of Hickam? What if we invested as much time and resources initiating medical education (IME) as we do on continuing medical education (CME)?

Our Time…Our Tusks

MSMA may be able to bridge the generational gap by serving as the watering hole. At this watering hole, older physicians could connect with and mentor them along the medical educational path, thereby avoiding the gap year(s) so that Missourians could have more access to physician care.

The watering hole could be located on a page of our website where high school students interested in medicine could go to quench their thirst for educational opportunities including ACT/PSAT/SAT prep courses, physician shadowing opportunities, mentoring opportunities, volunteer opportunities, and financing medical education including scholarship opportunities. It could also include a list of local events such as medical careers nights at local hospitals. A well created virtual watering hole could replace students' current mirage of medicine.

In Kansas City, the Northland Center for Advanced Professional Studies (NCAPS) Medicine and Healthcare strand provides interested high school juniors and seniors with internships at Liberty Hospital and North Kansas City Hospital. The NCAPS Medicine and Healthcare curriculum includes BLS/ACLS and "Stop The Bleed" classes.

The KC STEM Alliance has combined Project Lead The Way (PLTW) and FIRST to provide STEM education for all students. The Alliance's KC HealthTracks program provides KC high school students with information about health careers.

Many Missouri high schools host a local chapter of HOSA (Health Occupations Students of America)- Future Health Care Professionals club. HOSA is led by students around the globe with a mission to promote all types of healthcare career opportunities, not specifically medicine. The Science Olympiad is another great program, but it is not specific to the science of medicine, does not include the art of medicine, and may not have physician volunteers in attendance.

The University of Missouri-Columbia School of Medicine hosts the Mini-Medical school program, a weeklong course for rising seniors held twice each summer. The University of Missouri-Kansas City (UMKC) offers a six-year medical program straight out of high school. Several undergraduate universities in Missouri offer matriculation pathways that feed students with high GPAs directly from their university into seats reserved for them at affiliated medical schools in Missouri.

Emerging From the Musth

Missouri undergraduates could return to the watering hole for a sip of the same opportunities but flavored for their next trek, medical school. They would continue to have access to educational opportunities, physician shadowing opportunities, mentoring opportunities, volunteer opportunities, and scholarship opportunities. We could include opportunities specifically for undergraduates during their semester breaks, such as scribing employment, or the Stowers Summer Scholars Program. Additionally, we could provide students with guidance for creating a viable medical school application including: tips on preparing

for the MCAT, gaining healthcare experience, examples of effective CVs, techniques for a good interview, and a list of factors to consider when deciding upon medical schools to which they will apply.

Another opportunity in Kansas City is the Mission Vision Project "If you can see it, you can be it". MSMA member Michael L. Weaver, MD, serves as the president and chief executive officer of this Kansas City-based organization with the mission of increasing the number of underrepresented minority students educated in health sciences and retained in the KC Metro healthcare workforce. The Mission Vision Project holds an annual Critical Mass Gathering (CMG) event that assists undergraduate students with specialty selection, residency planning, financial guidance, and board test preparation. CMG participants include the UMKC, University of Kansas, Kansas City University, the Greater Kansas City Chapter of the National Medical Society, local hospitals, practicing physicians, and community organizations.

No More Beating Around the Bush…Time to Get Back to the Watering Hole!

MSMA provides the youngest elephants (the medical school students, residents, and fellows) with opportunities in leadership and advocacy. Medical school student members are provided with opportunities for scholarships through the Missouri State Medical Foundation. Resident and fellow members are provided with networking opportunities which may lead to career opportunities.

MSMA provides the newer elephants (the newly practicing physicians) with full MSMA membership benefits at discounted membership rates. In addition to full membership benefits, spouses are encouraged to enjoy the benefits of the MSMA Alliance.

Finally, we the older elephants (the practicing and retired physicians), "must" get back to the MSMA watering hole. If you are not already a member, then become a member. Join us so that you can make connections and transfer your knowledge, experience, culture, and values to the next generation of Missouri physicians.

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Report of the American Medical Association Annual Meeting

by Charles W. Van Way, III, MD & the Missouri AMA Delegation

The 2023 annual meeting of the AMA House of Delegates (HOD) was held in Chicago, in person, June 10-13, 2024. Thankfully, the COVID pandemic has about run its course. It's still with us, but under control.

The HOD is the policy-making body of the AMA. The Annual Meeting considered many issues. and also included inauguration of the new President and elections for President-Elect, Board of Trustees (BOT), several Councils, and the Speaker and Vice-Speaker.

Outgoing President, Jack Resnick, MD, spoke at length. He alluded to the external attacks on medicine in our present environment. Burnout remains a large problem. One in five physicians are considering leaving the profession. Medical disinformation remains a constant problem. He is especially concerned about efforts to decrease gun violence. Legislators and others want to tell us what treatments we can prescribe, what we can tell patients, and what parts of medical science we must ignore. We aren't in a race. We are in a multigenerational effort which never ends. We don't win every battle, but we keep going. He feels that most people are on our side, on the fundamental right of patients to make their own healthcare decisions.

There are victories. The FDA has made naloxone available without prescription. Oral contraceptives may be authorized for over-the-counter sales. Courts have turned back criminalization of aspects of medical care. In short, we are the keepers of the tradition of health care.

The AMA Recovery Plan for America's Physicians continues. Physicians have been taking care of everyone else, and now it's time to rebuild. The Recovery Plan has five elements: 1) fixing prior authorizatio; 2) reforming the Medicare payment system; 3)fighting "scope creep" of non-physician practitioners; 4) supporting telehealth; and 5) reducing physician burnout. All worthy goals, but are we succeeding? Physicians reporting at least one burnout symptom increased from 38% in 2020 to 63% in 2021. Medicare payment has been cut in real terms. Clearly, we have much more work to do.

There was ongoing concern that physicians are losing control over their work environment. This issue was mentioned in several presentations. It isn't a policy issue since the AMA has strong policy support for physician autonomy. But this concern was evident throughout the meeting. Specific examples were Resolution 237, which calls for an end to not-to-compete clauses in physician contracts, and Resolutions 219, 222, and 261 calling for repeal of the ban on physician ownership of hospitals. Resolution 720 calls for further attempts to document the costs of prior authorization policies. Resolution 727 calls for assessment of the effects of health system consolidation.

James Madara, MD, AMA Executive Director, highlighted the 175-year history of the AMA. We value the democratic process, but we also protect our own autonomy. AMA policy expresses the wisdom of the crowd. But the tension between democratic consensus and personal agency continues



Charles W. Van Way, III, MD, FACS, FCCP, FCCM, Missouri/AMA Delegate, and *Missouri Medicine* Contributing Editor, is Emeritus Professor of Surgery, University of Missouri – Kansas City, Kansas City, Missouri.



Your representatives to the AMA included in the Missouri Delegation, from left: Drs. Joe Corrado, Ravi Johar, Peggy Barjenbruch, George Hruza, Elie Azrack, Joanne Loethen, Charles Van Way, and Betty Drees.

to characterize the relationship between individual physicians and the AMA. There is a national tendency to define ourselves by where we differ rather than where we agree. We must increase cooperation and reduce personal agency. In other words, stop fighting the AMA and support it.

Jacqueline Nguyen is the current President of the AMA Alliance, its first southeast Asian President. She came to the US with her family, after the fall of Saigon. She greatly appreciates the opportunities she has been given. A lawyer, she works to give back to the community. The Alliance works on health-related causes, such as gun violence, opioid misuse, access to care, and physician burnout. The Alliance works to provide support needed by physician families.

Jesse Ehrenfeld, MD, MPH, was inaugurated on June 13 as the 178th president of the AMA. He is an anesthesiologist and clinical informaticist, serving as Senior Associate Dean at the Medical College of Wisconsin. As the first openly gay President of the AMA, he has experienced health care inequities. He spoke extensively of health equity, which will be his emphasis during his presidency.

Bruce Scott, MD is President-Elect of the AMA. For eight years, he has been Vice-Speaker and Speaker of the HOD. Lisa Egbert, MD, was elected as Speaker. John Armstrong, MD, a surgeon from Florida, was elected as Vice-Speaker.

The HOD guides the core business of the AMA, setting policy and recommending action to be taken. This is done in one of two ways. First, resolutions may be directly submitted to the HOD proposing policy or action. The HOD considers each of these, and may accept, reject, or modify them. Secondly, the BOT or one of the Councils may submit a report with recommendations for policy changes or actions. These recommendations are then discussed by the HOD. Often, these reports are the result of resolutions from a previous meeting.

Perhaps the most prominent issue brought up is the action AMA is taking to reform the Medicare physician payment system. See the website: https://fixmedicarenow.org. Resolutions 214, 234, and 257 expressed dedicated support for Medicare payment reform. These resolutions were combined into a strong statement of the urgent need for payment reform and a mandate for the AMA to conduct a national media and lobbying campaign to reform Medicare payment. This issue will probably be the AMA's highest priority over the next year. Resolution 724

called for improved payment models for underserved rural communities.

There were many reports and resolutions affecting medical education. Council on Medical Education (CME) Report #2 provided extensive information about the financing of medical education. Educational debt load remains high, at an average of more than $200,000. Encouragingly, while 70% of students have medical student debt, this is down from 85% in 2010. The decrease is largely among students from wealthy families. Overall, some 56% of medical students are from families in the upper fifth of the income distribution. While the report is informative, its recommendations largely reaffirm existing policies and encourage students to take advantage of loan forgiveness, grants, and scholarship programs. It was amended during the meeting to also call for forgiveness of medical student debt. Forgiving debt for some of society's highest earning people seems unlikely to happen, but perhaps it is worth asking. A related report, CME #6, called for lowering the cost of applying to medical school.





Above, Joanne Loethen, MD, far right, is on one of the AMA Reference Committees. Right: George Hruza, MD, testifies at a Reference Committee.

The passage to graduate medical education (GME) continues to be a significant barrier, with 6-8% of seniors in American MD and DO schools being unable to find further training through the match system. Resolution 302 called for the AMA to consider alternatives to the present match system. Certainly, some aspects of the system could be adjusted. For example, some programs exclude international applicants, which is clearly discriminatory. Resolution 315 condemned this practice. But the basic issue is the lack of GME positions. Resolution 312 proposed to create training opportunities in the Indian Health Service, like the Veterans Administration Health Care System. This would provide new training slots, especially in primary care, and would improve health care for a neglected segment of our population. It would require major upgrade to the HIS, which may be difficult to get through Congress. There were no other initiatives to increase residency positions. That said, the number of first-year positions continues to increase, reaching 30,000 in 2023. But the numbers of applicants, including qualified international graduates, continues to increase as well, as does the shortage of practicing physicians.

There is continued concern over the role of non-physician providers. Scope of practice issues and conflicts between training of physicians and training of non-physician providers were discussed. Movement of advanced practice providers between specialties can interfere with physician practices, because of the time and effort

invested in training such providers as advanced practice nurses.

Nutrition as an aspect of public health is a continuing concern of the AMA. Council on Science and Public Health (CSPH) Report #7 assessed the use of Body Mass Index (BMI). The Council was responding to a resolution to abandon its use, as being inaccurate and potentially discriminatory. While the Council did not recommend abandoning the use of BMI, the report extensively assessed alternative measures for body habitus and obesity. It recommended that BMI be used in conjunction with other measures such as waist circumference and waist-to-hip ratio. It also called for research into the measurement of body habitus. Besides this report, there were two resolutions dealing with aspects of nutrition. Resolution 236 called for increased funding for nutritional research, which is relatively underfunded by the NIH. Resolution 423 called for a report by the CSPH on efforts to decrease sodium use, generally considered to be excessive in the general population.

Legal restrictions on health care continue to proliferate. CSPH Report #1 opposes the scheduling of gabapentin as a class V drug, as has been proposed by consumer advocates to the FDA. Gabapentin is commonly prescribed for off-label indications. It has been made Schedule V drug in seven states and 13 have added it to their prescription drug monitoring programs, with the objective of making it reportable. The Council concluded that there was little evidence of harm from gabapentin, while there was considerable enthusiasm for its use as a potentiator of other drugs and in opioid withdrawal. Similarly, testosterone was made a Schedule III drug in 1990 to control overuse by athletes. But that effort failed, while raising a major barrier to the legitimate use of testosterone for hypogonadism and gender adjustment. Resolution 519 calls for de-scheduling testosterone. It was modified to call for removing other barriers to prescribing testosterone as well. Other barriers to gender-affirming care are also opposed by the AMA. Resolutions 8 and 15 call for a report on legislative efforts to criminalize aspects of medical care. Resolution 711, from Missouri, calls for removal of limits on reproductive health services and for cancelling any penalties stemming from criminal conviction under laws restricting medical practice.

BOT Report #17 discussed the AMA response to several public health issues, including climate change, public health systems, gun violence, infectious disease threats, and public misinformation. The report was strengthened by resolutions on support of public health systems, training programs, and other areas. There were related resolutions on other public health issues, including immigrant care (Resolution 210); care of incarcerated persons (CSPH Report #6, Resolutions 109, 429, and 432); care of foster children (Resolutions 216, 419, and 420); wheelchairs (Resolutions 10, 512); medical devices (CSPH Report #2); and qualified immunity for police officers (Resolution 31). Under the umbrella of public health, the AMA has policy on many issues in the political arena. These public policy concerns are often popular within the HOD. But the AMA has only a finite amount of political capital. It may be counterproductive to engage in such issues that do not affect the practice of medicine, as opposed to such issues as Medicare payment reform.

There was much concern over the dissemination of misinformation. Resolution 508 asks that better standards of media coverage in mass shootings and in opioid drug overdoses be supported by the AMA. Resolution 509 asks that the AMA help fight medical misinformation through social media, search engines, online companies, healthcare companies, and pretty much anyone else owning a website. Resolution 427 asked for restrictions on the media in its treatment of gun violence and Resolution 430 asked for age limits on websites for youth under 18. All of these are laudable, but just how they would be accomplished, and who would define

proper information, is not specified. Many of these recommendations raise significant First Amendment questions.

On a somewhat different issue, Resolution 517 called for research into the increased incidence of cardiovascular disease among certain south Asian populations. Resolution 518 expressed support for the use of animal models in research. Such research has come under legal challenge recently. A broad judicial determination against animal research would be catastrophic for medical research, although this lawsuit seems to be on narrow procedural grounds.

The drug epidemic continues to be a concern. Several resolutions advocated for aspects of harm reduction. This included Resolution 505, to increase access to opioid antagonist in underserved populations; Resolution 525, to decriminalize perinatal drug use; Resolution 203 to decriminalize buprenorphine possession; Resolution 217 for increased access to opioid antagonists in schools, including encouraging students to carry naloxone; and Resolution 221 for legalization of fentanyl test strips. As a perhaps logical extension of harm reduction, Resolution 203 called for total decriminalization of drug possession and use. This was not adopted, but was referred to the BOT. Resolution 521 called for continued use of screening for marijuana use. Resolution 212 called for restrictions on health claims for recreational marijuana. Resolution 515 called for restriction of kratom, an herbal agent which stimulates opioid receptors, and for its placement on the narcotics schedule. There was support for its regulation by the FDA, and for a ban on OTC sales, but much less for its placement on the narcotics schedule.

While several speakers referred to the ongoing crisis in gun violence, there were only a few resolutions proposed. Resolution 405 called for allowing physicians to invoke "red flag" laws on patients. Concern was expressed that this might impair trust between physician and patient, but the resolution was largely supported. Resolution 229 calls for extending the period during which convicted felons who have served their time cannot purchase or own firearms. Resolution 416 calls for increased restrictions on sales and transfer of firearms and ammunition.

The meeting of OSMAP, the Organization of State Medical Association Presidents, takes place at the AMA meeting. Speakers included Jack Resnick, MD, AMA President, and Gary Price, MD, President of the Physician Foundation. There was an extensive discussion on the ways that state medical societies can achieve financial independence from reliance on dues income alone. Many medical societies are financially challenged, often made worse by a general drop in membership. This is a severe problem in many state societies, and OSMAP intends to further address the problem.

Several physicians from Missouri serve in leadership roles. David Barbe, MD, is Past President of the AMA and the World Medical Association. Edmond Cabbabe, MD, serves as Chair of the Council for Long Range Planning and Development. Elie Azrak, MD, serves on the Board of AMPAC, the AMA Political Action Committee. Jerry Kennett, MD, serves on the Board of the AMA Foundation. Deepu Sudhakaran, MD, is on the Governing Council of the International Medical Graduate Section. Marc Mendelsohn, MD, was elected to the Council on Science and Public Health. Charles Van Way, III, MD, was elected Secretary of OSMAP.

This meeting considered more than 200 reports and resolutions. This is only a summary of the most significant. The proceedings of the meeting, as well as summaries of addresses by Drs. Reznick, Madara, Ehrenfeld and others, are available on the AMA website. Highlights from the meeting can be found at https://www.ama-assn.org/house-delegates/annual-meeting/highlights-2023-ama-annual-meeting. Details of the AMA Recovery Plan for American Physicians can be found https://www.ama-assn.org/amaone/ama-recovery-plan-america-s-physicians. The Interim Meeting of the HOD is scheduled to take place in National Harbor, Maryland, November 11-14, 2023. **MM**



NEW MSMA MEMBERS!

* = Medical Student

** = Resident/Fellow

Chase Branstetter, MD – Internal Medicine/Pediatrics**
Tori Bussanmas, MD – Pediatrics**
Megan Connolly, MD – Pediatrics – Richmond
Marcus Cronin, MD – Pediatrics**
Hannah Darland, MD – Unspecified**
Matthew Decker, MD,JD – Internal Medicine – Lee's Summit
David Elsenberg, MD, MPH, FACOG – OB/GYN – St. Louis
Anna Gerst, MD – Unspecified**
Jacob Gohdes, MD – Pediatrics**
Soheila Hamidpour, MD – Pathology – Leawood
Spencer Himpel, DO – Family Practice**
Kavita Jadhav, MD – Internal Medicine – Overland Park
Abigail Kissel, MD - Dev. Behavioral Pediatrics – St. Louis
Kamani Lankachandra, MD – Anatomic/Clinical Pathology
Molly Kubesh, MD – Pediatrics**
Ginger Nicol, MD – Child & Adolescent Psychiatry – St. Louis
Mildred Olivier, MD – Ophthalmology – St. Louis
Evanthia Omoscharka, MD – Pathology – Lenexa
Devin Perkins, MD – Family Practie**
John Peterson, MD – Gastroenterology - Webster Groves
Hussam Saleh, MD - Psychiatry - Fulton
Kristy Shang, MD – Family Practice**
Athena Strother, MD – Family Practice
Alexander Tagart, MD – Unspecified**
Sarah Von Thaer, MD – Anesthesiology
Pooja Vyas, DO – Internal Medicine – St, Louis

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Hamzah Abdeluahab*
Parker Adams*
Nabil Agag*
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Haya Ahmed*
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Jae Jung*
Mauzi Kadoma*
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Amar Karahodzic*
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Paris Kelly*
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Khalid Khan*
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Riley Wolk*
Megan Woods*
Mary (Molly) Woolery*
Josh Yagzi*
Brandon Yeoh*
Preston Yoon*
Sydney Young*
Philip Yusuf*
Taylor Zahner*
Mehraeil Zaki*
Jennifer Zheng*
Zainab Ziauddin*
Amber Zins*

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Washington University in St. Louis
School of Medicine

Washington University & the Future of Psychiatry

by Eric J. Lenze, MD & Charles F. Zorumski, MD

The Washington University in St. Louis (WUSTL) Department of Psychiatry is an international leader in its field with major programs across the academic missions of research, education, and clinical care. The educational mission of the department aims to train future leaders across all three missions. Clinical programs reflect strong commitment to the care of psychiatric patients in the St. Louis region, with emphasis on underserved and stigmatized populations. Research programs are innovative and poised to lead new directions in mechanistic understanding, novel therapeutics, and clinical outcomes. The department is currently in a major transition as we celebrate a new department head for the first time in over 25 years. In the following series of papers, we highlight some of our ongoing research that is positioned to have a major impact on psychiatry and medicine.

Our department has a long-standing legacy of innovation. The department is widely recognized as the home of medical model psychiatry and led the revolution that moved psychiatry to its current diagnostic system. These changes involved development and implementation of criteria-based diagnoses that began in the 1970s with the "Feighner Criteria," and subsequently resulted in DSM-III (Diagnostic and Statistical Manual of the American Psychiatric Association) and all subsequent versions of the DSM to date. Legendary individuals, including previous chairs Eli Robins, MD, and Samuel Guze, MD, drove this work. The department also played a major role in psychiatric epidemiology and genetics with pioneering work by Lee Robins, MD, and genetic studies of alcoholism by Don Goodwin, MD, Ted Reich, MD, and Robert Cloninger, MD. In preclinical neuroscience, John Olney pioneered the field of "excitotoxicity" (coining the term), which views the neurotransmitter, glutamate, as a double-edged sword that is both critical for brain function and an endogenous toxin contributing to neurodegeneration. The department also played key roles in using human neuroimaging to understand how changes in brain networks contribute to psychiatric illnesses. Early pioneers included Eric Reiman, MD, Wayne Drevets, MD, and Yvette Sheline, MD, and this work remains a driving force in the modern department. Current efforts include development of methods for precision brain mapping to examine network changes at the level of individual patients. Child and Adolescent Psychiatry has been a major focus and reflects the work of several luminaries including E. James Anthony, MD, Felton Earls, MD, Richard Todd, MD, and John Constantino, MD. The department has a major commitment to developing and testing new treatments, highlighted in the papers in this issue. A detailed history of our department can be found at: https://psychiatry.wustl.edu/about/book-on-the-history-of-the-department.

Research presently represents about 70% of departmental effort. Success in this work is marked by high impact publications and presently ranking fifth among Departments of Psychiatry in funding from the



Eric J. Lenze, MD, (left), Chair of the Department of Psychiatry and Charles F. Zorumski, MD, are in Taylor Family Institute for Innovative Psychiatric Research, Washington University School of Medicine, St. Louis, Missouri.

National Institutes of Health (NIH). Presently, 38 faculty members serve as principal investigators of grants from NIH. Research programs are focused in four major areas including human genetics, human neuroimaging and physiology, behavioral medicine, and preclinical neuroscience. Research in child psychiatry cuts across all areas. Below we highlight specific areas of focus.

Emotional and Cognitive Development in Children

Most psychiatric illnesses have origins in childhood, offering a strong rationale for early recognition and intervention. The department has several major programs in this arena including the Perinatal Behavioral Health Program (led by Cynthia Rogers, MD, and Shannon Lenze, PhD), Early Emotional Development Program (Joan Luby, MD, Deanna Barch, PhD, Chad Sylvester, MD, PhD, and Susan Perlman, PhD), and the Intellectual and Developmental Disease Research Center, Hermann Center and Autism Center (John Pruett, Jr., MD, PhD, Kelly Botteron, MD, and Natasha Marrus, MD, Phd).

Substance Use Disorders

Substance use is a major public health problem with over 100,000 deaths per year in the US from drug overdoses, and is a primary contributor to disability. Major programs in this area include the Family Research Center (Andrew Heath, DPhil, Pamela Madden, PhD, Arpana Agrawal, PhD, Elliot Nelson, MD, and Kathy Bucholz, PhD) and the Health and Behavior Research Center (Laura Bierut, MD, Patricia Cavazos-Rehg, PhD, Sarah Hartz, MD, PhD, Carrie Mintz, MD, and Alex Ramsey, PhD).

Behavioral Medicine

Psychiatry is an integral part of medicine and key issues include the interface between psychiatric disorders and medical/neurological illnesses. Areas of emphasis include childhood and adult obesity (Center for Healthy Weight and Wellness, Denise Wilfley, PhD, Robinson Welch, PhD, and Ellen Fitzsimmons-Craft, PhD), cardiovascular illnesses (Bob Carney, PhD, and Ken Freedland, PhD), diabetes (Tammy Hershey, PhD, and Sarah Eisenstein, PhD), aging-related illnesses and perioperative mental health (Healthy Mind Lab, Eric Lenze, MD, and Ginger Nicoll, MD), movement disorders (Kevin Black, MD) and early recognition of individuals at risk for psychotic illnesses (Washington Early Recognition Center, Daniel Mamah, MD).

Neurodegenerative Illnesses

This program examines complex mechanisms contributing to neurodegenerative illnesses including Alzheimer's disease, Parkinson's disease and others, and involves analyses of genomic, proteomic, metabolomic and brain imaging findings through the Center for Neurogenomics and Informatics (Carlos Cruchaga, PhD, Celeste Karch, PhD, and Oscar Harari, PhD) in collaboration with the Knight Alzheimer's Disease Research Center and Hope Center in the Department of Neurology.

New Treatments

This program is based on novel molecules and mechanisms in neuropsychiatric illnesses. Efforts also include repurposing currently approved medications for use in psychiatry and other areas of medicine. Key components include the Taylor Family Institute for Innovative Psychiatric Research, a multi-departmental effort aimed at novel molecules (neurosteroids and oxysterols) and treatments based on brain biology (Steve Mennerick, PhD, and Chuck Zorumski, MD), the Center for Brain Research in Mood Disorders, the Treatment Resistant Depression Program (Chuck Conway, MD), the Program in Interventional Psychiatry (Pilar Cristancho, MD) along with the Healthy Mind Lab (Eric Lenze, MD) and several other programs outlined above. Treatment development also includes novel forms of psychotherapy including parent-child interaction therapy for emotional development (PCIT-ED, Joan Luby, MD) and family-based treatments for obesity and eating disorders (Denise Wilfley, PhD).

In the following papers, we highlight a subset of departmental research poised to advance psychiatry in the 21st century. The future of psychiatry is extremely bright and WUSTL is well positioned to lead the effort.

Acknowledgments

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Disclosure

CFZ serves on the Scientific Advisory Board of Sage Therapeutics and has equity in Sage Therapeutics. Sage Therapeutics did not fund this work. **MM**

Education Innovations in the Department of Psychiatry at Washington University

by Brendan O'Connor, MD, Eric Spiegel, MD, Melissa A. Harbit, MD & Nuri B. Farber, MD

Washington University in St. Louis
School of Medicine

Psychiatry continues to evolve and our treatment delivery methods must evolve as well.



Brendan O'Connor, MD, Associate Professor, Eric Spiegel, MD, Associate Professor, Melissa A. Harbit, MD, Professor, and Nuri B. Farber, MD, (above), Professor, are all in the Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri.

Abstract

The Department of Psychiatry at Washington University has been innovating psychiatric education during the second millennium at all levels of training – undergraduate medical, general residency, and child and adolescent psychiatry (CAP) fellowship training. Undergraduate medical education now occurs in three phases. The 18-month pre-clerkship phase is divided into seven multidisciplinary modules that span basic, social, and clinical sciences. Psychiatry is part of the seven-week long Brain and Behavior module. The yearlong second phase includes a six-week traditional psychiatry clerkship-like experience bracketed by an introductory foundational week and a one-week consolidation period. The third phase is 18 months in length and provides in-depth exploration of both clinical and non-clinical areas. The residency training program has enlarged the number of residents undergoing training and simultaneously greatly expanded the clinical exposure to include rotations in eating disorders and perinatal psychiatry. In addition, our residents can choose to enhance their training in either our research or leadership focused options, both of which are also available to trainees in our child and adolescent program. Additionally, our CAP trainees are exposed to several unique areas including eating disorders and substance use disorders. We believe that these innovations across the educational spectrum allow us to prepare our learners for the practice of psychiatry in the 21st century.

Introduction

The Department of Psychiatry at Washington University has been at the forefront of psychiatry educational programs since the 1950s. At our foundation is the understanding that psychiatry is a field of medicine which necessitates continuous basic science and clinical research. The notion that psychiatry residents should be exposed to research as part of their training was novel in the 1950s when it was introduced at Washington University. While research literacy is now a required component of all training programs, conducting research is not a requirement in most training programs as it is in ours. The model has trained generations of critically thinking and compassionate, psychiatrists

who are leaders in mental health care around the country. This article will describe exciting advances at Washington University in undergraduate medical education, graduate medical education in our general psychiatry residency program, and fellowship training in CAP.

Innovation in Undergraduate Medical Education

The Undergraduate Medical Education program at Washington University has recently undergone a complete renewal of the curriculum for the MD program. Implemented in 2020, the new competency-based Gateway Curriculum was designed to produce physicians who are leaders in medicine, science, education, and advocacy. Curriculum renewal brought with it an exciting opportunity to ensure the integration of foundational, clinical, and social sciences content throughout training, to develop maximally effective educational strategies for students, and to expand the footprint of the discipline within the core curriculum. The new curriculum is organized into three phases—pre-clerkship, clerkship, and post-clerkship.

Phase 1 is approximately 18 months long and is organized into seven multidisciplinary modules designed to integrate basic, clinical, and social sciences not only within and between modules, but also with subsequent educational experiences during the clerkship and beyond. This horizontal and vertical integration is achieved through the deliberate coordination of module directors with directors of curricular threads covering topics in basic sciences, clinical sciences, and social, behavioral, and health systems sciences. These thread directors also coordinate closely with leadership from the clerkships and other advanced courses within the curriculum. Education in psychiatry initially takes place within the Brain and Behavior module and is integrated with content developed by thread leaders in anatomy, clinical skills, pharmacology, health equity and justice, and ethics and law.

Evidence-based, active learning strategies and educational technology are used to augment medical student engagement and learning. During the psychiatry portion of Brain and Behavior, a substantial amount of classroom learning takes the form of interactive patient presentations, case-based collaborative learning, and other flipped classroom[1] strategies. For example, following instruction in the fundamental basic and clinical science of psychopharmacology, students prepare for a flipped classroom exercise by taking a formative quiz, the results of which inform the session leader of student readiness for the in-class consolidation exercises. These exercises take the form of problems in psychopharmacology that are embedded within clinical cases and allow students to expand on important concepts ranging from therapeutic drug monitoring of lithium to relative costs of antipsychotics for the uninsured. Even more traditionally structured lectures are augmented with the use of audience response systems to facilitate student engagement. Active learning strategies have been well received by students in general, and the specific use of case-based collaborative learning and flipped classroom pedagogies described above received nearly universally positive feedback in our course.

The Psychiatry clerkship is one of six required clerkships that take place during Phase 2. The clerkship begins with a week of classroom-based learning called the Foundational Week. During this time, a similar portfolio of pedagogical strategies is used to support student application of and expansion on fundamental learning objectives that were first introduced during Brain and Behavior. Following the Foundational Week, students are not only prepared to take on meaningful patient care responsibilities on day one of their clinical assignments, but their involvement in the day-to-day patient care activities of their respective services is no longer disrupted by the need to attend didactics. The addition of the Foundational Week has nearly doubled the amount of classroom learning in psychiatry relative to what it had been prior to curriculum renewal. This expansion has provided the opportunity to use the additional time to incorporate skills workshops focusing on interview and mental status exam techniques which have received positive feedback from students. As is the case with the pre-clerkship phase, learning objectives for each clerkship are explicitly integrated across clerkships in collaboration with thread leaders to avoid curricular redundancies and gaps.

Following the Foundational Week, students now undergo six weeks of clinical assignments which represents a significant expansion of clinical training in psychiatry in keeping with the position statement issued by the Association of Directors in Medical

Student Education on the length of the psychiatry clerkship.[2] As a competency-based curriculum, evaluation of student performance during the clerkships relies on a transparent, multi-faceted, and observation-based system of assessment that provides regular feedback to students on their strengths and opportunities for growth. This system relies substantially on "just-in-time" assessments designed to capture cross-sectional information about student performance across a range of specifically designated patient care activities including collecting a history, conducting a mental status exam, and clinical reasoning as observed in both oral and written presentations. Students are also evaluated using more traditional longitudinal assessments that are completed within the context of a meeting between clerkship leadership and the attending supervisor for each student to support quality control and construct alignment.

The last week of the clerkship is devoted to a week of assessment, reflection, coaching, and community engagement. In addition to the clinical performance assessments described above, all students are required to pass the National Board of Medical Examiners subject exam in psychiatry and to undergo a two-station Observed Structured Clinical Examination. Students also meet with their longitudinal coaches to reflect on their experiences and performance during the clerkship.[3] The week concludes with a reflective discussion on student attendance at an Alcoholics Anonymous or Narcotics Anonymous meeting as well as a reflective discussion on a film featuring mental illness and mental healthcare.

Phase 3 of the curriculum lasts 18 months and provides students with the opportunity to explore further areas of clinical interests as well as other areas including advocacy/global health, education, innovation, and research. During this phase, students are required to complete a certain number of advanced clinical rotations in order to graduate, which may include a psychiatry advanced clinical rotation. These rotations are sub-internship-like experiences. We also offer a variety of clinical and non-clinical elective courses as well. A novel aspect of Phase 3 is the required Keystone Integrated Science Courses which integrate in depth scientific understanding of a topic with applied clinical care. We plan to create such courses focused on intellectual disabilities and treatment-resistant depression. We look forward to the continued development of our portfolio of advanced courses for students interested in the wide variety of scholarly and clinical experiences that characterize the field of psychiatry.

Innovation in Residency Education

The General Psychiatry Residency Training Program has been innovating its curriculum for approximately the past decade. One of our goals is to prepare residents to provide care to patients with a variety of illnesses and of differing complexities. To aid in this broadening of exposure the Department of Psychiatry has actively engaged with other healthcare providers in the St. Louis community. These curricular changes have been paired with successful growth of the program from 10 to 13 residents over the last several years, enabling us to provide greater access to care for our community. This expansion has allowed our residents to treat patients with a variety of eating disorders at the community-based McCallum Place, and to provide outpatient and residential treatment for patients with substance use disorders at both the John J. Cochran Veterans Hospital and Harris House. In addition to high acuity and medically complex patients that we treat at our main campus at Barnes-Jewish Hospital, our residents also treat patients at the Psychiatric Center Delmar Campus. This site allows for expanded access to care in the St. Louis region and provides a training opportunity for residents and students to care for less medically complex patients. Additionally, our residents now benefit from a perinatal psychiatry rotation. This rotation provides residents with the opportunity to evaluate and treat women with perinatal disorders, oftentimes with novel treatments including brexanolone and suboxone. They are also able to coordinate care with obstetricians as well as endocrinologists who evaluate and treat patients with gender-related complaints. These experiences provide some of the broadest training of psychiatry residents in the country. Going forward, our goal is additional expansion to provide greater access to care for our St. Louis community and to explore even more training opportunities for our residents.

Another highlight of our training program is offering a full 10 months of research and elective time. We have found that many graduating medical students entering psychiatry need this time and exposure to decide on their future career paths. Some of the most popular electives include toxicology, sleep medicine, forensic psychiatry, a multispecialty weight management clinic, and the Memory and Diagnostics

Center at our Alzheimer's Disease Research Center. While residents utilize these electives to broaden their training, they are also encouraged to create their own electives. The welcoming educational environment of our Washington University community allows for electives in a diversity of other related fields. Some of the more novel ones include electives in neuropathology, neurosurgery, and informatics.

In the last several years we have leveraged our elective time further to create two training options – PRREP (Psychiatry Residency Research Education Program) and LEAP (Leadership Education and Administration Program). These options are available to any of our residents and further allow them to augment the excellent clinical training that they receive. PRREP is supported by a NIMH R25 grant. It is divided into two phases. The first phase covers the first two years of training and is structured to allow residents, who have not had significant research experience, to explore research to determine whether it is a potential career option for them. For those who have had significant research experience phase one allows them to jump start their research career. A novel aspect of PRREP is that if a resident decides that a career in research is not for them, they are able to opt out of the program. Those wishing to continue on the research path proceed to the second phase, which covers the second half of training, including the fellowship training years for those trainees who transition to our CAP program. This second phase provides substantial hands-on research training and positions graduates who decide to pursue an academic research career to submit a K-level career training application in their first year after clinical training. This research training option has been highly successful, resulting in a doubling in the number of trainees who decide on a career in research. In addition, in the last five years our trainees have been authors on more than 100 publications.

The launch of PRREP generated significant enthusiasm among our trainees. Nearly everyone signed up for the program the first year. Only a few, however, continued on to phase two. We learned that while we recruit many residents interested in academia, not all are interested in being predominantly researchers. It was clear to us that many residents were looking for strong mentorship in other aspects of academic psychiatry. Thus, we developed LEAP to provide a structured mentorship program for residents interested in other aspects of academic psychiatry. Several exciting advancements in our training program have come from resident LEAP projects. As our residency recruitment turned virtual with the COVID pandemic, resident driven LEAP projects established our social media presence. Other projects have contributed to our resident recruitment and others have focused on educational measures research.

Innovation in Child and Adolescent Psychiatry

In coordination with the psychiatry residency program and school of medicine, the Child and Adolescent Psychiatry Fellowship at Washington University has been training leaders in the field for decades. We view child psychiatrists as leaders, whether that be in their community, in an educational role, or in adding to scientific understanding.

Before our fellows begin their second year, they have a series of conversations, lectures, and assigned readings focused on leadership. During this "Leadership Seminar," we use material from the worlds of business and medicine with the goal for the fellows to understand the importance of their role as a community leader.

Over the years, many notable child and adolescent psychiatry leaders began their careers by first training in the Washington University Psychiatry Residency program. Indeed, our close partnership with the general residency training program makes many of our educational advances possible. As described above, those "internal" residents can now continue their PRREP or LEAP training while they are fellows. In this way, they can seamlessly continue to focus a portion of their training on their own specific career goals. Even before PRREP began, our fellowship was a wonderful place to train side-by-side with accomplished scientists. PRREP now provides a structure to help new researchers scaffold the sometimes challenging "next steps" in a research career.

With continual advances in the understanding of child mental illness, our fellowship has undergone many changes to ensure that our fellows receive a rich and diverse education. We feel our diversity of rotations is one of our current strongest examples of this. Our fellows have a rotation at the Hawthorn state hospital (where they work with extremely complex cases) as well as in the acute inpatient psychiatric unit at St. Louis Children's Hospital. Also at Children's Hospital, we

have an opportunity to learn from and care for the psychiatric needs of medically complex patients. In the community, the fellows consult with the Special School District of St. Louis County and learn about the many ways that local educators assist students to learn, especially students with mental health concerns and/or developmental delays.

We have recently added rotations in locations that care for patients with specific diagnoses such as eating disorders and substance use disorders due to increasing understanding of the magnitude of the impact of these disorders on our youth and their increasing incidence. To individualize education, our fellows have the option to receive extra training in Applied Behavioral Analysis, Interventional Psychiatry, High Weight Eating Disorders, Perinatal Behavioral Health, LGBTQ Mental Health, Child Abuse Prevention, and other areas of practice.

We continue to add and modify didactic content to meet the needs of our learners in a world of ever-increasing knowledge about child mental health. Our fellows are taught by leading scientists, including experts in the fields of early emotional development, child maltreatment, genetics, early intervention, neuroscience, and medical ethics, to name a few. Advances in understanding childhood trauma and neuroscience are two topics that continue to shape our understanding of psychopathology. We are increasing didactic content by adding a formalized curriculum in both of these fields.

Finally, in order to practice effectively, child and adolescent psychiatrists must have a high degree of facility with psychotherapy and an understanding of how psychotherapies contribute to patient improvement. In our fellowship, we set aside a full clinic for psychotherapy for all second-year fellows. Supervisors watch through a one-way mirror and give live feedback on cases, which typically involve family therapy, cognitive behavioral therapy, and parent-child therapies. The trainees video record and present cases to one another for feedback. We believe this extensive psychotherapy training will assist our graduates in nearly every patient and family encounter in their future careers. Since fellows began training in this psychotherapy clinic, graduates cite this as one of the most important parts of their growth as a psychiatrist.

Our varied and unique clinical experiences, our dedicated individualized supervision, and didactic content taught by scientists on the cutting edge of current scientific understanding make our fellowship a singular and exemplary place to train. Training here produces CAP leaders that can contribute to our mission of protecting the lives and well-being of children and families through the prevention and treatment of child and adolescent mental health conditions.

Conclusion

Psychiatry continues to evolve and our treatment delivery methods must evolve as well. To supplement our longstanding required rotation in electroconvulsive therapy, we envision continued expansion and more immersion in interventional methods including transcranial magnetic stimulation, esketamine, deep brain stimulation, and vagal nerve stimulation. We also appreciate the significant demand for mental health services in our communities. Innovative care models such as collaborative care and shared treatment with Advanced Practice Providers will be part of our future delivery systems in psychiatry.[4-7] We envision continued expansion of our educational programs to include these models of care to meet the mental health demands of our communities. We are proud of the outstanding clinicians we train, many of whom stay in Missouri or the surrounding region. They are critical thinking, compassionate, physicians who leave our program competent and confident to practice independently.

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Disclosure

None reported. **MM**

New Directions in Child Psychiatry: Shaping Neurodevelopmental Trajectories

by Cynthia E. Rogers, MD & Joan Luby, MD

Washington University in St. Louis
SCHOOL OF MEDICINE

Multidisciplinary care targeted to the earliest ages is the direction that child psychiatry as a field should continue to develop if we want to improve child mental health.



Cynthia E. Rogers, MD, (above), Professor, and Joan Luby, MD, Professor, are in the Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri.

Abstract

Historically, the field of child psychiatry has lagged behind the field of general psychiatry in terms of research innovations and the availability of empirically supported treatment modalities.

However, over the last two decades there has been increasing interest in and research focused on the developmental origins of mental disorders examining both neurobiological and psychosocial etiologies.[1] This has catalyzed the field leading to advances in understanding the developmental psychopathology of mental disorders and the generation of novel early interventions that have shown significant promise.[2-4] Further, catalyzing this effort is new data demonstrating the powerful impact of psychosocial forces on neurodevelopment. New methodologies and discoveries in the basic areas of early childhood developmental psychology have led to a greater appreciation for the emotional and cognitive sophistication of children in the first three years of life. Advances in methods to understand pre-verbal children's emotional and attentional responses (through measures of eye gaze and suck for example) as well as observational methods to glean a variety of mental health relevant behaviors early in life (e.g. behavioral inhibition, pro-social behaviors and social motivation) have further elucidated and validated these capacities. In addition, measures of neural function using electroencephalogram and evoked response potentials (EEG/ERP) and functional magnetic resonance imaging (fMRI) as early as the neonatal period, with many analysis methods developed at WUSTL, have further informed this domain providing new insight into early brain and behavioral relationships as well as how intervention impact brain function.[5-7]

Application to Children

In sync with these advances for young children, and prior to that, in school age children and adolescents, the field of child psychiatry began to extrapolate and test whether adult diagnostic criteria (DSM-based) could be applied to children. In doing so, it became clear that unique developmental considerations

must be central and that it was necessary to developmentally modify criteria to describe how symptoms might manifest in the context of the life experiences and abilities of children. In addition, early studies demonstrating that children had unique responses to psychopharmacologic agents emerged and elucidated the need for developmentally specific considerations and distinct studies and of treatment modalities in child populations.[8,9]

Developmental considerations become even more significant in early childhood (under age 6), and this has been a central challenge in testing and developing criteria for clinical diagnoses in children as young as age 3. To investigate this question and validate diagnostic criteria for preschool age children, studies required the development of age appropriate psychiatric interviews, which only became available in the late 1990s.[10,11]

A central consideration for these assessments is the distinction between normative developmental extremes common early in development, and clinically significant symptoms. Another obstacle to overcome was the common misconception that symptoms arising in early childhood would be transient and not clinically significant.[12] However, once criteria for numerous DSM psychiatric disorders were established, the ability to identify and treat these disorders earlier in development became possible. Targeting psychopathology this early in development brings novel therapeutic opportunities, in particular the ability work through the caregiver-child relationship ("the dyad").

Importance of Perinatal Period

Another area in which significant progress had been made over the last two decades is understanding the effects of early life adversity and other social exposures early in life on risk for psychiatric disorders.[13,14] Building on decades of research on the negative effects of poverty on a variety of developmental outcomes, neuroscience approaches have documented associations between poverty, deprivation and experiences of abuse and threat on neurodevelopment and related cognitive and emotional outcomes. This has led to an increased emphasis on the social determinants of mental health in childhood and the need for protection from these early negative exposures for the prevention of both child and adult psychopathology.

Concomitantly, there has been increasing recognition of improving caregiver well-being as a potential prevention strategy to reduce development of child and adult psychopathology with an increasing emphasis on the effect of caregiver mental health during the perinatal period. Pregnancy and postpartum period are times of vulnerability for parents given increased stressors and role transitions. Perinatal mental health disorders, which affect approximately one in five pregnant caregivers and represent the most common complication of childbirth, are known risk factors for disrupted caregiver-infant relationships as well impaired cognitive and social-emotional development in children and increased risk of child psychiatric disorders.[15-20] These associations between exposure to perinatal mental health symptoms and child mental health are likely due to several known risks linked to perinatal mental health including factors affecting fetal development like increased substance use, poor nutrition, inadequate prenatal care which can all increase rates of low birth weight and preterm birth, both known risk factors for child psychiatric disorders.[21-27] Additionally, exposure to the psychiatric illnesses themselves and concomitant physiological changes like increased inflammation and hormonal deviations likely play a roles as well.[28] Further, after birth, childbearing parents with untreated perinatal mental health symptoms are less responsive to infant's cues and engage in fewer positive interactions with their infants.[23] Even more concerning, perinatal mental health conditions are the leading underlying cause of pregnancy-related deaths both nationally and here in Missouri.[29,30]

Given the impact that untreated perinatal mental health conditions can have on the developing infant, addressing caregiver mental health at the earliest stages is a critical preventative strategy to decrease the prevalence of child psychiatric disorders. Evidence supports caregiver treatment for mental health disorders resulting in improvements in infant development and

child mental health.[31,32] Unfortunately, less than 50% of childbearing parents with perinatal mental health symptoms seek treatment on their own, which highlights the need for proactive screening approaches.[33]

Perinatal Behavioral Health Service

All of this evidence led us to create the Washington University Perinatal Behavioral Health Service (PBHS) in 2012 to mitigate negative outcomes to caregivers and infants caused by the unmet caregiver mental health needs. PBHS has a special emphasis on providing quality, accessible care to patients in under-resourced communities and utilizes an interdisciplinary staff of clinicians who recognize the importance of treatment that addresses both the biological and psychosocial. Currently, PBHS provides comprehensive and culturally competent, trauma-responsive care, including mental health screenings, psychoeducation on perinatal mental health conditions, care coordination, psychotherapy and psychiatric services conveniently co-located within the Barnes-Jewish Hospital (BJH) and St. Louis Children's Hospital (SLCH) campuses. Since its inception, PBHS has served more than 14,000 patients and in 2021 alone, PBHS provided 2,327 screenings, 2,086 therapy appointments, and 684 psychiatry appointments for perinatal patients.

Additionally, our many community partnerships allow us to extend external resource referrals for in-home nurse visits, case management, housing, utilities, food, clothing, baby supplies, and other needed services. New parents and caregivers who are currently experiencing, or at risk for, perinatal mood and anxiety disorders, trauma disorders, substance use disorders, emotional distress, and/or other mental health conditions can access the services and support they need to care for themselves and their families. PBHS also serves parents and caregivers of children under the age of five whose conditions are medically complex, specifically children receiving care through the SLCH Heart Center and Epilepsy Monitoring Unit.

The opportunity to intervene during the prenatal period and in early childhood when the parent/child relationships are a central and powerful force in development has numerous advantages. First is that training caregivers to learn new parenting approaches and responses is an excellent long-term investment in the child's development as they can implement and carry forward these healthy approaches as the child develops, offering the opportunity for more sustained and enduring change. Another unique opportunity that arises when identifying and treating psychopathology early in development is the greater neuroplasticity and the potential for "sensitive periods" during this period when the effects of psychosocial interventions may have more powerful effects.[34,35] Along this line, several early interventions have shown remarkably large effect sizes suggesting neuroplasticity may be at play.[2,3,36-38] Such findings underscore the importance of early identification and intervention in mental disorders.

Center for Child and Family Development

Through generous philanthropic support of Bob and Signa Hermann, we have established the Hermann Center for Child and Family Development which allows us to provide the very early preventative intervention treatments that we have described here and to study their efficacy for varying patient and family presentations. The Hermann Center aims to provide the highest level of collaborative mental health support for children and families beginning as early as pregnancy to improve access to comprehensive mental health services for families with prevention and interventions services for both the child and caregiver.

Services that are provided include evidenced-based interventions aimed at preventing perinatal mental health conditions which are supported by the US Preventive Services Task Force as well as parent education, psychotherapy, and psychiatric care.[33] Additionally, the Herman Center delivers early interventions aimed at the parent/child dyad as noted above.[2-4] The Hermann Center also provides specialized care for children in foster care and those who have experienced trauma; it is a community resource navigation tool for all families that need it.

Through these services provided by an interdisciplinary clinical team, the Hermann Center tests models of treatment of children and their families that empower caregivers to nurture social, emotional, and neurodevelopmental foundations; strengthen parent/child relationships; utilize multi-disciplinary teams to promote well-being; and continue to research and develop interventions that

set a new standard of care within the community. This type of multidisciplinary care targeted to the earliest ages is the direction that child psychiatry as a field should continue to develop if we want to improve child mental health.

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Disclosure

None reported. **MM**

Supporting the Resilience and Mental Health of Missouri Healthcare Workers Through COVID-19 and Beyond: the Gateway2Wellness Program

by Ginger E. Nicol, MD, Chris Douglas, BS, Teddi Gray, CCRC, Vicki Martin, MA, Zhaohua Guo, PhD, Anna Kinghorn, MS, Ryan Colvin, MPH, Mat Reidhead, MA, Bradley A. Evanoff, MD & Jessica A. Gold, MD



Ginger E. Nicol, MD, (above), is at the Healthy Mind Lab, the Center for Mental Health & Wellness, and in the Mobile Health Research Core; Chris Douglas, BS, Vicki Martin, MA, and Zhaohua Guo, PhD, are at the Healthy Mind Lab; Teddi Gray, CCRC, is at the Healthy Mind Lab, and the Center for Mental Health & Wellness; **Jessica A. Gold, MD, MS**, is at the Center for Mental Health & Wellness; all are in the Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri. Anna Kinghorn, MS, Ryan Colvin, MPH, and Bradley A. Evanoff, MD, MPH, are in the Division of General Medical Sciences, and the Center for Healthy Work, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri. Mat Reidhead, MA, is at the Missouri Hospital Association, Jefferson City, Missouri.

Abstract

The COVID-19 pandemic is over, but US healthcare workers (HCWs) continue to report high levels of work-related exhaustion and burnout but are unlikely to seek help. Digital tools offer a scalable solution. Between February and June 2022, we surveyed Missouri hospital administrators to assess HCW mental health and identify related evidence-based or evidence-informed resources. Simultaneously, we conducted a digital survey and focus groups with HCWs and leaders at Washington University School of Medicine (WUSOM) in St. Louis to evaluate HCW mental health needs, and preferences for digital support. Here, we describe the results and subsequent development of the Gateway to Wellness (G2W) program, a digital precision engagement platform that links HCWs to the most effective tailored resources for their mental health needs.

Introduction

In mid-2020, at the height of the COVID-19 pandemic in New York City, 60% of HCWs reported significant psychological distress, but 49% answered "no" when asked if they were interested in using wellness resources.[1] Numerous studies conducted over the course of the pandemic indicate that symptoms of DSM-5 (5th Edition Diagnostic and Statistical Manual) disorders like anxiety, depression, and post-traumatic stress among HCWs persist beyond acute infection surges.[2] Similarly, burnout—recognized by the International Classification of Diseases, 11th Revision (ICD-11) as a syndrome of work-related exhaustion, detachment, and reduced professional efficiency specifically related to chronic workplace stress[3]—is higher now than at previous points in the pandemic.[4-6] The crisis prompted the US Surgeon General to issue an impact report outlining the scope of the problem and detailing federal investment in HCW mental health in May of 2022.[7] The term 'resilience,' is often used interchangeably with terms like toughness or grit, which refer to fixed traits. Rather, resilience

refers to emotional self-awareness and the ability to adapt to difficult circumstances by seeking help when needed.[8] These qualities can be cultivated or learned,[9] to the benefit of HCWs and the systems in which they work. But resilience without self-awareness can lead to adversity tolerance and emotional detachment[10]—the very definition of burnout.

Despite persistently higher levels of reported mental distress in the HCW population for decades, their use of mental health services has consistently been low.[11] Systemically, time constraints, lack of access, and cost may prevent healthcare workers from getting the help they need.[12,13] More insidiously, many HCWs are reluctant to seek mental health care due to stigma,[14] or worry it will impact their professional reputation or license to practice.[15] Reluctance to use available services is also related to perceived differences between personal needs and the relevance or impersonal nature of available services.[16,17] HCWs tend to normalize symptoms, believing they can manage it on their own, or doubt their ability to accurately identify mental health issues.[18,19] Finally, healthcare executives may be particularly vulnerable to burnout; in a recent survey of American College of Health Executives, 33% met criteria for burnout.[20] We know from prior study that executives in general minimize their own burnout, which can result in their overestimation of employees' mental health.[21] And poor emotional health of HCWs affects the entire health system,[22, 23] leading to high staff turnover and related costs of recruiting, hiring and training new workers, reducing system capacity to care for patients, or both.[24] One study estimated that burnout costs $4.6 billion dollars a year in the US, and at the organizational level, this amounts to about $7,600 per employed physician per year.[25]

Dr. Lorna Breen's tragic death by suicide in April 2020 was a wakeup call for healthcare providers and the organizations that employ them. In collaboration with the National Academy of Medicine,[26] the Foundation named for Dr. Breene[27] developed a set of simple recommendations healthcare organizations could take to prevent suicide in HCWs that was the impetus for many institutions to quickly put in motion assessment and prevention measures. Also in April, 2020, WUSOM conducted the EMPlOyee Well-Being during Epidemic Response (EMPOWER) study to evaluate HCW distress in contrast to awareness and utilization of available resources.[28] Unsurprisingly, HCW use of employer-offered resources was low in contrast to reported levels of distress. Participants cited cost, work-related time constraints and concerns about confidentiality as reasons for not seeking help. They also indicated a preference for digital resources and digital support for navigating available resources, strongly suggesting that a digital solution would be accepted, and in fact might be necessary for addressing mental health needs remotely, privately and quickly. These results formed the basis of the WUSOM response to a request for applications from the Health Resources and Services Administration (HRSA) to develop and implement programs protecting the mental health of HCWs. This paper reports the results of the initial needs assessment, which informed development of the Gateway to Wellness (G2W) platform, a digital, measurement-based approach with live navigation support to link HCWs to the most effective resources for their mental health needs.

Methods

Study Design, Setting, and Populations

To better understand the mental health of Missouri HCWs, we conducted a two-phase needs assessment.

Phase 1: We conducted in collaboration with the Missouri Hospital Association (MHA), a digital survey of health system administrator perspectives on the mental health of HCWs in their organizations and detailed the evidence-based and evidence-informed programs in place to support HCW resilience.

Phase 2: This involved a redeployment of the EMPOWER survey, followed by an invitation to participate in a virtual focus group, interview, or a digital follow-up survey of open-ended questions to further detail HCW needs and preferences for mental health and mental health services.

The interconnected WUSOM and BJC HealthCare (BJC) system of hospitals and clinics, based in eastern Missouri, provides care in rural, urban, and suburban areas across the state. Washington University employs >19,000 faculty and staff and supports medical student (>1,300) and resident and fellow (>1,000) clinical training. WUSOM also has one of the largest faculty practices in the country with more than 55 clinical sites across the state. BJC is among the nation's largest health care organizations, with >30,000 employees, 14 hospitals, and numerous outpatient facilities across eastern Missouri and southern Illinois. This study was approved by the WUSOM Institutional Review Board.

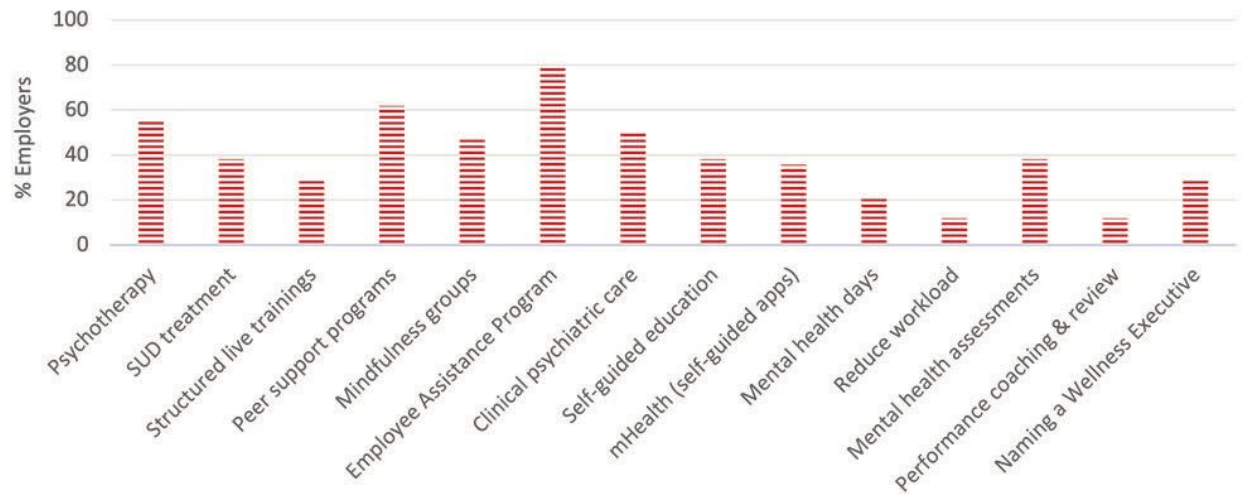


Figure 1. Mental Health Resources and Programs for Healthcare Workers in Missouri Health Systems

Needs Assessment Phase 1 Methods

In partnership with MHA, a digital survey was sent via email to 200 Missouri health system administrators in late February 2022 to assess their perceptions of HCW mental health and fatigue related to the pandemic, and to collect information on programs and resources in place to support HCW mental health. Participants were compensated for completing the survey.

Needs Assessment Phase 2 Methods

A final EMPOWER survey was sent to all Washington University employees (including HCWs and non-HCWs) in late February 2022. Psychological distress was measured by the 21-item Depression and Stress Scale (DASS-21).[29] Burnout symptom severity was measured with the 10-item burnout subscale of the Professional Fulfillment Inventory.[30] A series of questions about resilience and stigma were pulled from the six-item Brief Resilience Scale[31] and four questions related to mental health stigma were included.[32]

EMPOWER respondents who agreed to be contacted for additional assessments were invited via email to participate in a virtual focus group, 1:1 interview or to answer additional open-ended questions via a digital survey link. The goal of these focus groups and interviews was to identify mental health needs, openness to digital solutions for assessing and linking to personalized resources, and preferences for digital messaging and content.

The focus groups and interviews covered four different topics: 1) Medical trainee experience with seeking behavioral health support and recommended modes of program dissemination; 2) Experience with technology, preferred methods of contact, and recommended modes of program dissemination; 3) Reactions to the G2W dashboard, assessments, and program flow; 4) Behavioral health professionals' experience treating the HCW population and needs for supporting an influx of HCW patients from the G2W program. Participants were compensated for their participation.

Results

Phase 1 Results

We received responses from 45/200 (22.5%) Missouri hospital administrators, including from 16 hospital systems and three academic medical centers in Missouri. Thirteen respondents from Missouri organizations reported their work role was a function of their organization's Human Relations department. Five respondents reported a title associated with employee mental health (4) or organizational culture and development (1). One respondent was a Chief Medical Officer. Twenty-two respondents were departmental wellness leaders from within the WUSOM/BJC system.

Of the 19 organizations whose administrators responded to the survey, eight had employee populations <500; one had about 800 employees; six had 1,000-5,000 employees; two had 5,000-10,000 employees, and two had >30,000 employees. Eight organizations reported <10% of their employees

Table 1. Phase 1 and Phase 2 Needs Assessment Respondent Characteristics

Assessment Question & Response Options	n, (%) n=475
Depression and Stress Scale (DASS) responses of "moderate" "severe" or "extremely severe"	
Stress	59 (12.9)
Anxiety	78 (17.1)
Depression	79 (17.4)
Professional Fulfillment Inventory (PFI) score >1.33*	
Work exhaustion	261 (55.4)
Interpersonal disengagement	129 (27.6)
Burnout	205 (44.1)
Resilience (responses of "sometimes true" , "often true" or "always true"	
I'm able to adapt when changes occur	465 (99.1)
I tend to bounce back after illnesses, injury or other hardships	457 (97.9)
Mental Health Stigma responses of "agree" or "strongly agree"	
It is a sign of personal weakness or inadequacy to receive treatment for emotional or mental health problems	13 (2.8)
My supervisor would see me less favorably if they believed that I had an emotional or mental health problem	108 (23.0)
My co-workers would see me less favorably if they believed I had an emotional or mental health problem	119 (25.4)
Mental health care provided to faculty and staff at my institution is truly confidential	244 (52.0)
Reason for Nonuse of Available Resources	
Didn't feel I needed any mental health resources	221 (46.5)
Not aware of resources available	148 (31.2)
Too busy to access the resources	148 (31.2)
Privacy/confidentiality concerns	77 (16.2)
Using non-WU resources	58 (12.2)
Too many to choose from	12 (2.5)
Too difficult to access the resources	39 (8.2)
Lack of supervisor support	20 (4.2)
Resources are ineffective	10 (2.1)
*An overall score of >1.33 on the PFI is correlated with clinically significant symptoms of burnout.	

were from underrepresented racial, ethnic, or gender groups; six reported 10-20% of employees were from underrepresented groups; one organization reported 30-50% of employees were from underrepresented groups, and one organization reported 60-70% of employees were from underrepresented groups. Although 23.9% (11/45) of respondents observed general improvements in HCW mental health, 19.6% (9/45) continued to report HCW mental health as the worst it's been during the pandemic. Fatigue related to the pandemic was still significant, with 56.5% (25/45) of respondents reporting HCW fatigue as not good or the worst it's been during the pandemic. All organizations offered health insurance; five programs were self-insured.

Respondents were also asked to indicate whether their organizations offered any of 14 common evidence-based or evidence-informed programs to promote HCW resilience and mental health (Figure 1). These included: psychotherapy, Employee Assistance Programs (EAP), substance use treatment offered outside of EAP, clinical services offered outside of EAP, supervisor training, peer support, mindfulness programs, self-guided digital educational content, mobile health applications, encouraged use of mental health days, training to help HCWs reduce workload and redundancy, regular mental health assessments, incorporation of supervisor support of HCW mental health service use in performance metrics, and naming of a wellness executive.

Phase 2 Results

The February 2022 EMPOWER survey was sent to 11,790 Washington University employees; 2,646 responded (15.3%), 475 of whom were providing direct clinical care (Table 1). Responses to questions about depression, stress and anxiety, burnout, interpersonal disengagement, and work exhaustion, and resilience and mental health stigma are shown in Table 2. Notably, over half of respondents reported clinically significant work exhaustion, with just under half reporting significant burnout symptoms despite relatively low COVID infection rates at the time of the survey. And while more than half of respondents felt that mental health care provided by their employer was confidential, nearly a quarter of respondents reported that their supervisor and/or coworkers would think poorly of them for seeking help. Interestingly, the top three reasons for not using mental health resources included lack of need, lack of awareness, and lack of time over confidentiality concerns.

We also conducted 14 follow-up focus groups with 42 participants, including faculty members (n=13), clinical trainees (n=6) and staff members (n=23), and conducted interviews with WUSOM/BJC departmental and institutional leaders (n=37). Themes arising from focus groups included: 1) Personalized content and messaging that acknowledges contextual factors contributing to burnout and distress; 2) Mechanism for giving anonymous feedback about the program; 3) Resources and services need to be relevant

Table 2: Mental Health, Burnout, Stigma and Resource Utilization among WUSM Healthcare Workers

Assessment Question & Response Options	n, (%) n=475
Depression and Stress Scale (DASS) responses of "moderate" "severe" or "extremely severe"	
Stress	59 (12.9)
Anxiety	78 (17.1)
Depression	79 (17.4)
Professional Fulfillment Inventory (PFI) score >1.33*	
Work exhaustion	261 (55.4)
Interpersonal disengagement	129 (27.6)
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Resilience (responses of "sometimes true" , "often true" or "always true"	
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Mental health care provided to faculty and staff at my institution is truly confidential	244 (52.0)
Reason for Nonuse of Available Resources	
Didn't feel I needed any mental health resources	221 (46.5)
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Too busy to access the resources	148 (31.2)
Privacy/confidentiality concerns	77 (16.2)
Using non-WU resources	58 (12.2)
Too many to choose from	12 (2.5)
Too difficult to access the resources	39 (8.2)
Lack of supervisor support	20 (4.2)
Resources are ineffective	10 (2.1)
*An overall score of >1.33 on the PFI is correlated with clinically significant symptoms of burnout.	

and accessible; 4) Need treatment options outside of WUSOM for confidentiality; and 5) Options for completing assessments and accessing Navigator assistance via email as well as by text. Themes arising from interviews included: 1) Institutional support/ naming a Chief Wellness Officer; 2) Health insurance benefits and mental health services should be provided to employees of all types, not just those who are benefits-eligible; 3) Alignment of priorities between medical school and health system where applicable; 4) Institutionally-supported programs to reduce stigma of seeking mental health assistance; and 5) Digital tools that protect confidentiality and can reach HCWs providing care in rural settings.

Gateway to Wellness Digital Platform Concept & Development

An existing digital platform employed in delivering lifestyle change interventions to hospital workers,[33,34] and to individuals with serious mental illnesses receiving care in community mental health clinics[35] was identified as the framework for the G2W intervention (Figure 2). Features of G2W include electronic informed consent, a participant-facing dashboard that allows users to deploy digital assessments, track monthly scores, save, or swap preferred resources, and provide text feedback about the program.

The G2W program consists of scheduled monthly digital assessments and optional brief weekly check-ins sent to participants' cell phones via a link in a short message service (SMS) text message, and/or to their email, depending on user preference. The monthly assessment consists of 35 brief questions tracking five domains of mental wellbeing, including stress, mood, sleep, burnout, and emotional support. Participants receive their monthly assessment score along with a descriptive interpretation, and a personalized link to employer-offered resources across four tiers of symptom severity ranging from none or mild to critical. None to mild symptom resources include mindfulness groups, digital self-guided educational content, mobile health applications, and counseling. Clinical care provided by a medical professional is offered for moderate to severe symptoms.

In addition to the digital platform, a live mental health Navigator monitors assessments and can connect with participants by text, email, or phone call when behavioral assessments reveal crisis/extreme symptom severity. All participants will have access to secure, two-way SMS messaging with a Navigator for personalized problem-solving. Navigators can also contact participants if they haven't responded to weekly mental health checks for two weeks in a row (e.g., selecting "skip" counts as a response). G2W Navigators are certified in Adult Mental Health First Aid from the National Council for Mental Wellbeing[36] and knowledgeable about institutional and regional mental health resources available to HCW participants.

Discussion

Despite a relative reduction in COVID cases and illness severity across Missouri, health system leaders

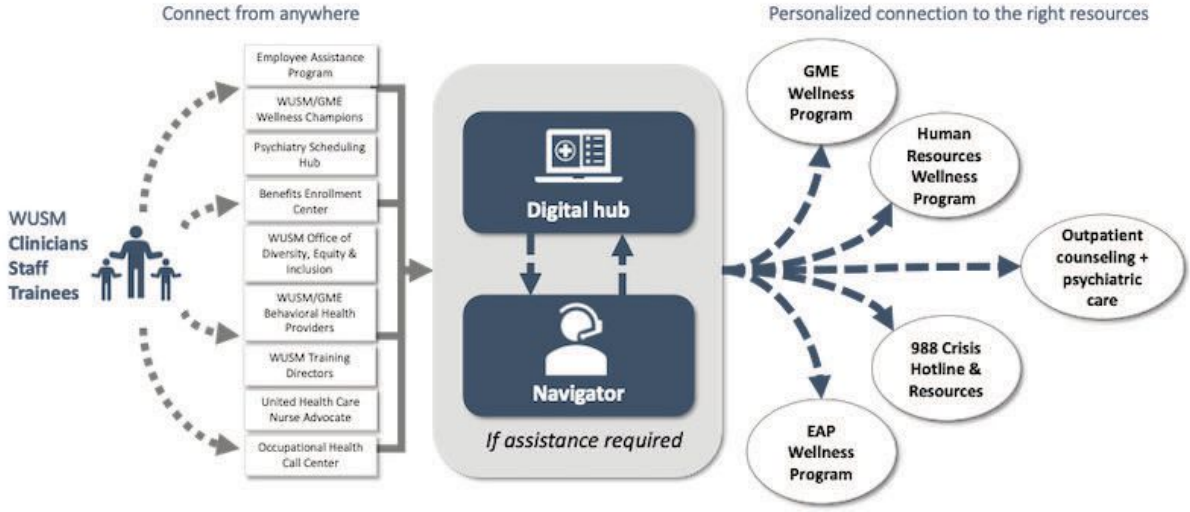


Figure 2. Gateway2Wellness Digital Platform and Program Overview

and HCWs both report high levels of psychological distress, burnout, and work-related exhaustion. At the beginning of the pandemic, 14.5% HCWs in the WUSOM system reported moderate to severe stress, 17.2% reported moderate to severe anxiety, and 16.4% reported moderate to severe depression.[28] In contrast, our recent assessment indicates a modest improvement in self-reported stress (12.9%), while anxiety symptoms remained unchanged (17.1%) and symptoms of depression worsened (17.4%). Most notably, the number of clinical workers endorsing clinically significant symptoms of burnout and exhaustion increased from 32% to 44% and 51% to 55%, respectively.

This report highlights four additional important findings: 1) HCW concerns are shifting away from mental and emotional distress to exhaustion and burnout; 2) Resource utilization remains low compared to the level of reported distress; 3) Reasons for non-use of available resources continue to reflect low awareness and limited time to access them; and 4) Perceived stigma against seeking mental health treatment remains prevalent.

These results extend observations in other health systems,[37] and suggest that contextual factors—such as shifting societal needs and a disintegrated health system—are now impacting HCW mental health more so than are infection rates. There is good news here too, though, in that there is now established guidance for changing contextual factors impacting HCW mental health, like workplace culture. A list of evidence-based strategies health systems and HCWs can use now to promote resilience can be found in Figure 3.

Limitations

This work is subject to important limitations; namely that it is specific to Missouri organizations and workers and may not be generalizable to the rest of the US health care system. Secondly, the small sample size in the Phase 1 needs assessment, combined with the low response rates in both phases of the needs assessment, may not fully represent the needs of all HCWs. In particular, HCWs in rural areas and underrepresented communities likely have significantly different mental health needs, with different barriers to accessing care. However, these data provide a starting point from which to develop, implement and test the effectiveness of a digital solution for reducing barriers to HCWs seeking psychological support.

Conclusion

The COVID pandemic exacerbated the already high prevalence of burnout, mental health disorders and emotional distress among HCW, spurring national action to improve the mental health of HCW. Digital care coordination, as conceptualized in the G2W project, offers a viable solution for promoting HCW use of mental health resources, especially for HCWs in rural areas where there may be few mental health providers. Digital assessment and linkage to existing

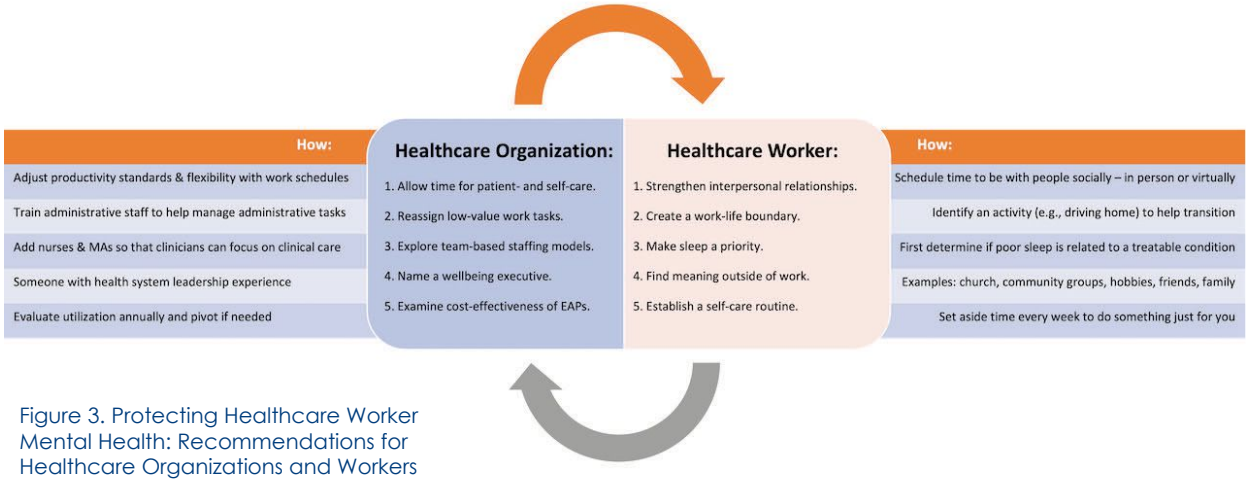


Figure 3. Protecting Healthcare Worker Mental Health: Recommendations for Healthcare Organizations and Workers

resources via an automated algorithm, with connection to a live mental health Navigator for more personalized self-care planning and problem-solving is one evidence-based approach to increasing prevention and leveraging early treatment opportunities.[38] Moreover, digital tools offer a degree of autonomy and privacy, allowing HCWs to learn about and access resources on their own terms.

Following the development of the G2W platform in 2022, this personalized digital intervention is being evaluated in WUSOM HCWs in 2023, with plans to expand its use in other Missouri health systems in subsequent years if initial testing shows improvement in HCW mental health outcomes. Supporting the mental health of HCWs is a long-term goal of existential importance to health care systems. Increasing access to appropriate and effective mental health treatment and support services is a critical element for achieving this goal; health care leaders must also take action to address modifiable sources of stress among HCW, to reduce stigma around mental health, and to create a culture of care and respect for our colleagues.

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Leveraging Implementation Science in the Treatment of Tobacco Use Disorder

by Alex T. Ramsey, PhD, Patricia A. Cavazos-Rehg, PhD, Li-Shiun Chen, MD & Laura J. Bierut, MD

Washington University in St. Louis
School of Medicine

Implementation science holds the keys to the uptake and routine use of evidence-based treatments and should be more fully leveraged in the tobacco use disorder field.



Alex T. Ramsey, PhD, Associate Professor, Patricia A. Cavazos-Rehg, PhD, Professor, Li-Shiun Chen, MD, Professor, and **Laura J. Bierut, MD**, Alumni Endowed Professor, are all in the Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri.

Abstract

The tobacco use disorder field has an armamentarium of approaches to help people quit smoking: medication-based treatment for tobacco use, digital therapeutics for just-in-time behavioral interventions, genetic and metabolic biomarkers to guide tobacco treatment, to name a few. Whether the treatment approach is old or new, an underlying truth remains: the benefit is only as great as the extent to which these treatment approaches reach individuals who need them most and prove effective and feasible to implement in real-world settings. Further, certain treatments tend to be used more robustly in practice, namely, those that address a great need yet are low in cost, burden, and risk of clinical harms. This is where implementation science comes in, providing guidance on how best to get effective treatments adopted and used in clinical and community settings. Implementation science holds the keys to the uptake and routine use of evidence-based treatments and should be more fully leveraged in the tobacco use disorder field. At the same time, disruptive technologies in treatment are breaking new ground, pushing the field of implementation science to build a bigger "toolbox" of ways to improve access and quality of treatment in an ever-evolving landscape.

In this paper, we underscore this synergy between tobacco treatment and implementation science. We spotlight emerging trends in tobacco use, effective and emerging treatment approaches for tobacco use, and ways that implementation science intersects with the current and evolving landscape of tobacco use and substance use disorder more broadly.

Current Landscape of Tobacco Use

Despite the reduction in cigarette smoking over the past decades, tobacco use remains highly prevalent, and smoking leads to devastating personal and societal consequences. Nearly half a million deaths per year result from cigarette smoking in the US.[1] Unfortunately, the prevalence of cigarette use in Missouri is high, with 17.3% of the adult population currently smoking.[2] Missouri faces this tremendous health burden while also being ranked 51st in the US for its cigarette tax and receiving the lowest rating in smoke-free air and tobacco control and cessation

funding.[3] The high prevalence of smoking and smoking mortality, along with tobacco-friendly laws and policies, is particularly troubling when considering the evidence of treatment effectiveness to promote smoking cessation, which highlights a persistent treatment gap and an opportunity to accelerate our translation of evidence to practice.

While the prevalence and treatment gap pose chronic challenges, the ever-evolving tobacco use landscape requires dynamic approaches to treatment. Perhaps the most compelling and paradigm-shifting trend is marked by the shift from combustible cigarettes to electronic cigarettes (e-cigarettes). This paper focuses on emerging trends in tobacco use, implications for treatment, and the role of implementation science in addressing formidable challenges in treating combustible and e-cigarette use amid changes in the landscape of tobacco use.

Combustible Cigarettes

One of the greatest public health successes over the past 50 years has been the reduction in combustible cigarette smoking, and the rapid decline in combustible cigarette use continues. In 2005, over 20% of US adults smoked cigarettes and by 2020, the smoking prevalence had decreased to 12.5% of adults.[4] Youth smoking has decreased even more rapidly. In 2000, 20.6% of students in twelfth grade smoked cigarettes daily compared to only 1.6% in 2022.[5] Many public health initiatives continue to target combustible cigarette smoking reduction with the ultimate goal of eliminating all tobacco use. Perhaps the most surprising effort to reduce smoking has been the stated goal of several large tobacco companies of eliminating combustible cigarettes sales while pivoting to the marketing of non-combustible tobacco products.[6] The reduction in combustible cigarette smoking will have positive health effects over the next several decades.

Electronic Cigarettes

The past decade has seen an exponential increase in the use of new types of tobacco products including e-cigarettes and other non-combustible tobacco products. These products offer a harm reduction approach for adults who smoke combustible cigarettes and a potential path to smoking cessation.[7] While the reduction of combustible cigarette smoking among adults continues, a growing concern is the introduction of e-cigarette use in youth. As shown in Figures 1 and 2, the 2022 Monitoring the Future report documents over 6% of twelfth grade students report using e-cigarettes daily, and over 20% have used e-cigarettes within the past 30 days.[5] Fortunately, despite the increases in e-cigarette use among youth in recent years, combustible cigarette use continues to decline in this age group.

While long-term health consequences remain a point of debate, emerging data have linked e-cigarette use to chronic respiratory conditions, asthma, and risks to heart health.[8] Specifically among teens and young adults, the nicotine in e-cigarettes can be harmful to the developing brain, altering mood, learning, impulse control, and increasing the likelihood of developing depression, anxiety, and substance use disorders.[9] More than half (55.3%) of teens and young adults state that they started using e-cigarettes because they were "curious."[10] In the coming decade, we are likely to see a further transition from combustible to e-cigarette use. The long-term health consequences, though likely to be less severe than with combustible cigarettes, remain to be defined. In addition, nicotine in e-cigarettes will be addictive, and approaches will be needed to aid individuals with cessation.

E-cigarette use is increasingly common among patients in the health care system, especially among patients with serious mental illness.[11] Although the prevalence of dual use of combustible cigarettes and e-cigarettes increased significantly in recent years, the probability of smoking cessation is higher among those with dual use compared to those who use combustible cigarettes only.[12] In addition, a recent Cochrane review showed high-certainty evidence that e-cigarettes with nicotine increased smoking cessation rates compared to pharmacologic nicotine replacement therapy.[7] Importantly though, individuals who dually use combustible cigarettes and e-cigarettes benefit from evidence-based tobacco treatment such as cessation pharmacotherapy and counseling.[12]

Current Landscape of Tobacco Treatment

With the current state of tobacco use in the US—declining but still high levels of combustible cigarette smoking and rising levels of e-cigarette use among youth—the effectiveness and implementation of evidence-based tobacco treatment remain critically important. Combining medication-based treatment for smoking cessation and counseling is the most effective treatment for smoking cessation.[1]

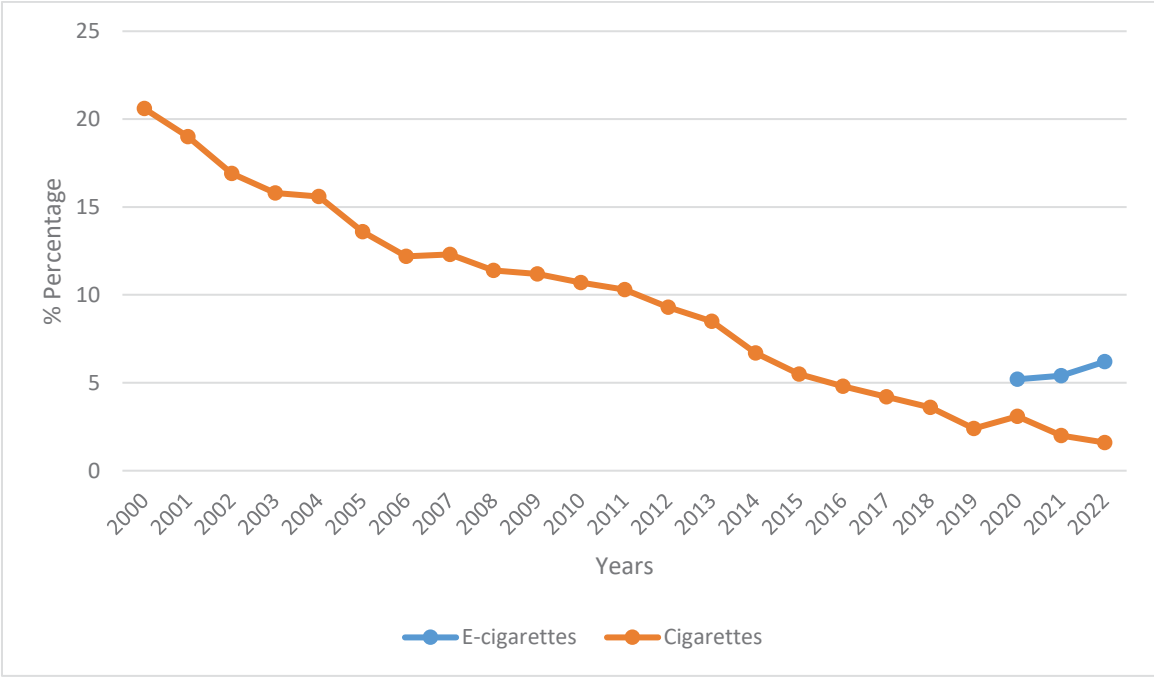


Figure 1. Trends in daily use of electronic and combustible cigarettes in Twelfth grade
Source: Monitoring the Future (monitoringthefuture.org/)

Medication-Based Tobacco Treatment

There are several evidence-based pharmacotherapies to treat smoking, and the two most effective options include nicotine replacement therapies and varenicline. Nearly 70% of smokers currently desire to quit.[1,13] Nevertheless, only one-third of smokers use an effective smoking cessation medication in community settings,[14] and only 5% of smokers are able to successfully quit smoking in a given year.[1,13]

Nicotine replacement therapies, including the nicotine patch, gum, and lozenge, are available over the counter and can also be prescribed. The nicotine patch reduces cigarette cravings for up to a full day by transmitting a steady level of nicotine through the skin. This nicotine replacement can be supplemented with nicotine gum or lozenges that work more quickly to suppress cigarette cravings. This approach of combination nicotine replacement therapy is generally more effective than using only one nicotine replacement method because of the underdosing of nicotine during a cessation attempt.[1,13]

Varenicline is a prescription-based treatment that is typically initiated prior to a quit attempt and then continued for at least 12 weeks. Varenicline, a partial nicotine agonist, is particularly effective because it diminishes a patient's desire for nicotine and prevents symptoms of withdrawal.[1,13]

Non-Pharmacological Tobacco Treatment

There are also a wide variety of non-pharmacological treatments for tobacco, including counseling and behavioral approaches. For instance, each state has a "quitline" (1-800-QUIT NOW) providing access to trained counselors who connect individuals who smoke to cessation medications and use principles of motivational interviewing and cognitive-behavioral therapy to help create a plan to quit smoking.[1,13] Quitlines have been shown effective particularly when individuals who smoke have access to multiple sessions and nicotine replacement therapy; unfortunately, most quitlines offer one session and limited access to nicotine replacement.[1] In addition, other mobile phone-based programs such as SmokefreeTXT and Smokefree apps (e.g., QuitGuide, quitSTART) offer free and convenient methods to receive on-demand support, game-based distraction from cravings, and guidance to reinforce a current or upcoming quit attempt. Importantly,

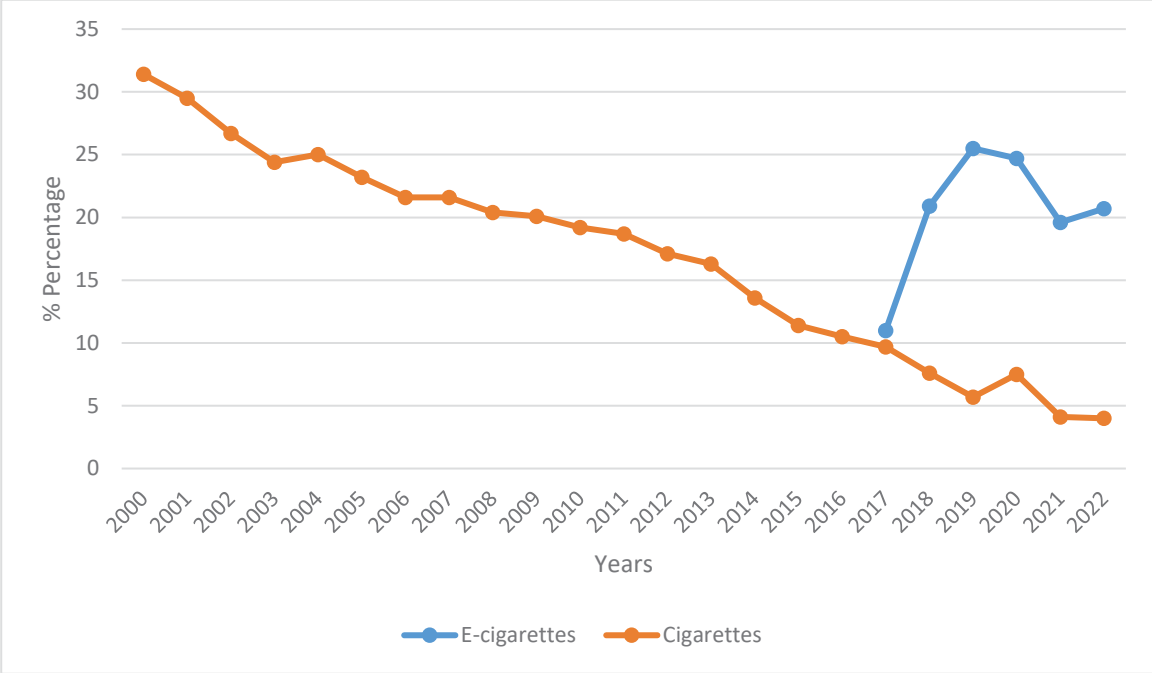


Figure 2. Trends in past-30 day use of electronic and combustible cigarettes in Twelfth grade
Source: Monitoring the Future (monitoringthefuture.org/)

even brief counseling by health care providers (three minutes) improves smoking cessation.[15]

Barriers to Uptake and the Need for Multilevel Interventions and Implementation Strategies

Despite the availability of evidence-based tobacco treatments, smoking cessation success is limited by a cascade of barriers at multiple levels. Specifically, smoking is only discussed with physicians in about 20% of patient visits, and less than 10% of patients who smoke receive a prescription for smoking cessation medications.[1,16] Further, less than one-third of those who try to quit smoking use any proven cessation treatments (behavioral counseling and/or medication).[1,17] In addition, medication effectiveness is limited, with less than 30% of patients quitting smoking upon receipt of cessation medications.[18,19]

This limited effectiveness has a compounding effect on the barriers to medication use, as even the perception of low effectiveness reduces the likelihood of patients being prescribed and adhering to available, evidence-based tobacco treatments that give patients the best chance possible to quit smoking. The cumulative effects of these constraints yield a low expected rate of smoking cessation, with less than 5% probability of quitting in a given year among patients who smoke.[1,13] Due to these barriers at multiple levels—physician, patient, and the perceived and actual limitations on effectiveness of tobacco treatments—there is a great need for interventions and implementation strategies to improve low physician prescribing, low patient uptake, and limited medication effectiveness. Implementation science is an emerging discipline that is uniquely primed to address these barriers and stimulate the uptake and routine use of effective treatments in clinical and community settings.

Current Landscape of Implementation Science

Implementation science is defined as the systematic study of methods and strategies that facilitate the uptake of research findings and evidence-based practices into regular use by practitioners and policymakers.[20] The typical focus of implementation science has centered on long-standing and well-established evidence-based practices. This dedicated attention to promoting the use of "on-the-shelf" practices, policies, and programs is important. For the

small fraction of research findings that are translated into implementable evidence-based practices, the process of moving from innovation to everyday practice is reported to take on average 17 years.[21,22]

To address more "upstream" barriers contributing to this 17-year gap, many in the field of implementation science have called for greater consideration of implementation "prerequisites" among interventions that are in earlier stages of translation.[23] For example, newer treatment approaches with a certain profile are theorized to be used more robustly in practice, namely, those that are high in demand yet low in cost with minimal risk of clinical harms.[24] Similarly, taking a more anticipatory approach of identifying likely "accelerators and inhibitors" of implementation with any new treatment (e.g., intervention scalability, implementation capacity, misaligned perceptions across physicians and patients) can speed the implementation of treatments for tobacco and other substance use disorders.[25] Such pre-implementation efforts may increase the likelihood of, and reduce the timeframe required, for evidence to make its way into real-world practice.

Specifically for tobacco treatment, accelerators include the low cost, low risk, and low clinician burden associated with providing smoking cessation medication and counseling to patients. On the other hand, inhibitors include the perception that smoking cessation medications are not effective or safe and a reluctance among clinicians to treat smoking. Prior research found misalignment between clinician and patient perspectives, with clinicians reporting perceived low interest among patients who smoke, despite the vast majority of patients reporting desire to quit and an interest in tobacco treatments.[26] Two important prerequisites for tobacco treatment—anticipatory strategies to accelerate the implementation of these effective medication and counseling approaches—are to 1) ensure that both patients and clinicians share the understanding that patients want help to quit smoking and that evidence-based tobacco treatments are effective and safe; and 2) find innovative approaches that continue to improve the effectiveness and promote the use of tobacco treatments.

Successful Models to Implement Tobacco Treatment

Multilevel barriers have been identified across healthcare systems and different specialties including patients with serious mental illnesses, cancer, and acute medical conditions.[11,26] Addressing these barriers, multilevel strategies involving use of electronic health records functionalities, team-based approaches, and provider feedback have enabled point-of-care tobacco treatment, resulting in increased and sustained reach and effectiveness of tobacco treatment.[15,27–29] Importantly, point-of-care tobacco treatment was shown to be a cost-effective implementation strategy in resource-limited settings.[30] Finally, recent data from 28 large cancer centers implementing tobacco treatment highlighted that local context (e.g., program characteristics) should drive the implementation strategies used.[31] These contextual factors can be categorized in ways that enable future centers to model their programs on similarly-profiled centers.

Intersection of Implementation Science and Innovative Approaches to Tobacco Treatment

The field of implementation science is in its adolescence, enriching its methods, partnerships, and role within health and healthcare, but also embarking on new challenges and new territory that had previously not been studied by implementation scientists. Increasingly, health sciences are applying an implementation science lens to guide the development, testing, and eventual implementation of emerging treatment innovations. This trend toward designing for dissemination and implementation[32] is gaining momentum in healthcare research, including in the addictions field. We highlight a couple key areas, genetic and other biomarkers and digital technologies, which reflect emerging approaches with potential for high impact in tobacco treatment if guided by principles of implementation science.

Genetics and Other Biomarkers

The use of genetics and other biomarkers has embarked on multiple healthcare sectors and is emerging in the addictions field. These advances are primed to benefit tobacco treatment, in particular. Potential future applications of genomic information include informing risk stratification, guiding the selection and dosing of personalized treatments, and motivating behavior change and the use of evidence- and guideline-based care among patients and clinicians.[33]

Genomic Information Informing Risk Stratification

The past decade has seen an unparalleled gain in genomic knowledge, and we can now identify who is at high risk of initiating smoking behaviors, smoking more heavily, and having difficulty quitting smoking.[34]

In addition, genomic information has demonstrated prognostic validity by identifying variation in risk of smoking-related diseases such as lung cancer and chronic obstructive pulmonary disease.[33,34] This information can be useful in prioritizing prevention and treatment efforts for those at highest risk.

Genetically-Guided Treatment

Given the barriers to clinician and patient uptake of evidence-based tobacco treatment highlighted above, innovative approaches are needed to personalize and enhance the effectiveness of tobacco treatments so that they will be prescribed and highly recommended by clinicians and then used and adhered to by patients. Genetics and other biomarkers are primed to help determine which tobacco treatments will work best for which individuals. For instance, variation in nicotinic receptors and nicotine metabolism can guide whether varenicline versus nicotine replacement therapy is likely to have greater effectiveness and fewer side effects.[35,36] In addition to improving success rates among treated patients who smoke, genetically-guided treatment may also stimulate implementation by improving the perceived value of these treatments among clinicians and patients.

Increasing Motivation for Behavior Change

Return of genetic risk feedback is a promising approach to nudging patients to use evidence-based tobacco treatments. When paired with positive framing of the benefits of engaging in healthier behavior change, as well as recommendations and resources to enact on behavioral intentions, genetic risk feedback tools provide the opportunity for a teachable moment that can activate behavior change among individuals who smoke.

Digital Technologies

Digital technologies such as mobile health (mHealth) apps have been used to address a wide range of addiction-related problems and have potential for broad reach at low cost for individuals who smoke. A key implementation challenge has been determining who pays for these services and for how long. Another key prerequisite of mHealth tools is that they are designed with the end-user in mind. Human-centered design therefore presents a promising approach to ensuring that digital technologies are likely to be used in real-world contexts. This process involves engaging in iterative cycles of stakeholder-driven needs assessment, technological development with user input and testing, and progressively scaling toward real-world implementation.

Social media can also facilitate implementation by reducing barriers to in-person disclosure and help-seeking behaviors with system features allowing for anonymous or mediated communication between those with similar experiences and less fear of judgment or social stigma.[37] Thus, user-generated content can be used not only for surveillance of public health issues, but also to better understand the symptoms, motivations, and needs of mental health and substance use populations. Use of social media involving disclosure of substance use does come with potential risks related to misinformation, employment considerations, and content or responses that could trigger additional substance use cravings; the potential risks and benefits should be weighed carefully on an individual basis. However, with proper safeguards and precautions in place, social media can serve to identify potential recipients of treatment as many individuals posting about e-cigarettes on social media could benefit from interventions aimed at preventing or reducing substance use.

Digital interventions have been shown to contribute to substance use cessation with comparable effects to in-person care,[38,39] including for combustible and e-cigarette smoking. However, promotion of uptake and sustained engagement over time can be challenging for interventions merely providing static psychoeducational resources. The integration of innovative and interactive components has been crucial to promote user engagement over time, especially for behaviors related to substance use disorders which have high rates of relapse.[39,40]

Conclusion

Leveraging principles from implementation science will be critical in facilitating the adoption, routine use, and sustainability of evidence-based tobacco treatments. The research highlighted here demonstrates the successes and growth opportunities in smoking cessation but naturally extends to the substance use disorder field more broadly. As new, "disruptive" technologies in tobacco treatment such as genomics and mHealth technologies continue to surface and attract consumer demand, they apply forces to the field of implementation science, which aims to guide the appropriate integration of evidence into real-world practice. In doing so, these emerging innovations will continue to push the field of

implementation science to build a bigger "toolbox" of ways to improve access and quality in the ever-evolving landscape of tobacco and other substance use disorder treatment.

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Better Biomarkers, Faster Drugs, Stronger Models: Progress Towards Precision Psychiatry

by Joshua S. Siegel, MD, PhD, Craig Pearson, MS & Eric J. Lenze, MD

Parallel advances in how we understand, measure, and treat psychopathology are enabling a paradigm shift towards precision psychiatry. This shift will also require pathways for widespread clinical adoption of novel tools and treatments.



Joshua S. Siegel, MD, PhD, (above), Instructor of Psychiatry, Craig Pearson, MS, medical student, and Eric J. Lenze, MD, Chair of the Department of Psychiatry and Director of the Health Mind Lab, are all at Washington University School of Medicine, St. Louis, Missouri.

Abstract

The 21st century has brought novel therapies and new therapeutic targets for major depressive disorder (MDD). Until recently all antidepressant medications targeted monoamines—serotonin, norepinephrine, and dopamine—and their regulatory systems. But growing evidence has suggested that individuals who fail to respond to a monoaminergic treatment are likely to fail to respond to other monoaminergic options. The emergence in recent years of treatment targets beyond the monoaminergic systems (e.g. κ-opioid antagonists, ketamine and other NMDA modulators, neurosteroids) has cultivated hopes for not only greater efficacy in treating depression, but also improved precision in targeting specific phenotypes and symptoms. Concurrently, an expanding repertoire of diagnostic and assessment tools—such as smartphone-based experience sampling and brain imaging—is moving the field toward more reliable and symptom-specific measurement with greater descriptive and prescriptive power. Taken together, these diagnostic tools and treatment options herald a new era of "precision psychiatry"—the selection and implementation of an optimal treatment for an individual patient's particular needs.

Anhedonia offers an example of the new precision psychiatry. Anhedonia has moved from merely one among several criteria for depression to a transdiagnostic psychopathology which can be understood neurobiologically, assessed quantitatively, and centered as a primary target in research and development of novel pharmacotherapies. We describe functional testing of reward circuits in the development of kappa-opioid antagonists for anhedonia. This offers a lens for understanding how and under what circumstances other novel treatments, such as psychedelics, might find a place in the future landscape of precision psychiatric care.

A Brief history of Antidepressant Drug Development

In the 1950s, researchers at Hoffmann-La Roche discovered that iproniazid—a derivative of isoniazid, a drug used to treat tuberculosis—caused patients with depressive symptoms to become

happier and more energetic, with improved appetite and sleep.[1] In the same decade, the tricyclic compound imipramine was found to improve mood and alleviate symptoms of depressed patients. The FDA approved both iproniazid and imipramine for use in major depressive disorder (MDD). The hypothesis that low levels of monoamines (such as norepinephrine and serotonin) might be common among people with depression spurred efforts to develop other monoaminergic drugs over the subsequent decades. These compounds largely shared the same targets; the innovation lay in progressively improving their side effect profiles. Since the approval of fluoxetine in 1987, mainstream psychiatric pharmacology has placed selective serotonin reuptake inhibitors (SSRIs) as the first-line treatment for depression, due primarily to their safety and ease of use. Despite these advances, only approximately 40-50% of treatment-naïve individuals remit. The landmark STAR*D trial demonstrated that individuals who fail to respond to two monoaminergic treatments are very unlikely to respond to a third monoaminergic option.[2]

The significant burden of MDD coupled with the high failure rate of conventional treatments has motivated a search for novel therapies, as well as phenotypes and biomarkers which might more precisely guide the choice of treatment. Below, we discuss how these are progressing in parallel towards precision psychiatry.

Novel Pharmacotherapeutics

The observation that subanesthetic ketamine, a non-competitive channel blocker of N-methyl-d-aspartate (NMDA) glutamate receptors, produces rapid recovery over hours in some individuals who had failed monoamine therapies[3] precipitated a paradigm shift, introducing the concept of so-called "rapid antidepressants." This inspired a search for structurally or mechanistically related compounds, with a particular interest in removing the dissociative side effects of ketamine.

Glutamate (the endogenous neurotransmitter for NMDA receptors) is an amino acid rather than a monoamine. Together, glutamate and GABA account for >95% of neurotransmission in the brain, whereas monoamines (serotonin, dopamine, norepinephrine) make up less than 0.001%.[4] In the last decade, a number of other drugs targeting amino acid receptors have shown promise as rapid antidepressants and remain under investigation.[5] Dextromethorphan is one such drug which, in combination with bupropion to inhibit its metabolism and boost its concentration to therapeutic levels, has now achieved FDA approval for treatment resistant depression (TRD).[6] Like ketamine, it is an NMDA antagonist, though it has other effects (such as serotonin reuptake inhibition and sigma-1 agonism).[7] Other examples include lanicemine, a metabotropic glutamate receptor modulator,[8] and nitrous oxide, an NMDA antagonist which appears to produce similar antidepressant effects to ketamine.[9] Neurosteroids are also emerging as a promising class of treatments. See review by Steven Mennerick and Charles Zorumski in this issue for further discussion.

In parallel with the advances precipitated by ketamine, renewed interest has been given to psychedelic compounds. LSD and psilocybin were first studied by Western biomedical researchers in clinical trials in the 1950s and 1960s but subsequently halted when psychedelics became DEA schedule 1 drugs. Since the early 2000s, studies largely focused on psilocybin have demonstrated rapid-acting and sustained effects on patients with MDD, including treatment-resistant depression.[10] Psychedelics produce their characteristic perceptual effects via biased agonism of the 5HT2A receptor. Preclinical evidence suggesting that the therapeutic effects of psychedelics may be dissociable from their perceptual effects (in rodents) has prompted interest in the development of non-hallucinogenic 5HT2A agonists as potential treatments for mood and addiction disorders.[11,12]

The opioid system has also emerged as a promising target for mood disorders. κ-opioid receptor antagonists (such as JNJ-67953964), show promise as antidepressants with efficacy in targeting reward/motivation symptoms. Below, we outline a framework for precision psychiatry that can guide future drug development and clinical practice and we present, as an example, the approach taken to validate human target engagement by κ-opioid receptor antagonist JNJ-67953964 using functional magnetic resonance imaging (fMRI).[13]

Towards Precision Psychiatry

The modern diagnostic and statistical manual (DSM) has attempted to classify psychopathology based on objective epidemiological data and represents a huge advance – particularly in reliability – over prior approaches to psychiatric diagnosis.

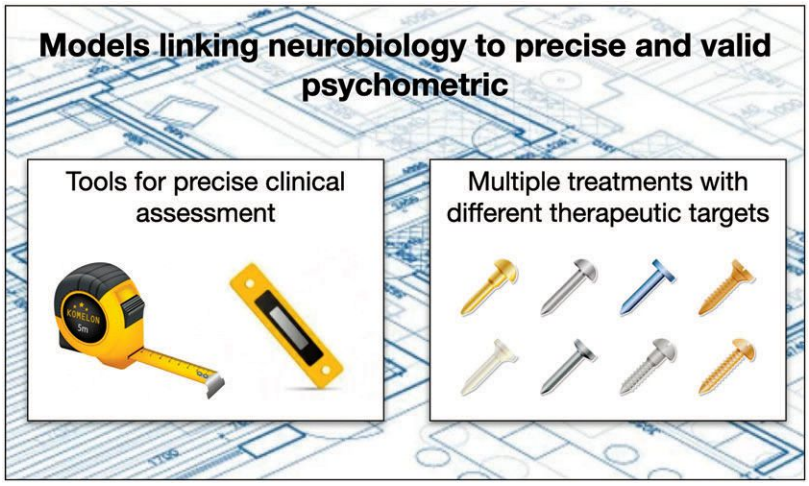


Figure 1. Blueprint for Precision Psychiatry

However, diagnostic nosology driven by the DSM continues a symptom-based approach to illness rather than a neurobiological basis, which allows for considerable heterogeneity of phenotypes within each diagnosis. This heterogeneity has clouded attempts to identify clear biomarkers and develop targeted treatments. Any study that includes this phenotypic variability will demonstrate muted effect sizes due to potential differences in underlying etiology. As a consequence, randomized controlled trials (RCTs) for neurobehavioral interventions have typically used suboptimal behavioral measures, rigid treatment protocols (i.e. fixed dosing), and largely avoided clinical biomarkers.[14]

Spurred on by the convergence of the growing range of treatment options and improving understanding of neurocircuitry, precision psychiatry is emerging as an antidote to the heterogeneity of psychiatric disorders. Precision medicine can be defined as a treatment approach that accounts for individual variation, with the primary goal of providing the right treatment at the right dose to the right patient at the right time.[15] The ability of precision medicine to improve neurobehavioral interventions depends on advances in multiple linked domains: 1) better models linking psychopathology to neurobiology; 2) more precise biomarker measurement; and 3) flexible delivery of multiple treatment options (Figure 1). We have presented evidence that pharmacological treatment options have advanced considerably. Below, we consider how understanding and measurement have advanced and where further progress is needed.

Neurobiological Precision

To overcome these limitations of the DSM diagnostic system, the National Institute of Mental Health (NIMH) has established the research domain criteria (RDoC) framework. The term "RdoC" was intentionally meant to contrast with the Research Diagnostic Criteria (the forerunner of DSM-III), indicating that RdoC assesses patients according to empirically defined neurobiologically based domains (such as anhedonia). This neuroscience-based approach increases the likelihood that the neural circuitry relevant to the condition of interest has been established and biomarkers exist. Because of the sheer complexity of human neurobiology, this model necessitates research that spans from the molecular and genetic up to the systems and psychological levels.

Temporal Precision

Another limitation of the DSM-based approach is its poor temporal resolution. Investigations of biomarkers based on diagnostic nosology have depended on the premise that depression is comprised of specific neurobiological traits (rather than a state) that remains stable over weeks to months. This premise is likely valid, however when applied in clinical research, it fails to control for changes in mood and cognition over minutes/hours, diurnal fluctuations, or other timescales of neurobiological importance which may be larger, and perhaps more important, than trait effects.

Novel Biomarkers

A range of approaches show promise as tools to improve both temporal and neurobiological precision. A useful depression biomarker should demonstrate a large effect size, i.e. a large and reliable change relative to random variance, after successful treatment. Promising biomarkers include ecological momentary assessments (EMA) of mood and behavior, more biologically sensitive and reliable symptoms scales, more sensitive and biologically validated psychometric assessment, and neuroimaging, such as positron emission tomography (PET), fMRI, functional near infrared spectroscopy

(fNIRS), electroencephalography (EEG), and transcranial magnetic stimulation-EEG (TMS-EEG).

The rapid adoption of smartphones offers a low hanging fruit for obtaining much higher fidelity temporal assessment.[16] Through a smartphone, EMA can track an individual's mood and behavior both actively (by repeatedly asking an individual to report mood and other subjective or behavioral data in the moment) and passively (by gathering data on an individual's behavior/experience). For example, Ajilore's BiAffect keyboard[17] passively tracks the keystroke patterns of individuals during routine use of their mobile phones and analyzes patterns in keystroke behavior over time. In a study of individuals with bipolar affective disorder, patterns of keyboard strokes predicted both manic and depressive symptoms, suggesting that patterns of keyboard usage might have the capacity to rapidly detect changes in affective states and allow earlier intervention. Geolocation tracking is another promising monitoring strategy; for example, roaming entropy (diversity in patterns of movement through ones environment) may predict mood changes before they happen.[18] Further research is needed to validate these techniques.

Human neuroimaging has long been a tool for both mechanistic and pharmacotherapeutic research in psychiatry. Advances in PET, fMRI, fNIRS, EEG, and TMS-EEG offer an expanded repertoire of experimental and clinical potential. Historically, PET has been the most useful human brain imaging modality for establishing target engagement on a pharmacodynamic (i.e., receptor binding) level. The use of D2 (dopamine receptor)-binding radiotracers has been applied to target engagement as well as establishing the safety and dosing of novel antipsychotics.[19] Functional targets for antidepressants have not been as easy to define. But advances in mechanistic models of stress and depression, such as the neurotrophic model[20] offer promising targets. Several PET radiotracers have been proposed to measure neurotrophic effects in humans with MDD. Radiotracers measuring synaptic vesicle glycoprotein 2A (SV2A),[21] cAMP signalling,[22] and AMPA receptor density[23] have all have shown potential for provide inroads into understanding drug-induced neurotrophic stimulation[24] and better modeling the intersection of different drug classes with disease subtypes.

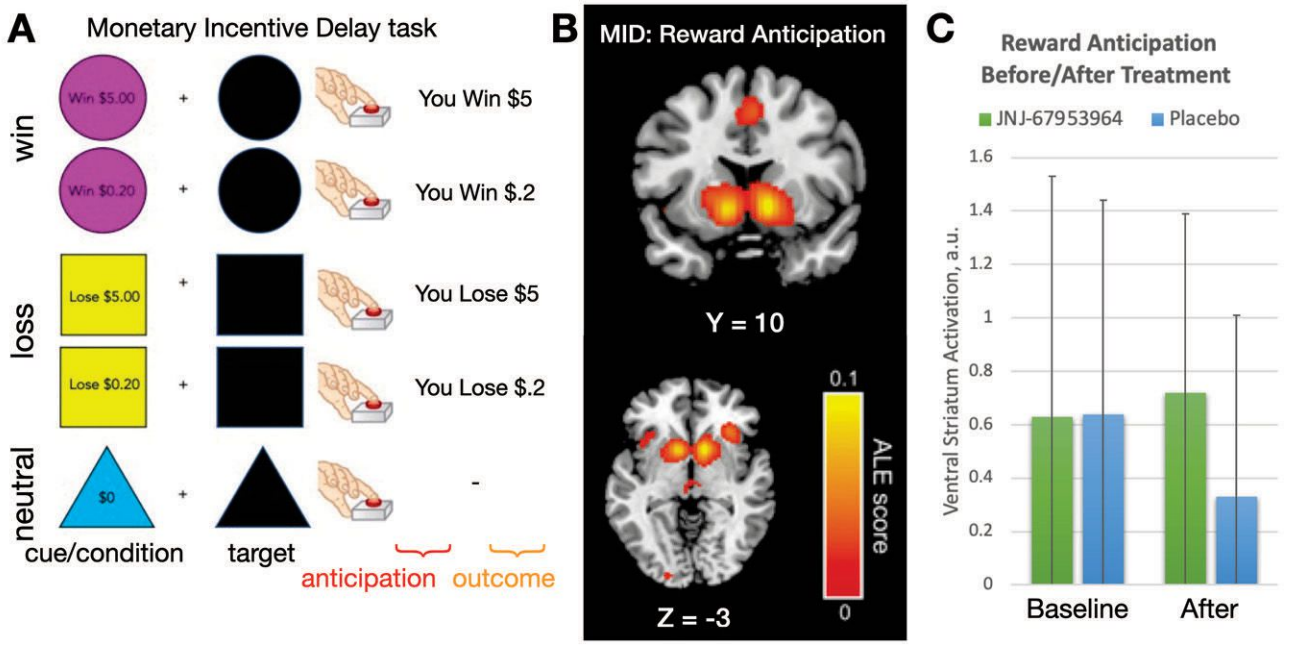
Task and resting fMRI are promising non-invasive tools to aid in development and targeting of antidepressants. While large resting fMRI studies have suggested that brain-behavior effect sizes are small,[25] brain-drug effect sizes may be considerably larger. The ability to identify brain signatures of known antidepressants could enable screening of novel or repurposed molecules for antidepressant potential. Moreover, the precision functional mapping (PFM) strategy developed at Washington University may increase reliability and specificity of fMRI. PFM combines dense repeated sampling and individual-specific analysis to detect effects of interventions in small cohorts.[26]

These examples are a small subset of the many tools developed by biomedical research that are at or nearing demonstration of clinical utility. To realize the potential of precision psychiatry, these tools must bridge from translational research into clinical practice (the so called 'valley of death'). Clinical adoption of these tools must start with large clinical trials that utilize precision psychiatry methods and tools.[14] In parallel, clinical research and meta-analysis must consider how specific dimensions of psychopathology (rather than a broader DSM diagnosis) can be used to identify which treatment option is best suited to which patient.

Anhedonia: An Example of Using Neurobiological Models and Biomarkers to Develop Targeted Therapy

Anhedonia is the reduced capacity to anticipate or experience pleasure or reward. It is a core symptom of numerous psychopathologies with high heritability and relatively small correlation to overall ratings of anxiety or depression.[27] And yet, the conventional professional guidelines recommend a DSM-based, one-size-fits-all approach in individuals with MDD who have deficits in motivation and hedonic pleasure. Regrettably, the application of this approach favors drugs shown to be ineffective in treating anhedonia per se. Indeed, the first-line pharmacotherapy for MDD (i.e., SSRIs) has been repeatedly shown to blunt emotion and reward processing, with the likely side effect of worsening anhedonia rather than alleviating it.[28]

Because anhedonia itself is not a DSM diagnosis, biotechnology and pharmaceutical companies have not traditionally emphasized it as a meaningful treatment target. Thus, limited efficacy of current antidepressants for anhedonia has been compounded by limited pathways to creating new effective treatments. An unfortunate consequence is that anhedonia has become



Figures 2 A, B, C. Target engagement in Anhedonia using the Monetary Incentive Delay fMRI.

A) In each trial of the Monetary Incentive Delay task, participants can win or lose money by responding to simple visual stimuli with a button press. Brain activity is measured during anticipation and outcome phases. Adapted from Knudson et al., 2000.

B) A meta-analysis of 50 published MID studies shows activation in the Ventral Striatum during reward anticipation (reproduced with permission from Oldham et al., 2018).

C) Ventral striatum (nucleus accumbens) activation during reward anticipation before and after 8 weeks of daily kappa opioid receptor antagonist (JNJ-67953964) vs placebo (Krystal et al., 2020) showing an interaction of time by treatment ($P<0.01$). Error bars represent standard deviation.

a negative prognostic factor in predicting successful treatment of depression.[29]

Notwithstanding, translational neuroscience research has developed increasingly nuanced understanding of the cortico-striatal circuitry involved in reward and how it is altered in anhedonia and can be corrected pharmacologically.[30] Advances in fMRI have made it possible to probe reward circuitry in humans with increasing sensitivity and advances in anhedonia clinical scales have enabled improved reliability and validity of clinical assessments. Below, we describe how this has opened the door to developing novel pharmacotherapies for anhedonia.

Anhedonia Model and Biomarker

The Monetary Incentive Delay (MID) fMRI task measures brain activity during anticipation and receipt of monetary reward/loss (Figures 2A).[31] Individuals with anhedonia show blunted activity during reward anticipation in the nucleus accumbens (NAcc), a subcortical brain region which plays a key role in motivation and reward. Encodes subjective value during anticipation and consumption of reward. This has been observed across psychiatric diagnoses.[32–35] Successful treatment of anhedonia corresponds to increased NAcc responses.[36] Because of these studies, and more than 50 others,[37] the MID has become one of the most clinically validated fMRI paradigms to study anhedonia (Figure 2B.)

The MID task has demonstrated clinical value for assessing the reward system in numerous trials. For example, MID studies have found that serotonin-norepinephrine reuptake inhibitors have superior effects on reward response over selective serotonin reuptake inhibitors,[38] dopamine agonists increased striatal reward anticipation,[39] and atypical antipsychotics are superior to typical antipsychotics in patients with blunted reward.[40] Conversely, buprenorphine augmentation of antidepressant therapy showed no increase in reward

response, which corresponded to a lack of benefit in anhedonia symptoms.[41]

These promising studies led to a multi-site phase II placebo-controlled RCT of a kappa-opioid antagonist JNJ-67953964 for the treatment of anhedonia, in which the primary outcome was NAcc activation during reward anticipation on the monetary incentive delay fMRI task (Figure 2C).[13] JNJ-67953964 produced a moderate improvement in NAcc activation and a large improvement in self-reported anhedonia, as measured with the Snaith Hamilton Anhedonia/Pleasure Scale (SHAPS). The drug is currently in multiple phase-III trials. Notably, the FDA has still required an indication for 'MDD with anhedonia'.

Rapid Antidepressants for Anhedonia?

Armed with more precise measurements of neurobiological, behavioral, and subjective assessments of anhedonia and reward, researchers are now able to better evaluate novel treatments. Among these novel treatments, the rapid antidepressants ketamine and psilocybin have shown promise.

Ketamine and psilocybin appear to rapidly alter function in the reward systems. Rapid induction of plasticity-related immediate early genes by these compounds is followed by dendritic spine growth[42] and synaptogenesis in the mPFC and limbic system.[42] In a small RCT ketamine rapidly improved anhedonic symptoms and changes in metabolism in the striatum.[43] In a systematic replication of patients diagnosed with MDD, ketamine produced these anti-anhedonic effects independently of its general antidepressant efficacy.[44]

A growing body of studies have also suggested mechanism and efficacy of psychedelics for the treatment of anhedonia. 5-HT_{2A} serotonin receptors, the primary target for psychedelic drugs, are expressed at high levels in the cortico-mesolimbic reward circuitry, including the cerebral cortex, ventral striatum, and hippocampus.[45] Psychedelics appear to increased responsiveness to reward by increasing oxytocin expression through a 5HT-dependent pathway.[46] In a head-to-head clinical trial comparing psilocybin with daily escitalopram for TRD, the two drugs did not significantly separate on depression scales, however the psilocybin cohort showed superior recovery of reward and motivation deficits (Cohen's d = 0.68 on SHAPS, d = 1.24 on Laukes Emotional Intensity Scale).[47] Recently, micro-doses of LSD were found to increase reward-related signal on an EEG version of the MID task.[48]

Given that traditional antidepressants are poorly suited to treating anhedonia, a closer focus on how and in-whom novel antidepressants modulate reward circuits will have direct and clinically significant impact. In combination with precise measures of anhedonia in clinical care, this will enable greater precision in psychiatric care.

Summary

Parallel advances in how we understand, measure, and treat psychopathology are enabling a paradigm shift towards precision psychiatry. This shift will also require pathways for widespread clinical adoption of novel tools and treatments. While anhedonia is a singular domain of the depression syndrome, the success highlighted above opens the door to embracing similar approaches for other domains, such as sleep, energy, or suicidal ideation. It will require a shared vision between drug developers, drug regulators, and clinical providers to achieve greater precision in psychiatric care.

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The Taylor Family Institute at Washington University: Novel Treatments in Psychiatry

by Charles F. Zorumski, MD & Steven J. Mennerick, PhD

Washington University in St. Louis
School of Medicine

Unrestricted and flexible sources of support to develop and sustain innovative programs are required; this is what the Taylor family created, helping to fuel high-risk and potentially high-reward preclinical and clinical studies.



Charles F. Zorumski, MD, (above), Professor, and Steven J. Mennerick, PhD, Professor, are in the Department of Psychiatry, and the Taylor Family Institute for Innovative Psychiatric Research and Silvio O. Conte Neuroscience Center at Washington University School of Medicine, St. Louis, Missouri.

Abstract

Efforts to develop more effective treatments for psychiatric illnesses will require innovative approaches that address changes in brain networks underlying cognition, emotion and motivation, cardinal symptoms that cut across all psychiatric disorders. This effort will include new molecular entities that modulate neuronal excitability, synapses, cellular stress and inflammation. Other opportunities will come from repurposing existing treatments. This overview highlights current and future goals in treatment development in the Taylor Family Institute for Innovative Psychiatric Research at Washington University.

Introduction

Psychiatry is undergoing a revolution in therapeutics. Novel molecules with distinct mechanisms of action are now approved for clinical use and further developments are on the horizon. Two examples are esketamine and brexanolone, approved for treatment resistant major depression (TRMD) and postpartum depression (PPD), respectively. Esketamine is the more active enantiomer of the anesthetic ketamine, and produces rapid, but transient relief of depression and acute suicidal ideation.[1] Enantiomers are mirror-image molecules that have identical physiochemical properties except for their "handedness" (rotation of polarized light); typically one enantiomer is more potent at receptors, as is the case with esketamine. Brexanolone is an intravenous formulation of the neurosteroid, allopregnanolone (AlloP), administered as a 60-hour infusion resulting in rapid improvement in women with moderate to severe PPD.[2] Under the auspices of the Taylor Family Institute and, more recently the Silvo O. Conte Neuroscience Center, the Department of Psychiatry at Washington University has a substantial commitment to new therapeutics and is at the forefront of several major developments. This year marks the tenth anniversary of the Institute, and here we describe ongoing work and future directions.

Brief History

The Taylor Family Institute was launched in 2013 with the generous support of Andrew and Barbara Taylor and the Crawford Taylor Foundation.

At its inception, the Institute was built on a program of preclinical studies examining the medicinal chemistry and biology of neurosteroids, including AlloP. The initial Institute arose from a 20-year multi-disciplinary collaboration among members of four Washington University departments including Psychiatry, Anesthesiology, Developmental Biology, and Radiology, and had at its outset the goal of developing neurosteroids for clinical purposes. The rationale for neuropsychiatric indications, especially depression-related disorders, was just coalescing at the time of program launch, spurred in part by the success of ketamine. Study of ketamine was expanding pursuit of treatments for depression beyond traditional medications. Over its first decade, the Institute has maintained a focus on neurosteroids, but efforts have expanded to include other novel treatments and clinical trials in patients with severe psychiatric and medical illnesses.

Why the Taylor Family Institute?

Treatment development in psychiatry is extremely challenging, fraught with multiple obstacles and high likelihood of failure. Traditional funding mechanisms, such as government grants, support pieces of this work that help to identify potential new treatments, but are not typically attuned to supporting complete research pipelines needed to generate clinical treatments. Aside from scope, limitations in traditional grant mechanisms include lapses and delays between applications and funding. Further compounding the problem, the pharmaceutical industry has limited risk tolerance for new neuropsychiatric treatments. Hence, unrestricted and flexible sources of support to develop and sustain innovative programs are required; this is what the Taylor family created, helping to fuel high-risk and potentially high-reward preclinical and clinical studies.

Several principles guide research in the Institute. First, we posit that there is no health without mental health. Second, we define psychiatric illnesses as dysfunction in brain networks that underlie cognition, emotion and motivation; symptoms in these domains cut across major psychiatric illnesses. Third, new treatments will derive from understanding and improving the function of brain networks rendered dysfunctional by stress and illness. Based on these principles, the goal of the Institute is to develop new ways to prevent, treat and possibly cure psychiatric illnesses. Neurosteroids served as the nexus for this approach, based on work already underway at Washington University.[3]

Why Neurosteroids?

The term "neurosteroid" refers to endogenous molecules made in the nervous system from cholesterol. They are a subset of a broader class of endogenous and synthetic steroids that modulate brain function, called "neuroactive steroids" (NAS).[4] Certain NAS are highly potent and effective modulators of major neurotransmitter systems, including the primary fast inhibitory neurotransmitter, γ-aminobutyric acid (GABA), and glutamate, the principal fast excitatory transmitter.[5] Together, GABA and glutamate account for the great majority of rapid signaling within local brain regions and across brain networks. Thus, they offer powerful ways to modulate brain systems that underlie psychiatric disorders. The prototype for therapeutic neurosteroids is AlloP, a progesterone derivative synthesized in brain in response to neuronal stress, including metabolic, toxic, and behavioral stressors.[5,6] AlloP is among the most potent and effective positive allosteric modulators (PAMs) of GABA-A receptors yet described, affecting all known GABA-A receptor subtypes. The term PAM refers to molecules that enhance the function of a receptor by binding to sites on the protein that are distinct from where the activating agonist binds (in this case the neurotransmitter, GABA). As a pharmacological class, AlloP and related NAS, exhibit some similarity to other clinically used GABA-A receptor PAMs, including certain anesthetics and anticonvulsants. Other NAS are positive and negative modulators of GABA-A receptors and a class of glutamate receptors called N-methyl-D-aspartate receptors (NMDARs) that is critical for information processing, learning and memory.[5]

Because NAS modulate major transmitter

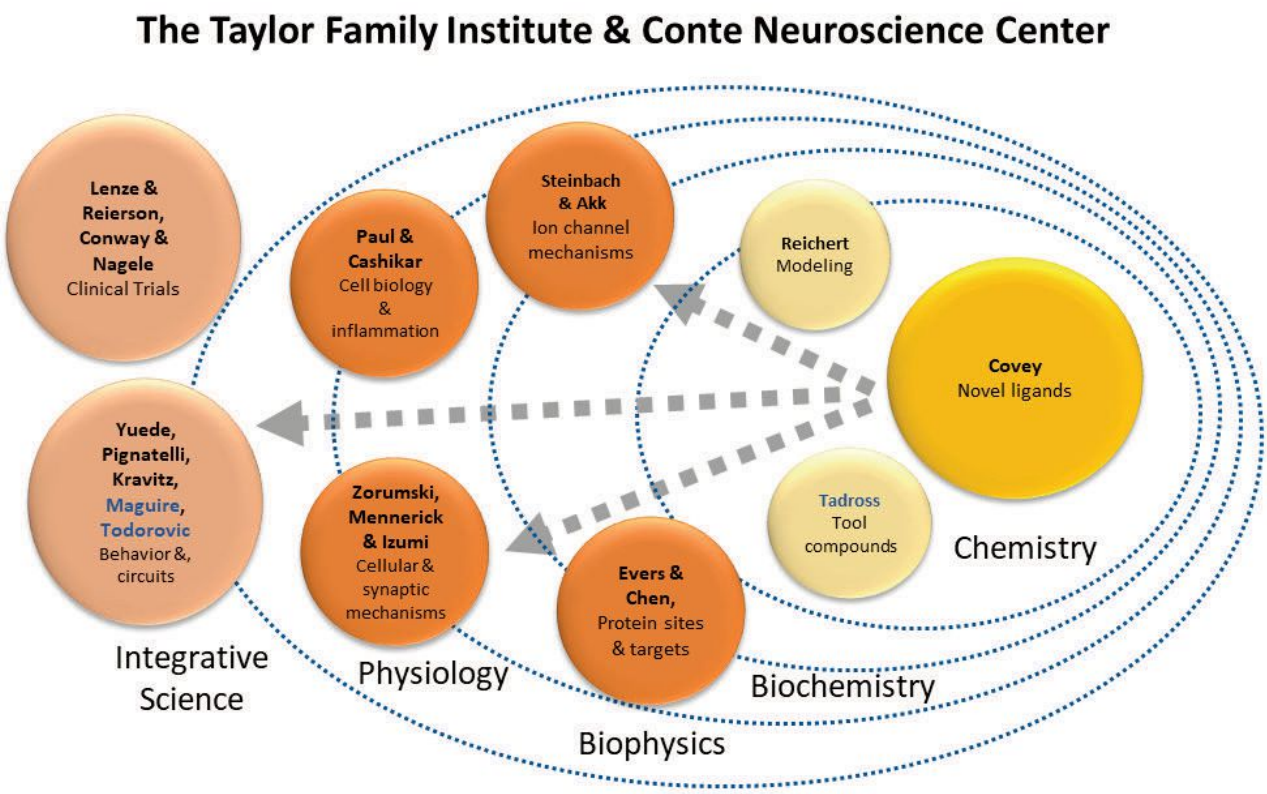


Figure 1.
The diagram depicts the scientists and operations of the Taylor Family Institute and Conte Neuroscience Center. These programs are built upon multidisciplinary science starting with a preclinical program in medicinal chemistry and includes biochemical, biophysical, physiological and behavioral studies with extension to human clinical trials. Further information is available at our websites: https://taylorfamilyinstitute.wustl.edu/ and https://sites.wustl.edu/conte/ .

systems, they have potential for broad therapeutic impact in stress-related disorders (depression and anxiety), neurodegenerative disorders (Alzheimer's disease and others), traumatic brain injury and glaucoma. NAS could also be helpful in treating memory impairment and chronic pain, and as sedatives and anesthetics. These agents also have potential in neurodevelopmental syndromes such as autism, epilepsy, and schizophrenia. While most therapeutic development of NAS to date has been for major depression and PPD, the other potential therapeutic targets remain viable. Compounds with such broad actions, affecting virtually every circuit in the brain, were viewed with skepticism for many years as treatments for psychiatric indications. Fortunately, it appears that use of these compounds at doses below sedative/anesthetic levels helps with selectivity, improving patient tolerability. The term "selectivity" refers to the ability of a ligand to affect only the desired target (in this case GABA-A receptors) while avoiding off-target effects.

Evolution of the Taylor Family Institute

At its outset, the Institute promoted the idea that neurosteroids could be developed as treatments in neuropsychiatry, and was based on a commitment to medicinal chemistry and understanding structure-activity relationships for actions at GABA and glutamate receptors. The chemistry effort is driven by Doug Covey, PhD, (Department of Developmental Biology), an internationally known expert in steroid chemistry.[3] Synthetic efforts in the Covey lab partnered with molecular modelling studies by Dave Reichert, PhD, (Department of

Radiology), molecular pharmacology studies identifying specific protein targets and sites of action by Alex Evers, MD, (Department of Anesthesiology), biophysical studies of ion channel effects by Joe Henry Steinbach, PhD, and Gustav Akk, PhD, (Department of Anesthesiology) and studies of cellular, synaptic and network effects by Steve Mennerick, MD, Yuki Izumi, MD, PhD, and Chuck Zorumski, MD, (Department of Psychiatry). Over nearly 30 years of collaboration, this group has amassed detailed information about the effects of NAS and a large library of novel molecules including potential lead compounds for therapeutic development based on the neurosteroid platform.[3] As the Institute formed, the group recognized the need to translate chemical, molecular and physiological studies to preclinical studies of behavior, and enlisted David Wozniak, PhD, (Department of Psychiatry), an expert in animal behavior. Figure 1 shows a diagram of the Institute and its evolution as explained later in the text.

Because of complexities and costs of drug development, efforts to turn preclinical science into human treatments require industry relationships. At the onset, members of the Institute formed a relationship with Sage Therapeutics, which, at the time was a start-up company dedicated to developing NAS as neurotherapeutics. Sage Therapeutics was founded by Steve Paul, MD, a renowned psychiatrist and neurochemist who previously worked in the intramural research program at the National Institute of Mental Health (NIMH) and later as Vice-President for Research at Eli Lily. While at NIMH in the mid-1980s, Paul did seminal work identifying AlloP as a neurosteroid that modulates GABA-A receptors.[4] It was Paul's work on neurosteroids that formed the basis of the initial collaboration between Covey and Zorumski in the late 1980s. As he formed Sage Therapeutics, Paul recruited Covey as co-founder, forming an academic-industry relationship to promote NAS development. Over a relatively short time in the life of drug development, a creative group of scientists at Sage Therapeutics spearheaded the development of brexanolone and other steroids and oxysterols that will be described below. As this work evolved, Paul also joined Washington University and the Taylor Family Institute along with Anil Cashikar, PhD, from the Department of Cell Biology, adding expertise in neurochemistry and cellular function.

As the Institute progressed, opportunities arose to extend work to clinical studies on other novel treatments. As described below, this work led to efforts to repurpose clinically used medications for psychiatry and other illnesses.

Neurosteroids as Novel Therapies

Brexanolone

The first neurosteroid approved for clinical use in psychiatry is brexanolone (Zulresso). This agent is the neurosteroid, AlloP, formulated for intravenous infusion in a cyclodextrin (Captisol).[2] Cyclodextrins are heterocyclic sugars that have a hydrophobic inner core and a hydrophilic external region, allowing aqueous solubilization of highly lipophilic molecules like steroids. The development of brexanolone resulted from the creative efforts of scientists at Sage Therapeutics. Early on, the drug was considered as a potential therapeutic for PPD with a rationale based on neurosteroid changes known to occur during and following pregnancy. Levels of progesterone and AlloP increase dramatically during late pregnancy and plummet rapidly in the postpartum period leading to an imbalance in excitatory and inhibitory transmission in the brain and resultant mood symptoms.[7] The concept in these studies, developed by Sage Therapeutics, was to administer brexanolone as an infusion over 60 hours ramping to levels achieved in pregnancy (near 100 nM) before tapering by the end of infusion. Brexanolone had highly successful open label and Phase 2B studies that preceded two successful Phase 3 studies in PPD, and the drug received FDA approval in March 2019. Intriguingly, the benefits of brexanolone were apparent by the end of administration and persisted at least 30 days afterwards.[3] This suggests that downstream, longer-lived changes in neurocircuits triggered by AlloP may

ultimately be responsible for benefit. Brexanolone is generally well tolerated, but is subject to a Risk Evaluation and Mitigation Strategy (REMS) to ensure safety because of sedation and loss of consciousness in some patients. Presently, it is unknown whether brexanolone is effective in non-PPD major depression.

Zuranolone

A limitation of brexanolone is that the drug is administered as an intravenous infusion. To overcome this limitation, Sage Therapeutics developed a novel NAS, zuranolone (SAGE-217), which is a synthetic chemical engineered to increase oral bioavailability and water solubility. Zuranolone has effects on GABA-A receptors similar to AlloP, but has a distinct chemical structure. This agent is administered orally once daily over a course of 14 days, and is in late stage clinical trials for major depressive disorder (MDD) in men and women, and for PPD. Zuranolone has had several successful pivotal trials for MDD[8] with one negative trial; the drug also had two successful Phase 3 trials for PPD.[9] Akin to brexanolone, zuranolone has rapid antidepressant and anxiolytic effects that are observed within three days after initiation. Effects appear to be maintained for the 14-day course and for at least 30 days after the drug is stopped. Zuranolone is well tolerated, with sedation being the major side effect. The concept to use an antidepressant as a brief course is novel and could have a major impact on psychiatric therapeutics, with recent work indicating courses of zuranolone can be repeated as needed and given in conjunction with other psychiatric treatments.

Oxysterols

While not technically neurosteroids, side-chain oxidized derivatives of cholesterol, called oxysterols, represent another potential therapeutic avenue. 24S-Hydroxycholesterol (24S-HC) is the major cholesterol metabolite in brain and is a path by which the brain rids itself of excess cholesterol.[10] In collaboration with Sage Therapeutics, members of the Taylor Family Institute found that 24S-HC is a potent and effective positive allosteric modulator (PAM) of NMDARs. 24S-HC and synthetic derivatives enhance NMDAR function and promote synaptic plasticity and learning in rodents.[11] These agents also overcome psychotomimetic-like effects of phencyclidine (PCP)-like drugs in rodents, and prevent adverse effects of anti-NMDAR antibodies (causative agents in a type of encephalitis) in preclinical studies.[12] A potential therapeutic agent based on 24S-HC, SAGE-718, is now in Phase 2 human studies in neurodegenerative illnesses.[13] There is also a possibility of developing agents that alter the activity of the key synthetic enzyme that generates 24S-HC, CYP46A1. Both positive and negative modulators of CYP46A1 have therapeutic potential in epilepsy, neurodevelopmental disorders and cognitive dysfunction.[14]

Other oxysterols are also of therapeutic interest. In particular, 25-hydroxycholesterol (25-HC), is synthesized primarily in monocytes in the periphery and microglia in the brain, and modulates inflammatory responses.[10,15] The role of neuroinflammation in neuropsychiatric illnesses including neurodegenerative and primary psychiatric illnesses is of considerable interest in therapeutic development. 25-HC also is a weak partial agonist at a putative oxysterol site on NMDARs, inhibiting the effects of stronger agonists such as 24S-HC,[16] possibly pointing directions to develop antagonists against oxysterols.

Beyond Neurosteroids: Repurposing Approved Medications

Nitrous oxide and TRMD

The success of ketamine as a rapid treatment for TRMD and acute suicidality expanded thinking about psychiatric therapeutics. Ketamine is a dissociative anesthetic and psychotomimetic that acts, at least in part, by inhibiting NMDARs at sub-anesthetic doses.[1] Ketamine may act preferentially on GABAergic interneurons to disinhibit excitatory (glutamate) neurons, leading to persisting enhancement of glutamate-mediated synaptic transmission in hippocampus and prefrontal cortex. Earlier preclinical studies by Institute members showed that nitrous oxide

is also a non-competitive NMDAR antagonist, though with biophysical mechanisms distinct from ketamine.[17] Based on the success of ketamine, Chuck Conway (Psychiatry) and Peter Nagele (Anesthesiology), clinical members of the Taylor Family Institute, designed a proof-of-concept study of nitrous oxide in patients with TRMD. They conducted a double blind, placebo-controlled, crossover, clinical trial using a one hour inhalation of 50% nitrous oxide (a dose used in dental anesthesia) in patients with severe, highly refractory TRMD. This trial showed rapid benefits within a day after exposure that lasted at least one week.[18] In a subsequent Phase 2 trial, the same investigators showed antidepressant effects of both 25% and 50% nitrous oxide in TRMD that lasted at least two weeks on average.[19] Ongoing studies are using human neuroimaging to probe network effects of nitrous oxide with other studies examining mechanisms of action in preclinical models; in preclinical studies nitrous oxide exerts ketamine-like effects on hippocampal network function.[20]

Fluvoxamine and COVID-19

Although many psychiatric medications have primary actions on monoamine neurotransmitters (serotonin, dopamine and norepinephrine), these agents have diverse effects that could be beneficial for non-psychiatric illnesses.[21] Indeed, certain antidepressants can treat migraine headaches, gastrointestinal disorders and chronic pain. There is also interest in possible use of the selective serotonin reuptake inhibitor (SSRI), fluvoxamine, for inflammatory disorders. Fluvoxamine is a potent agonist at sigma-1 receptors (S1Rs), important modulators of cellular stress and inflammation.[21] Early in the course of the COVID-19 pandemic, Eric Lenze and Angela Reiersen (Psychiatry) recognized the potential of fluvoxamine as a treatment to prevent deterioration in newly diagnosed outpatients with COVID-19. Beginning in April 2020, near the onset of the pandemic, they demonstrated promising efficacy of fluvoxamine in an innovative, double blind, placebo controlled, contactless, proof-of-concept study.[22] This study was replicated in an open label trial and in a larger controlled trial.[21] Understanding that fluvoxamine targets stress pathways opens the door to repurposing other agents to treat conditions involving inflammation. Whether fluvoxamine and other psychiatric medications can treat and/or prevent long-COVID in survivors of the infection remains unknown. It is also unclear whether fluvoxamine's antidepressant effects could involve neuroinflammation. Coming full circle with other work in the Taylor Family Institute, it is intriguing that fluvoxamine and fluoxetine, also stimulate endogenous production of AlloP. How endogenous steroids participate in therapeutic effects of these SSRIs is presently unknown.[5,6]

Future Directions

As the Taylor Family Institute enters its second decade, we hope to build on the successes outlined above. As noted, oxysterols and neuroinflammation offer great promise for new treatments. Neurosteroids also have important intracellular effects, only starting to be revealed, which offer potential as treatments for neuropsychiatric and neurodegenerative conditions. We have found that AlloP and its unnatural enantiomer (a unique synthetic molecule that lacks effects on GABA receptors) are highly effective in preclinical models of neurodegeneration by enhancing, in part, the cellular process of autophagy,[23,24] a mechanism by which cells regulate their stress responses and inflammation.

A major new development in our work is the funding of a Silvio O. Conte Neuroscience Center by the National Institute of Mental Health (NIMH). This center complements and extends work in the Institute and provides collaboration with key investigators at Tufts University (Jamie Maguire), Duke University (Mike Tadross) and University of Colorado (Slobodan Todorovic), with emphasis on novel mechanisms involved in brain network effects. The Conte Center specifically is tasked with understanding mechanisms beyond GABA-A receptors, such as intracellular pathways noted above that could drive important behavioral

therapeutic effects of NAS and related compounds. Further expanding these studies, new preclinical Institute recruits, Marco Pignatelli and Lex Kravitz, are making strides in understanding neurocircuits and behaviors. Figure 1 shows the current configuration of the Taylor Family Institute and Conte Center.

Beyond these studies, patient-derived inducible cells offer potential for personalized therapeutics, and precision functional neuroimaging studies in humans promise to promote understanding of how individual patients are affected by illness and respond to treatment. The Institute is excited to define the range of neuropsychiatric illnesses responsive to neurosteroids and oxysterols as it is increasingly clear that we are now just scratching the surface of cholesterol-derived neuromodulators as therapeutics.

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Household Income and Parental Educational Level Affect Post-Operative Opioid Usage in Pediatric Orthopaedic Patients

by Michael A. Ewing MD, Lauren N. Livesay, BS, James L. Cook, DVM, PhD, Emily V. Leary, PhD, Daniel G. Hoernschemeyer, MD & Sumit K. Gupta, MD

Our study demonstrates pediatric patients require smaller amounts of opioid medications than generally prescribed.



Michael A. Ewing MD, Lauren N. Livesay, BS, are in the Department of Orthopaedic Surgery; James L. Cook, DVM, PhD, and Emily V. Leary, PhD, are in the Department of Orthopaedic Surgery and the Thompson Laboratory for Regenerative Orthopaedics; and Daniel G. Hoernschemeyer, MD, and Sumit K. Gupta, MD, (above) are in the Department of Orthopaedic Surgery and Women's and Children's Hospital; all are at the University of Missouri - Columbia, Columbia, Missouri.

Abstract

Opioid medications are commonly prescribed after pediatric orthopaedic surgery, but there is a critical need to optimize prescribing practice. This study identifies socio-economic characteristics, surgical characteristics, and patient reported psychological factors influencing postoperative opioid use in this population and found that post-operative opioid use in this pediatric orthopaedic population is multifactorial. Physicians should consider implementing protocols for initial opioid prescriptions to cover two to three days following common orthopaedic surgeries for most pediatric patients.

Introduction

Opioid medications are widely prescribed for pediatric patients upon discharge after surgical procedures.[1–3] However, there continues to be significant variability in prescribing practices.[4,5] Opioid use in the pediatric orthopaedic population is not standardized, and the factors associated with post-operative need for opioid medication remain largely unknown, such that concern for over-prescribing, both in number and when not needed, continues.[6] Temporal trends show an increase in the number of musculoskeletal injuries seen in children,[1] and it is clear there is a concomitant increase in the amount of opioids prescribed to pediatric orthopaedic patients over the previous decade.[1,10] Studies suggest up to 25% of high school seniors are exposed to prescription opioids.[11] This is especially troublesome when considering the risk of opioid misuse is 33% higher in adults who were legally prescribed opioids when they were of high-school age.[12]

Over-prescription of opioids is a problem for pediatric patients undergoing orthopaedic procedures.[8,9] Patients undergoing supracondylar humerus fracture pinning are prescribed 4-10 times the amount that is actually consumed on average.[1,13,14] In addition, posterior spinal fusion patients routinely do not use all the opioids they are prescribed.[15,16] Oversupply of these pills is a critical problem as these extra pills may be misused or diverted.[17,18]

There are many factors that influence post-operative pain in pediatric patients, and

incomplete delineation of their contributions has led to significant variation in prescribing patterns, largely based on physician preference and non-evidence-based "standard" protocols.[4,5] In addition to the type or length of surgery performed, the ability to cope, socio-economic status, expectations, and cultural norms may affect the pain experienced by patients undergoing surgery.[1,6,19,20] It remains imperative to include these factors in determining evidence-based opioid prescribing practices.

Therefore, this prospective study will identify socio-economic characteristics (caregiver income, caregiver education, caregiver employment status, patient race, patient ethnicity, patient gender), surgical characteristics, and patient reported psychological factors (positive affectivity, psychological stress experience, and anxiety) which influence opioid or other pain medication usage after pediatric orthopaedic procedures. Specifically, we hypothesize that lower caregiver income, less educated caregivers, longer surgeries, and greater adverse psychological factors will increase odds of opioid use and both the total amount of opioids used and the duration of any pain medications in outpatient pediatric orthopaedic surgeries.

Methods

Pediatric patients between 4-17 years of age undergoing outpatient orthopaedic surgery at a tertiary referral center were eligible for inclusion. Exclusion criteria included suspected or confirmed non-accidental trauma, pregnancy, non-English speaking, inability to provide assent/consent, inability to agree to telephone-based data collection, and patients currently using opioids for other reasons. All patients were given acetaminophen and ibuprofen for post-discharge pain control, with opioids prescribed for breakthrough pain using weight based protocols. Patients and caregivers were instructed to wean opioid use to nighttime only and eventually discontinue use as soon as they felt pain was adequately controlled with acetaminophen and ibuprofen. Oxycodone was the only opioid prescribed in this study, in either pill or liquid form according to family preference, at a dose of less than or equal to 0.1mg/kg/dose using physician discretion.

Patient demographics (e.g., age, body mass index (BMI), sex, education level of caregiver, ethnicity of caregiver, race of caregiver, and annual household income) and pediatric patient reported outcome measurement information system for PROMIS (Patient-Reported Outcomes Measurement Information Systems) scores (Positive Affect, Psychological Stress Experiences, and Emotional Distress – Anxiety) were collected from patients and from their caregivers by research staff prior to surgery. Standardized PROMIS scores were used for all analyses.[21,22] Higher standardized scores for pediatric PROMIS Psychological Stress, Experiences, and Emotional Distress – Anxiety indicate greater stress and anxiety, respectively, while higher standardized scores for pediatric PROMIS Positive Affect indicate improved positive affective experiences. PROMIS scores are standardized such that a score of 50 is the population mean with a standard deviation of 10. Surgical information (i.e. type, anatomic location, length of surgery, estimated blood loss, surgical timing [trauma vs. elective (non-fracture)], as well as type and presence of implants) was obtained from the electronic medical record. Implants were characterized as hardware (plates, screws), percutaneous hardware (Kirschner wires, flex nails), or none.

Amount of opioid use within the first seven days post-discharge was recorded postoperatively. Patients' caregivers were given a logbook with instructions to record pain scores and the type and dose of medication every time they were administered. The duration of pain medication (days) included both non-opioid and opioid post-operative pain medication. To reduce recall bias, and ensure better compliance to document all pain medication use, all families were contacted by research staff on post-operative day two or three to remind them about the logbook use. Opioid amounts were standardized to milligram morphine equivalents (MME) for analysis.[23]

Categorical and continuous data were summarized using means and standard deviations or frequencies and percentages. Relationships between opioid utilization (yes/no) and each demographic and psychometric outcome were separately evaluated using logistic regression analyses. Corresponding odds ratios and their 95% confidence intervals are reported; odds ratios for continuous variables are reported at the mean value. For those that used post-operative opioids, relationships between total amount of post-operative opioids utilized (in MME) with each demographic and psychometric characteristic were separately tested using linear regression. For all patients, the relationships between the duration of post-operative opioid utilization

(in days) and each patient and caregiver characteristic were tested using linear regression. All analyses were calculated using R (version 3.6.1). The study was approved by the relevant Institutional Review Board and patient assent, with caregiver consent, was obtained for all participants.

Results

Overall, 86 patients were enrolled in the study (Figure 1). However, 26 patients could not be reached by phone or email to obtain pain medication usage data, and five patients reported that they did not record the data. The remaining 55 patients (29 male, 26 female) had mean age 12.30 ± 3.37 years with complete data available for analysis (Table 1A). Mean BMI was 23.72 ± 11.28 mg/m2 and all pediatric PROMIS scores (Positive Affect, Psychological Stress, and Emotional Distress-Anxiety) were near the standardized average of 50 with standardized population standard deviation of 10. The patient's caregivers were mostly white (80%), non-Hispanic/Latino (74.6%), college educated (47.3%), and had a household income of at least $50,000 per year (47.3%) (Table 1B).

Most surgeries were elective (65.5%) and slightly more surgeries were performed on the lower extremities (47.3%) compared to the upper extremities (41.8%). The mean length of surgery was 63.16±47.33 minutes and mean blood loss was 80.47 ±70.79 mL. Of the elective surgeries, 10 were considered minor bone by the attending surgeon (27.8%), eight were minor soft tissue (22.2%), and eight were hardware removal (22.2%; Table 2). For all patients, opioid and non-opioid duration of post-operative pain medication were 3.63 ± 3.00 days. Nineteen patients (34.6%) used prescribed opioids following discharge. For these 19 patients, the mean total MME, for patients taking postoperative opioids, was 47.9 ± 45.2.

Length of surgery showed significant, positive relationships with mean total MME (Table 3). For every 10-minute increase in surgery length, the total MME used increased by 0.49 MME. Similarly, length of surgery and blood loss were also positively associated with opioid use, such that for every 10mL increase in blood loss, the odds of opioid use increase by 13%. However, for those who have an extra 10 minutes of surgery, the odds of opioid use increased by 3%, with confidence interval (1.00, 1.05). Increased length of surgery and opioid use increased the duration of pain medication by 3.6 days. Pediatric PROMIS emotional distress-anxiety was the only psychometric characterization associated with any outcome, specifically, for each unit increase in this PROMIS score (where larger scores indicate worse outcomes), the MME utilized after surgery decreased by 2.52 . However, the 95% CI were wide (-5.02, -0.01).

With respect to other demographics, only caregiver education and household income were associated with the duration that postoperative pain medication was administered (Table 4). Interestingly, those caregivers with a high school education were associated with a longer duration of pain medication, compared to both those with less than a high school education and more than a high school education, 4.07 and 3.65 days, respectively. Further, those with annual household incomes between $25,000 and $49,999 had 3.38 days longer duration of pain medication compared to those with annual household incomes between $50,000 and $74,999.

Figure 1. CONSORT Diagram

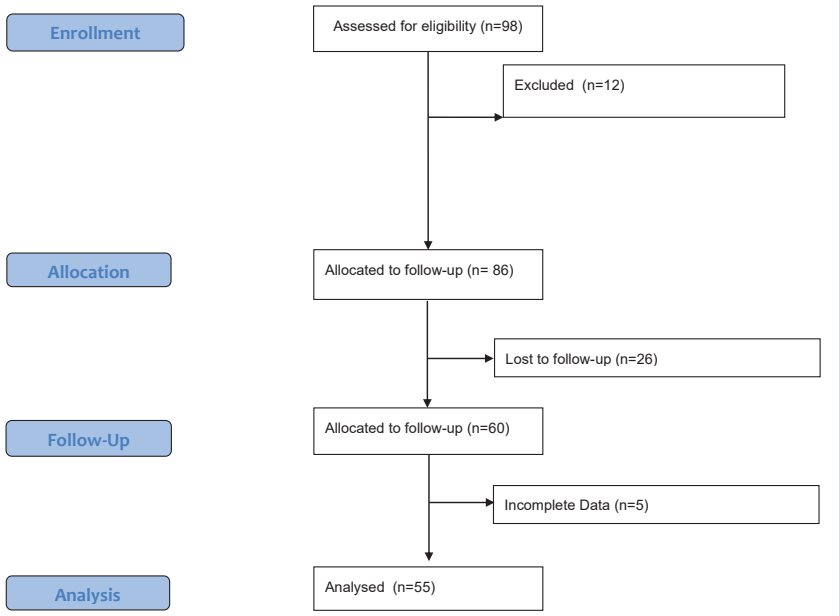


Table 1A. Demographics and Surgical Characteristics for Pediatric Patients

Type	Characteristic	Level	Patients (N = 55) *no. (%) or mean ±std*
Patients	Age	all	12.30±3.37
		4-9 yrs	10 (18.18%)
		10-14 yrs	34 (61.82%)
		15-17 yrs	11 (20.00%)
	Sex	Male	29 (52.73%)
		Female	26 (47.27%)
	BMI	All	23.72 ±11.28
		<18.5	17 (30.91%)
		18.5-24.9	20 (36.36%)
		25-29.9	8 (14.55%)
		>30	6 (10.91%)
		No data	4 (7.27%)
	Anatomical Location	Upper Extremity	23 (41.82%)
		Lower Extremity	26 (47.27%)
		No data	6 (10.91%)
	Surgical Timing	Trauma	19 (34.54%)
		Elective	36 (65.45%)
	Use of Hardware/Implants	No implants	18 (32.73%)
		Hardware	16 (29.09%)
		Percutaneous implants	11 (20.00%)
		Other implants	4 (7.27%)
		No data	6 (10.91%)
	Blood Loss (mL)		80.47±70.79
	Length of surgery (in minutes)		63.16±47.33
	Pediatric PROMIS Positive Affective		48.73±8.68
	Pediatric PROMIS Psychological Stress Experience Score		51.82±8.43
	Pediatric PROMIS Emotional Distress – Anxiety Score		50.81±10.84
	Used Opioids After Discharge?	Yes	19 (34.55%)
		No	36 (65.45%)
	Number of Days Pain meds used (opioid/ non-opioid)		3.63±3.00
	Mean total mg morphine equivalent for opioids		47.94±45.22

Table 1B. Demographics for Caregivers

Type	Characteristic	Level	Patients (N = 55) *no. (%) or mean ±std*
Caregivers	Education Level	Less than High School	5 (9.09%)
		High School/GED	8 (14.55%)
		Associate's Degree	6 (10.91%)
		Bachelor's Degree	19 (34.55%)
		Master's Degree	5 (9.09%)
		Doctorate	2 (3.64%)
		No data	10 (18.18%)
	Household Income	Less than $25,000	4 (7.27%)
		$25,000 - $49, 999	9 (16.36%)
		$50,000 - $74,999	13 (23.64%)
		$75,000 - $99,999	6 (10.91%)
		$100,000 - $149,999	7 (12.73%)
		$150,000+	5 (9.09%)
		No data	11 (20.00%)
	Race	White	44 (80.00%)
		No data	11 (20.00%)
	Ethnicity	Hispanic/Latino	2 (3.64%)
		Not Hispanic/Latino	41 (74.55%)
		No data	12 (21.82%)

Table 3. Associations of outcomes with continuous categorical demographic, surgical, and psychometric characteristics for pediatric patients

Characteristic	Opioid Use (Yes/No)		Total amt opioid (MME)**		Duration of Pain Meds (Days)	
	Odds Ratio*	95% CI	Estimate	95% CI	Estimate	95% CI
Blood loss (per 10mL)	**1.1324**	**[1.0259, 1.2905]**	0.84	[-2.24, 3.91]	0.12	[-0.01, 0.26]
Length of surgery (per 10 min)	**1.0261**	**[1.0075, 1.0506]**	**0.49**	**[0.12, 0.87]**	**0.04**	**[0.02, 0.05]**
Age (yrs)	1.2222	[1.0039, 1.5483]	4.83	[-2.21, 11.88]	0.27	[-0.01, 0.55]
BMI (kg/m²)	1.0474	[0.9369, 1.1970]	3.37	[-0.07, 6.80]	0.15	[-0.01, 0.32]
Opioid use	N/A	N/A	N/A	N/A	**3.60**	**[1.94, 5.27]**
Pediatric PROMIS Positive Affective Score	1.0020	[0.9197, 1.0924]	2.55	[-0.59, 5.68]	0.10	[-0.04, 0.23]
Pediatric PROMIS Psychological Stress Experience Score	1.0569	[0.9631, 1.1751]	-2.07	[-5.07, 0.92]	-0.03	[-0.18, 0.13]
Pediatric PROMIS Emotional Distress – Anxiety Score	0.9621	[0.8864, 1.0362]	**-2.52**	**[-5.02, -0.01]**	-0.04	[-0.17, 0.08]

Bolded values indicate significance at alpha = 0.05
**Odds ratios calculated at the mean value*
***Note that this only includes patients who reported opioid use.*

Discussion

The present study sought to explore patterns of opioid use following pediatric orthopaedic surgery. We observed evidence in support of our hypothesis that lower caregiver income, and longer surgeries would increase opioid use or duration of post-operative pain medication. Further, there was an association with caregiver education and duration of pain medication, but association was not consistent and in fact, unintuitive. In this study, only 35% of patients reported utilizing prescribed opioids within seven days after discharge. The average duration of home opioid use was 3.6 ± 3.0 days with average MME 47.9 ± 45.2, suggesting that even patients who use opioids may require less than a week of post-operative opioids. Caregiver education and income had relationships to overall duration of both opioid/non-opioid post-operative pain medication, with high school-educated caregivers and those with annual income of $25,000 to $49,999 reported longer durations of post-operative pain medication use. Surgical characteristics, including blood loss and length of surgery, were related to opioid use, amount of opioid use, and overall duration of both opioid/non-opioid post-operative pain medication.

While this pediatric, outpatient cohort included multiple types of surgical procedures, the results align with the findings of Nelson et al.,[13] who found most pediatric patients required less than seven doses of opioid following treatment of supracondylar humerus fractures. This is in stark contrast to the prescribing patterns described by Iobst et al.,[5] who reported an average of 28.4 doses prescribed for pediatric fracture patients. Meyer and colleagues[24] report similar prescribing patterns, with an average of 30.1 and 31.9 doses prescribed for elbow and femur fracture patients, respectively. These latter two studies describe opioid prescriptions of approximately a week's supply, which is approximately twice that used by patients in our cohort. These previous studies were also heterogenous with their prescription of ibuprofen and acetaminophen as first-line agents for postoperative pain.[5,24] Studies have demonstrated acetaminophen

Table 4. Associations of outcomes with categorical demographic, surgical, and psychometric characteristics of pediatric patients and caregiver.

Type	Characteristic (group vs reference)	Opioid Use (Yes/No)		Total amt opioid (MME)*		Duration Pain Meds (days)	
		OR	95% CI	Estimate	95% CI	Estimate	95% CI
Patient	Trauma vs Elective	0.89	[0.25, 3.16]	-27.75	[-71.10, 15.60]	-1.20	[-3.23, 0.83]
	Lower vs Upper Extremity	2.55	[0.70, 9.31]	27.75	[-15.60, 71.60]	1.48	[-0.52, 3.48]
	Hardware vs No Implant	4.05	[0.81, 20.20]	1.29	[--54.93, 57.51]	0.64	[-1.76, 3.04]
	Percutaneous Implants vs No Implant	0.77	[0.14, 4.39]	-14.50	[-88.11, 59.11]	-1.59	[-4.17, 1.00]
	Female vs Male	0.71	[0.20, 2.57]	6.37	[--40.20, 52.94]	0.08	[-2.01, 2.16]
Caregiver	Less than High School vs. High School/GED	0.33	[0.02, 6.65]	-32.50	[-146.99, 81.99]	**-4.07**	**[-8.11, -0.02]**
	More than High School vs. High School/GED	0.56	[0.08, 4.01]	-7.99	[-72.57, 56.59]	**-3.65**	**[-6.37, -0.93]**
	Not Employed/Not working vs Employed/Working	0.54	[0.04, 6.58]	-26.22	[-124.29, 71.84]	0.43	[-3.29, 4.14]
	$75,000 – $99,999 vs $25,000 – $49,999 household annual income	0.75	[0.03, 17.51]	11.88	[-73.94, 97.69]	-3.00	[-6.96, 0.96]
	$50,000 – $74,999 vs $25,000 –$49,999 household annual income	0.15	[0.01, 2.06]	-3.13	[-88.94, 82.69]	**-3.38**	**[-6.75, -0.01]**
	≤ $24,999 vs $25,000 – $49,999 household annual income	0.25	[0.01, 8.56]	-24.38	[-149.99, 101.24]	-1.50	[-6.44, 3.44]
	Hispanic/Latino vs Non-Hispanic/Latino caregiver	NA	NA	NA	NA	NA	NA
	Non-white vs White caregiver	NA	NA	NA	NA	NA	NA

Bolded values indicate significance at alpha = 0.05

**Note that this only includes patients who reported opioid use.*

and ibuprofen to be at least as effective at managing pain in the pediatric orthopaedic population compared to opioids.[25,26] Opioid prescription reduction has also been achieved with the use of appropriate use guidelines. For physicians from this study, if a patient needed additional opioids beyond that originally prescribed, they could be seen in clinic or call the clinic. Their request would be evaluated by a physician and if reasonable and within a week of surgery, they may be renewed once if deemed appropriate by the renewing physician. Any further assessments would require re-assessment in the pediatric orthopaedic clinic. Based on these findings in conjunction with the availability and efficiency of electronic prescribing for controlled substances, when additional medications are needed, pediatric orthopaedic physicians should consider implementing protocols for initial opioid prescriptions to cover two to three days for most outpatients.[27]

With regard to total amount of opioid utilized, the patients in this study used an average 47.94 ± 45.22 MME of pain medication. This represents 6.3 ± 6.02 doses of 5 mg oxycodone. Our data further suggest most children are prescribed more opioids than are routinely necessary, and there is area for improvement in prescribing practices. Identifying these relationships, ideally with prospective study, may be helpful in determining which patients would benefit from opioid medications, avoiding unnecessary prescriptions and refining prescribing practices. More research is warranted to further optimize and standardize prescribing practices, with a continued emphasis on multi-modal approaches for post-operative pain control.

Little evidence was observed with respect to psychological factors and the relationship to opioid use, with the exception of the curious relationship between pediatric PROMIS Emotional Distress-Anxiety score and total amount of opioid used. However, Pediatric PROMIS Emotional Distress - Anxiety scores were negatively associated with amount of opioids used, such that patients who are more emotionally distressed or anxious used fewer opioids. It is not known if this inverse relationship between anxiety and opioid use

is due to patient's fear of these medications or their parents. Further study will be needed to understand the reasons explaining these observations. While these instruments have been validated for evaluating the extent of these traits in children in the general US population, they were not specifically designed to evaluate post-operative pain.[21,22]

Further, parents and practitioners may not be good judges of the amount of pain experienced by pediatric patients. A prospective study by Singer et al.[28] evaluating emergency department patients concluded that parents and medical practitioners were, in fact, poor judges of the severity of children's pain, with poor correlation between patient, parent, and practitioner visual analog scale ratings. While the VAS remains a validated measure of pain in the pediatric population, Kelly and colleagues report poor reliability of parent ratings compared to pain rating reported by the child, with no clear consistency with parents under or overerating their child's pain.[29] Thus, pain is difficult to judge in the pediatric population, and better instruments for quantifying pediatric pain are needed to further inform prescribing practices.

Our data suggest that patient age is not associated with post-operative opioid use, although most of our patients were between the ages of 10-14 years of age. Adolescents are widely viewed as the most susceptible pediatric patient population to opioid misuse and diversion,[11] however, we did not find increased opioid utilization in this cohort. Our findings do not align with those of Simril and colleagues, who reported contrasting prescription practices for patients over age 12 years compared to those under five, with older patients receiving higher doses of opioids.[30] This is an important consideration given the propensity to undertreat pain in younger children; however this could not be adequately explored in this analysis due to small numbers of younger children.[31,32]

Our study is not without limitations. First, our data were largely dependent upon patient and parent self-reporting, such that risks for inaccurate information and recall bias exist. This study examined only post-discharge opioid consumption, so the opioids patients received during inpatient care were not included for analysis. The sample size for this study is relatively small with a relatively narrow demographic range. Furthermore, our study did not contain homogenous surgical groups, although all outpatient surgeries were considered. It is possible that our cohort was not representative of all outpatient pediatric orthopaedic surgeries. As a single-center study, generalization may be limited. Finally, this study had only short-term follow-up (up to seven days post-operatively), so longer-term outcomes were not analyzed.

Conclusion

In this cohort, many pediatric patients experienced adequate pain control without the use of opioids, and pediatric patients who utilized post-operative opioids rarely did so for more than five days post-operatively. Our study demonstrates pediatric patients requiring smaller amounts of opioid medications than generally prescribed, and many pediatric patients do not utilize a post-discharge opioid prescription at all when acetaminophen and ibuprofen are used for postoperative pain management. However, physicians should consider implementing protocols for initial opioid prescriptions to cover two to three days following common and uncomplicated orthopaedic surgeries for most pediatric patients. Further research is needed to fully delineate the factors that can predict medication needs for effective pain control in individual pediatric orthopaedic patients.

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Molecular Tumor Board Case Series: Targeting KRAS G12C in Lung Cancer

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

Saint Luke's CANCER INSTITUTE

Clinical next-generation sequencing testing alone may not be adequate but when combined with molecular tumor boards may provide significant clinical benefit for patients with advanced stage cancers.



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

Abstract

Next-generation sequencing (NGS) identifies biomarkers with prognostic and predictive importance in patients with cancer. The enormous amounts of data generated by comprehensive NGS adds complexity to the identification of valid drug therapy targets. Rapid progress made in targeted drug development creates the need for novel methods to access these treatments for patients. Molecular tumor boards (MTB) not only aid in identifying targetable gene mutations by carefully reviewing NGS data, they can also take lead in creating patient access to the appropriate targeted therapy. Here we describe two patients with Kirsten Rat Sarcoma (KRAS) G12C mutation positive lung adenocarcinoma for whom MTB was able to procure AMG510 or sotorasib, a covalent KRAS G12C inhibitor, by expanded access program ahead of FDA approval.

Introduction

Kirsten rat sarcoma (KRAS) gene is the most frequently mutated oncogene in human cancers, and had long been deemed 'undruggable'.[1] KRAS encodes a guanosine triphosphatase (GTP-ase) that cycles between active and inactivate conformations to regulate signal transduction.[2] The KRAS p.G12C mutation occurs in approximately 13% of non-small cell lung cancer (NSCLC) and 1 to 3% of other solid cancers.[3] The glycine to cysteine mutation at position 12 favors the active form of KRAS, resulting in active KRAS signaling and enhanced survival in tumor cells.[2-3] Sotorasib (AMGEN510) irreversibly inhibits KRAS G12C by trapping KRAS in its inactive state.[4]

Prior to FDA approval in May 2021 for KRAS G12C-mutated locally advanced or metastatic NSCLC, access to sotorasib was restricted to clinical trial. Clinical trial access is limited for the real-world patient population with multiple comorbidities, substantial social and financial constraints, and limited travel options.[5] However, such drugs may be available on expanded access or "compassionate use" basis before approval and may be an option in some patients who have exhausted standard of care therapies. Comprehensive NGS can identify biomarkers for pipeline therapies that may become standard of care, like sotorasib. Early identification of such biomarkers by molecular tumor boards can speed clinical trial accrual or identification of expanded access therapies

in patients with limited options. This case series exemplifies the role of MTB in identifying actionable targets and achieving access to targeted therapies for two patients with KRAS G12C mutation positive lung adenocarcinoma.[1]

Patient Case 1

Patient 1 is a 70-year-old Caucasian female diagnosed with adenocarcinoma of the lung after presenting in October 2019 for a follow-up after surgery on her left hip. She reported chest discomfort and CT chest on November 15, 2019, identified right hilar fullness; subsequent Positron Emission Tomography/Computerized Tomography (PET/CT) confirmed metabolic activity in right hilar lymphadenopathy, bilateral adrenal glands, lesions in thoracic spine, ilium, and right acetabulum. Biopsy of the right lung lesion on December 16, 2019, confirmed poorly differentiated lung adenocarcinoma. Initial molecular testing revealed PD-L1 20% with PCR negative for EGFR, ALK, and ROS1 rearrangements. KRAS testing was not performed. Patient was initiated on carboplatin, pemetrexed, and pembrolizumab on January 6, 2020, with progression on restaging scans February 2020 after two cycles. Palliative docetaxel and ramucirumab were started March 18, 2020, with improvement on CT scan after two cycles and stable disease after four cycles. Therapy was held after six cycles due to adverse effects. Subsequent CT abdomen pelvis identified progression in bilateral adrenal masses and new retroperitoneal periaortic lymphadenopathy. CT-guided biopsy of the left adrenal mass was positive for adenocarcinoma. This specimen was sent for comprehensive molecular testing and revealed an activating mutation in KRAS G12C.

Pembrolizumab and radiation to the adrenal mass were given next, with disease progressing after two cycles of pembrolizumab, with decline in performance status down to ECOG 2. Goals of care were discussed, and patient considered supportive care with hospice but wanted to pursue targeted options if available. Given her molecular profile, sotorasib was a potential option, recently been granted a breakthrough designation by the FDA. However, it had not yet been approved by the FDA and the patient had not met the criteria for clinical trial participation. The MTB initiated the process to open the sotorasib expanded access protocol (EAP) and on March 3, 2021, after receiving IRB approval and patient consent, the patient was started on sotorasib. By March 31, patient noted reduction of pain, decrease in size right scapular mass and improved energy level, with ECOG performance status improving to 1. She reported manageable adverse effects including one episode of flushing and mild nausea without vomiting that resolved with anti-emetics. CT scans on April 19, 2021 showed response in the abdomen with stable disease in the chest. MRI brain identified resolution of multiple sub-centimeter metastases. However, repeat imaging from May 24, 2021, showed oligoprogression with increased disease in both adrenal glands and increased size of enhancing lesion in the left sylvian fissure. She continued to receive sotorasib while receiving radiation to brain and new lesions in her right leg, until her performance status declined to ECOG 3. Sotorasib was discontinued on September 27, 2021, 6.5 months from treatment start.

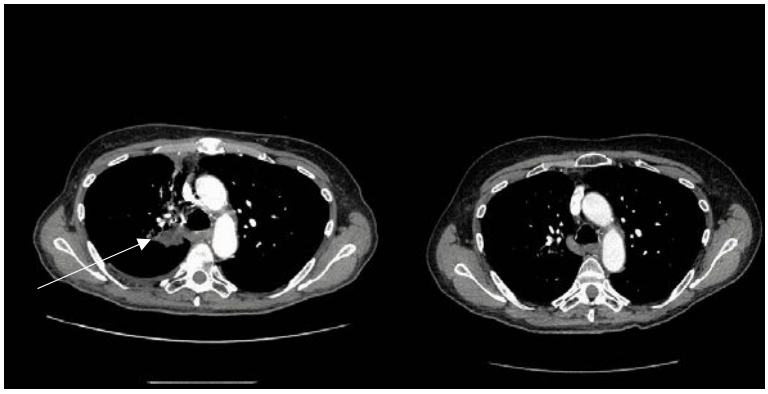
Patient Case 2

Patient 2 is a 64-year-old Caucasian male never smoker, referred to pulmonology by his primary care for persistent dry cough for several months. He was diagnosed with left lower lobe moderately differentiated lung adenocarcinoma in October 2019. He underwent left lower lobectomy with lymph node dissection November 8, 2019. His final TNM stage was IIIB with positive N2 lymph nodes. He received four cycles of adjuvant cisplatin and pemetrexed from December 2019 till February 2020, followed by radiation to the left lower lung bronchial stump and mediastinum for a total of 5400 cGy in 27 fractions from April 2020 to May 2020. Molecular testing of the surgical specimen revealed KRAS G12C mutation PD-L1 was negative.

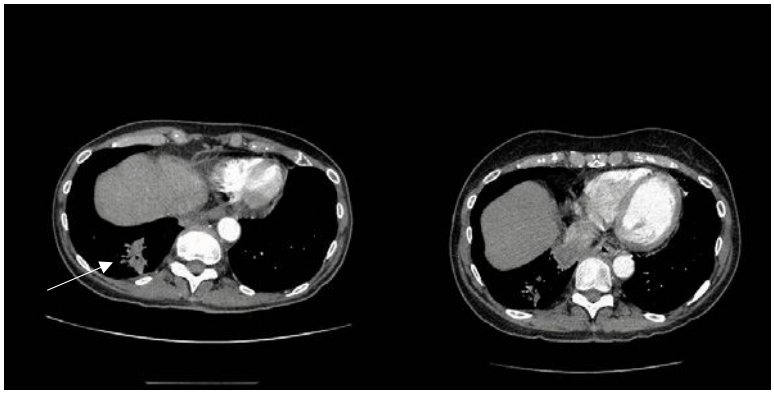
Patient reported increased shortness of air and intermittent cough in November 2020 with increase in size of right lung nodules on CT scan. Patient underwent a PET scan which identified FDG uptake in the right lung as well as paratracheal and subcarinal lymph nodes. Endobronchial Ultrasound (EBUS) biopsy of the station seven lymph node was positive for adenocarcinoma, consistent with pulmonary primary.

Following his biopsy, patient was offered chemo-immunotherapy, which he declined. Instead he received nivolumab and ipilimumab in February 2021. Six weeks later, after one dose of ipilimumab and three doses of nivolumab, the patient felt that his quality of life had decreased since initiating therapy, due to

Figure 1. Tumor response to treatment with sotorasib in patient case 2.



CT chest images – pre and on treatment with sotorasib



CT abdomen images – pre and on treatment with sotorasib

worsening fatigue and shortness of breath and decided to stop treatment. The patient was discussed at MTB and clinical trial with sotorasib was recommended. However, he did not meet criteria to participate in sotorasib clinical trials. Instead he enrolled in the sotorasib expanded access program we had opened at our institution, and began treatment in April 2021. The following month he reported significant improvement in performance status and noted near resolution of his fatigue. Scans performed two months later showed improvement in the disease status (Figure 1). He was treated for seven months with stable disease before ultimately experiencing progression.

Discussion

For many types of cancer, diagnostic testing incorporates tumor genomic testing as standard of care. The size and breadth of somatic gene panels varies widely by platform. Limited gene panels test specific genes of interest to guide therapeutic decisions, while more comprehensive panels may include entire exome, transcriptome, report microsatellite stability and tumor mutational burden. Interpreting clinical actionability of comprehensive NGS results can be difficult. Studies of comprehensive NGS testing report a wide range of clinical actionability ranging from 40 to 94%, making it challenging to assess the degree of clinical benefit gained.[6] While recent guidelines by the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) support personalized cancer therapy and NGS, both bodies caution the need to weigh the cost versus benefit of NGS.[7-8]

However, in the rapidly evolving field of medical oncology, guidelines may not keep up with new discoveries. The ESMO precision medicine working group[8] recommends tumor multigene NGS to assess for level I alterations associated with drugs found to improve outcomes in clinical trials and considered standard of care therapies.

Limited gene panel testing may be more cost-effective but must be weighed carefully against the rapid testing and approval of biomarker tested therapies.[9] ESMO recommendations for limited gene panels covering level I alterations for example would exclude testing of KRAS G12C mutations for NSCLC. However, these recommendations were released ahead of the approval of drugs targeting KRAS G12C. EGFR exon 20 insertion mutations are also not routinely tested in limited gene panels and are not a level I alteration; amivantamab and mobocertinib are now FDA-approved for NSCLC with this alteration.[10-11]

The early identification of biomarker-directed therapies is essential for patients with advanced cancer. Studies have found that prescreening NSCLC for activating EGFR mutations for anti-EGFR tyrosine kinase inhibitor therapy leads to substantial increase in response rates (>50%) and overall survival. Molecular tumor boards may assist with biomarker detection and therapeutic categorization.[12] A study by the University

of Michigan conducted from 2011 to 2018 of >1,000 patients using a 1,700 gene panel profile and utilizing a molecular tumor board separated patient results into three tiers corresponding with the potential actionability and evidence level based off of ESMO Scale of Clinical Actionability for Molecular Targets (ESCAT).[6] Tiers 1 and 2 are considered possibly clinically actionable with Tier 1 having clinical utility according to FDA approvals or professional guidelines and Tier 2 undergoing clinical trials for approval or off-label therapies. Of 1,015 patients with successful NGS testing, it was noted that 288 (28%) of patients had a Tier 1 mutation and 744 (73.3%) had a Tier 2 mutation. Of these, 132 (13%) were treated with sequence-directed therapy (SDT). This disparity between Tier 1 and 2 mutations and matriculation to SDTs will likely narrow with increased targeted drug approvals and improved access to clinical trials. In addition, the utility of MTBs will likely increase with increased access to NGS; from 2011 to 2019 NGS testing rates went from <1% to 40% in metastatic solid tumors including melanoma, lung, breast, and colon cancers.[13] The role for NGS testing continues to expand beyond patients with advanced stage tumors. NGS testing is becoming standard of care to select appropriate adjuvant treatment in patients with early-stage NSCLC who have undergone curative surgical resection.[14] In addition, newer techniques that leverage artificial intelligence or tumor microenvironments to analyze NGS findings to identify signatures that help choose appropriate chemotherapy regimens could significantly expand the role for NGS testing.[15-16] In the near future, NGS testing is likely to be standard of care in most if not all patients diagnosed with solid tumors.

Conclusion

Our patients received and responded to an investigational KRAS G12C inhibitor. These patients had limited therapeutic options and were unable to participate in a clinical trial. Early identification and coordination with pharmacy, clinical research including institutional review board and drug manufacturer by the MTB was critical to obtaining access to sotorasib. These two cases illustrate the key role played by the MTB in identifying an emerging drug, sotorasib, as a potential option to target KRAS G12C mutation and then collaborating with clinical research teams to open the appropriate study for these two patients. Therefore, clinical NGS testing alone may not be adequate but when combined with MTB may provide significant clinical benefit for patients with advanced stage cancers.

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Disclosure

None reported. **MM**

Improving Access to Care for Vulnerable Missourians: The Hotspot Project

by Olabode Ogundele, MA, Rachel Mutrux, Kimberly Hoffman, PhD & Mirna Becevic, PhD

Missouri Telehealth Network
University of Missouri
Show-Me ECHO

The hotspot distribution project helped the most vulnerable Missourians access needed care during the public health emergency.



Olabode Ogundele, MA, MSHI, (above), is at the Institute for Data Science and Informatics and the Missouri Telehealth Network; Rachel Mutrux, is with the Missouri Telehealth Network; Kimberly Hoffman, PhD, is in the Department of Family and Community Medicine, School of Medicine; and Mirna Becevic, PhD, is at the Institute for Data Science and Informatics and the Missouri Telehealth Network, and in the Department of Dermatology School of Medicine; all are at the University of Missouri - Columbia, Columbia, Missouri.

Abstract

Context

Many rural areas across the country are considered "health and technology desserts." They lack access to healthcare facilities and broadband connectivity for telehealth services. With the emergence of the COVID-19 pandemic and social distancing requirements, rural residents have become even more vulnerable.

Purpose

To evaluate the utility of distribution of internet hotspots to rural and underserved Missourians for telehealth access.

Methods

Mobile wi-fi devices (hotspots) were distributed to Federally Qualified Healthcare Centers and Community Mental Health Centers to be used by clinics and patients for telemedicine visits through the Missouri Telehealth Network project. We analyzed six sets of surveys from clinic administrators, collected between January and June 2021, to assess usage, technical utility of hotspots, and satisfaction with the project.

Findings

A total of 163 (71.5%) survey responses were received. Seventy-seven percent (7,981) of the 10,345 ordered hotspots were distributed. Hotspots were used for video visits, with an average of 5,915.66 monthly visits (range: 3,449 – 8,420). Seven facilities reported technical issues. Open-ended survey responses reported overall satisfaction with the project. The project allowed convenient access to telehealth services for both routine and specialty care, while decreasing patient and staff exposure to COVID-19. Hot-spot service enabled patient access to educational opportunities and providers noticed a decrease in no-shows.

Conclusion

The importance of internet connectivity in enabling access and means to care for rural, underserved communities cannot be overemphasized. The hotspot distribution project helped the most vulnerable Missourians access needed care during the public health emergency.

Introduction

At the time of this writing, in Missouri, 14 hospitals have closed since 2014—nine rural and eight acute care hospitals.[1] In a primarily rural state (97% of Missouri land is classified as rural), access to healthcare services is challenging for rural and underserved residents primarily due to maldistribution of providers and other socio-economic reasons. Hospital closures are further limiting access to care and creating "healthcare deserts" in many counties across the state. Healthcare deserts are characterized by lack of adequate number of health professionals and resources due to remoteness and high needs of care.[2]

Rural areas are reported to have 39.8 primary care physicians (PCPs) per 100,000 residents, compared to urban areas with 53.3 PCPs per 100,000 population.[3] In addition to maldistribution of PCPs, there are also only 30 specialists per 100,000 residents in rural communities compared to 263 specialists per 100,000 residents in urban areas.[4] This maldistribution and remoteness make it difficult to access care. The long travel times, inadequate resources, lack of timely and appropriate access to healthcare services in rural and underserved areas may have negative effect on patients' experience of care and their health outcomes.[5]

Missouri has over 6.1 million residents living in its 115 counties. Nearly 34% of these residents live in the 99 rural counties of the state.[6] This means that around 2.06 million rural Missourians will experience an uneven health risk compared to urban Missourians, due to limited access to health resources and services. Despite the perception of telemedicine as a solution to remote access to care for rural patients,[7] many rural Missourians do not have internet access suitable for telehealth.[6] The lack of adequate internet connectivity in many rural communities is an obstacle for adoption of adequate telemedicine applications,[8] and given healthcare's increasing reliance on a technology like telemedicine, internet access has become a social determinant of health.[9]

Table 1: Survey Response Rate

Survey	Count	Response rate
1/13/2021	33	87%
2/9/2021	28	74%
3/9/2021	30	79%
4/13/2021	27	71%
5/11/2021	22	58%
6/8/2021	23	61%

During the COVID-19 public health emergency, stay-at-home order, and subsequent social distancing requirements, healthcare organizations quickly adopted or expanded their telehealth and telemedicine programs to ensure continuity of care while minimizing unnecessary exposure for patients and staff. This was a great option for many patients, however, the most vulnerable Missourians in many rural communities were not able to access these services because of lack of connectivity at home and/or appropriate technological devices.

Around 555,000 (30.2%) of the 1.83 million rural Missourians evaluated in 2020 did not have access to high-speed internet according to the Federal Communications Commission (FCC);[10] a number that is likely underreported due to the flaw with Form 477 reporting apartment complexes and blocks that have internet access. For instance, there is the issue of the FCC counting the entire census block as covered whenever an Internet Service Provider (ISP) offers service to at least one household in a census block. This flaw disproportionately affects rural communities.[11] The lack of broadband access creates "technology deserts," a digital divide between rural and urban areas, causing more barriers to healthcare access.

The Missouri Department of Economic Development (MO-DED) worked with the key stakeholders related to broadband and

telemedicine during the pandemic to implement projects with the aim of improving access to telehealth for rural and underserved Missourians. The University of Missouri's Missouri Telehealth Network (MTN) was chosen as a partner-lead on a project "Hotspots for Health." The MTN partnered with cellular telephone companies to procure hotspots for Federally Qualified Health Centers (FQHCs) and Community Mental Health Centers (CMHCs). Each FQHC and CMHC were eligible to order up to 300 hotspots from any vendors best suited for their geographical location and access. In addition to patients of the participating clinics, staff, healthcare providers, and mobile health vans were also qualified to receive hotspots.

In this study we evaluate the MTN's "Hotspot for Health" project from January through June 2021 and its role in providing care to rural and vulnerable Missouri residents during the COVID-19 pandemic.

Figure 1: Monthly total number of hotspots distributed

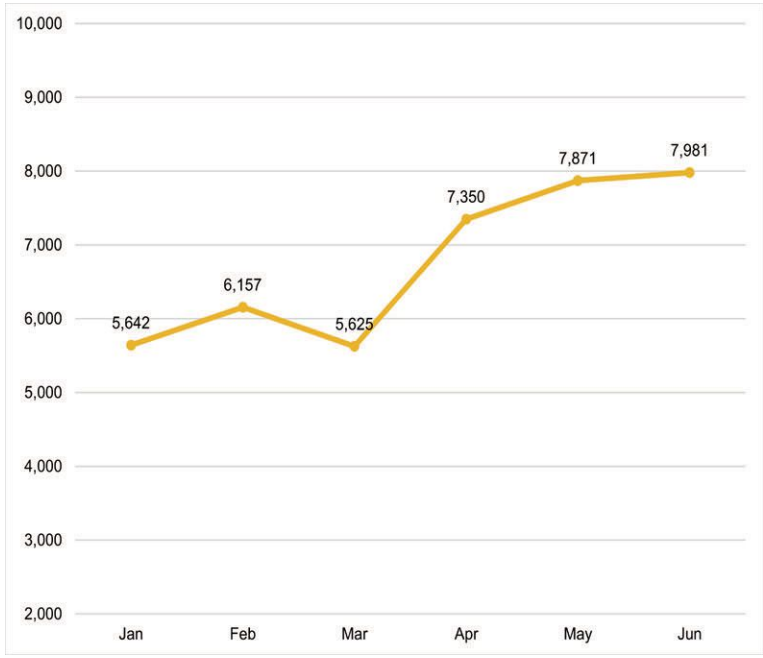
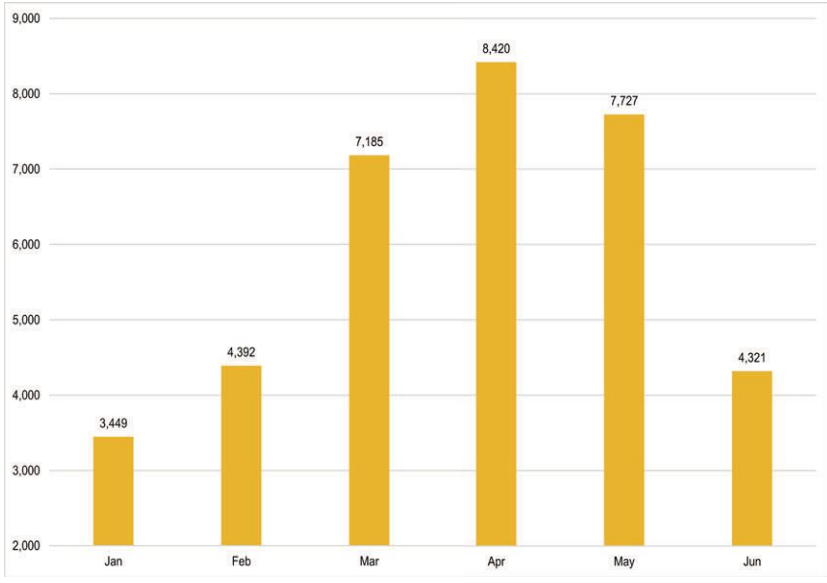


Figure 2: Number of telemedicine visits per month using hotspots



Methods

The University of Missouri (MU) Institutional Review Board (IRB) approved the project as quality improvement (IRB #2086242). The project was funded by the Missouri Department of Economic Development (MO-DED). The clinics contacted for mobile wi-fi devices (hotspots) distribution to be used by patients for telehealth visits were 38 health centers across 26 counties. Of those, 20 clinics were FQHCs, 14 CMHCs, and four were both FQHCs and CMHCs. The hotspot vendors were four cellular telephone companies: Verizon, US-Cellular, AT&T, and T-Mobile, which were determined based on their geographical suitability and availability.

Study Instrument

A 17-question survey was designed by the MTN evaluation and operations leadership. Most of the questions were in the open-ended

Figure 3: Number of clinics reporting technical issues

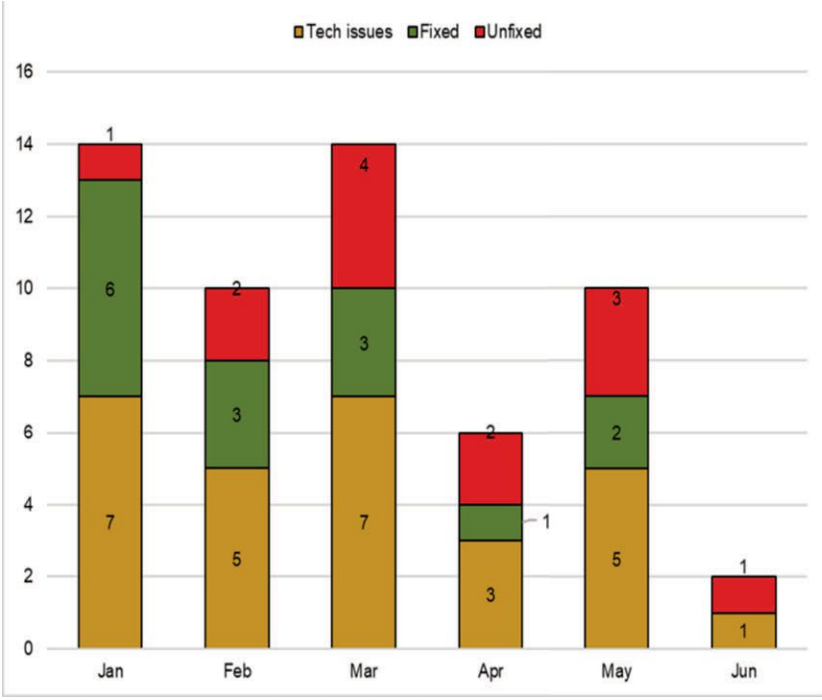
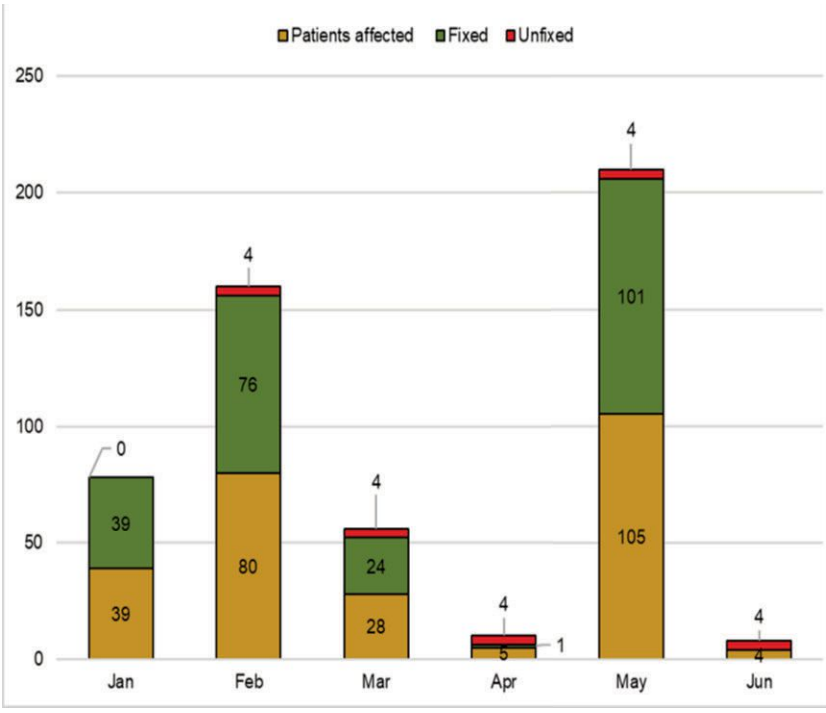


Figure 4: Number of patients affected by tech issues



free text format (n=12). Two questions were yes or no (if the site experienced technical issues, and if those issues were corrected) and an additional two questions were multiple choice (which site was contacted to help correct technical issues, and how it was corrected) format. The survey was designed and administered using REDCap (Research Electronic Data Capture), an online web application used to securely build and manage surveys and databases (REDCap from Vanderbilt University: https://www.project-redcap.org/). The survey was distributed to clinic managers and/or administrators between January 13 and June 8, 2021.

Results

Geographical Distribution

The hotspots were distributed to healthcare facilities in 38 locations, which then identified patients who received the hotspot for telemedicine usage. The hotspot services are provided by four vendors: Verizon, US-Cellular, AT&T, and T-Mobile.

The number of distributed hotspots increased steadily from January (n=5,642) to June (n=7,981) (Figure 1). The drop in the number of distributed hotspots as seen in Figure 1 can be attributed to patients who returned

their hotspot devices and were seeking in person consultation. Seventy-seven percent (n=7,981) of the 10,345 ordered hotspots had been distributed by June 2021.

Survey Results

A total of 38 clinic administrators or managers received the monthly surveys. The highest survey response was achieved in January 87% (n=33), and the lowest response was in May 58% (n=22) (Table 1).

Telemedicine visits peaked in April with 8,420 visits reported, after which we observed a steady decline with only 4,321 visits reported in June (Figure 2).

Technical issues

The number of facilities with technical issues remained low during the six months of the project, with most issues resolved in a timely manner (Figure 3). The highest number of facilities (n=7) with technical issues were reported in January (n=7) and March (n=7) and the lowest number was reported in June (n=1). The proportion of patients affected by technical issues was also low (Figure 4).

Respondents answered free text open-ended questions about how the hotspot project improved access to care for their patient population. We received 176 responses that were grouped into five thematic categories: general comments, healthcare access, patient benefits, provider/service benefits, and others.

Healthcare Access (n=76)

A total of 76 survey responses discussed healthcare access as one of the results of the hotspot distribution project. Responses indicated improved access to care for patients that otherwise did not have internet access at home. They also reported that devices were easy to use, which allowed patients to continue receiving clinical care, and attending group and individual behavioral services during the stay-at-home order. Hotspots increased access for people who lacked transportation and other resources.

Patient Benefits (n=31)

A total of 31 responses address patient benefits. In addition to accessing healthcare, hotspots allowed patients to access learning and educational opportunities, and to stay connected with others. It was also reported that utilization of telemedicine services allowed patients to conveniently access care while decreasing unnecessary exposure to COVID-19. Participants noted that the telemedicine appointments were more engaging and allowed for social connection to others.

Provider/Service Benefits (n=28)

A total of 28 responses identified provider/service benefits. Respondents observed a decrease in no-shows as a result of increased telemedicine usage. They also reported expanding services to areas that they had previously not been able to serve.

General Comments about the Hotspot Program (n=18)

There were 18 general comments across the six administered surveys. Several participants made general positive comments about how internet hotspot availability made a difference for their patients/clients. They indicated overall satisfaction with the project.

Other (n=22)

The largest number of "Other" comments (15) relate to issues with distribution of hotspots. Respondents indicated that some patients preferred in-person care to telemedicine visits. This may have resulted in their refusal to accept hotspots, schedule, or keep telemedicine appointments.

Discussion

The availability of broadband internet service is a prerequisite to access telemedicine and resolves the issue of access to care in rural underserved communities. Those who reside in areas with adequate internet access are more likely to utilize telemedicine than those with little access. We found that the distribution of mobile internet hotspots increases residents of underserved areas' access to care during the COVID-19 pandemic which highlighted the importance of telemedicine and remote care. Similar to the findings of our hotspot distribution project, Quinton et. al reported that the association of internet access availability is one of the factors associated with the utilization of telemedicine for the rural and

working-class community in the US.[12]

Satisfaction with the project was reported by administrators. The success can be attributed to the perceived usefulness of the hotspot devices to access services, given the suitability of telemedicine for care delivery during a global pandemic like the COVID-19.[13] Research findings have indicated high patient satisfaction when they are able to access virtual care during the Covid-19 pandemic.[14] We observed that the satisfaction in this project may also be associated with ease of use, underlining the importance of usability towards achieving any technology goal and acceptance. Despite the enormous success of the project, results from the survey indicate some patients' preferences for in-person care, which are likely to have resulted in the refusal of mobile hotspots, and refusal to schedule and keep telemedicine appointments. Technical issues could also have affected patient satisfaction, and willingness to use or continue using the hotspots, which could lead to overall fragmented care.

We also observed the benefits of internet accessibility for clinicians and healthcare centers as well. The increased use of telemedicine due to internet access allows patients the ability to keep their appointments, and the health centers were able to expand services into areas they had not previously been able to serve. This expansion of healthcare services to allow FQHCs and CMHCs to serve as provider sites enabled them to ensure the continuation of care for their patients during the stay-at-home order.

Our study was limited by geographic location, and the results may not be generalizable to urban states or countries. In addition, this project involved FQHCs and CMHCs, which would have left out patients, administrators, and providers from other types of health centers and facilities. We recommend future research to expand further and evaluate the impact of mobile hotspot device distribution on patients' outcomes.

Conclusion

Investments in technologies that aid telemedicine have become inevitable in the context of the COVID-19 pandemic. The provision of broadband internet for remote underserved areas is a step in the right direction to leverage service for remote care access and the reduction of health disparities between rural and urban populations.

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Disclosure

None reported. **MM**

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