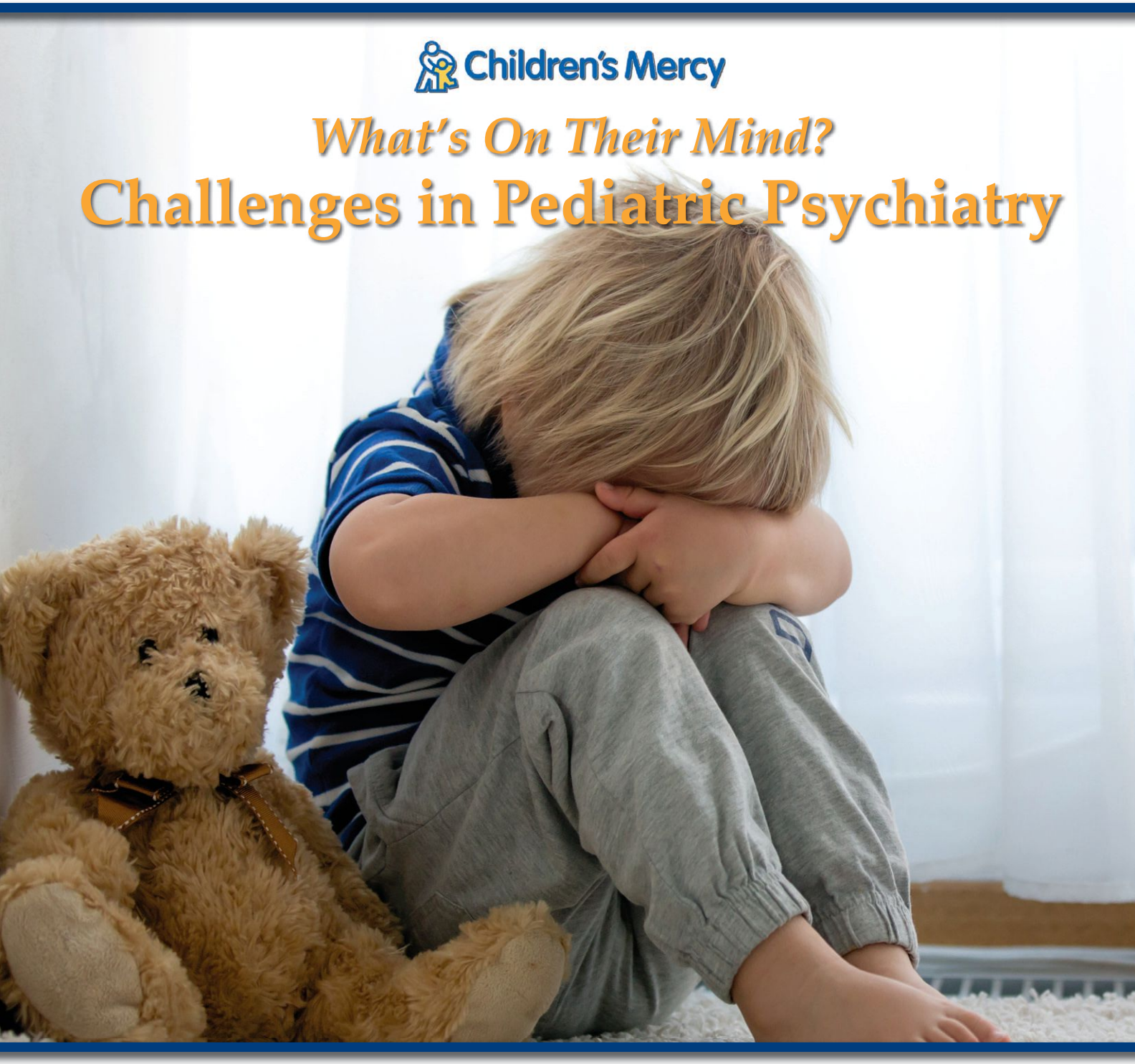
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Navigating Access: The Future of Compounded GLP-1 Receptor Agonists for Weight Loss

by Jarred Dudding, PharmD



GLP-1 receptor agonists are among the most effective weight management therapies available, offering substantial reductions in body weight along with improvements in metabolic and cardiovascular health markers; however, their high cost limits access for many patients.

Over the past several years, glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide and tirzepatide have emerged as breakthrough therapies in the fight against obesity and related metabolic disorders. Initially developed for type 2 diabetes, these agents have been repurposed and embraced by a broader patient population seeking meaningful weight loss and improved metabolic health. Their surging popularity has also revealed critical vulnerabilities in affordability and access.

With brand-name versions like Wegovy, Ozempic, and Mounjaro, often priced at more than $1,000 per month and limited insurance coverage, compounded versions of these agents have filled a temporary but vital gap. Recent regulatory shifts by the US Food and Drug Administration (FDA) have cast doubt on the future of compounded GLP-1 agonists, leaving patients, prescribers, and compounders in a state of uncertainty. (https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss)



Jarred Dudding, PharmD, is Director of Quality Assurance, Apollo Care, LLC, a commercial 503(b) Outsourcing Facility in Columbia, Missouri, USA.

A Surge in Demand and a Regulatory Opening

FDA regulations under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act permit pharmacies to compound drug products that are on the FDA shortage list. Semaglutide and tirzepatide were added to the list in 2022 and 2023, respectively, due to supply constraints and high demand.

This designation allowed compounding pharmacies, both traditional 503A pharmacies, and FDA-registered 503B outsourcing facilities, to prepare sterile injectable formulations of these medications for patients with a valid prescription. For many patients, the result was access to affordable alternatives at a fraction of the price of branded products.

A Changing Landscape: FDA Rescinds Shortage Designation

In February 2025, the FDA removed semaglutide from the drug shortage list.[1] Tirzepatide followed in April. This regulatory change effectively prohibited pharmacies from continuing to compound these agents under the exemption based on shortages. The Agency gave pharmacies a wind-down period to cease compounding and distributing these medications. For 503A facilities, that deadline passed in April 2025. For 503B outsourcing facilities, the cutoff was May 22, 2025.



The use and sales of GLP-1 agonists as well as the clinical success are unmatched in the history of weight loss products. *Source: Grand View Research*

These changes, though anticipated, ignited concern across the industry. Tens of thousands of patients who had successfully relied on compounded GLP-1s for access and affordability were now faced with limited options: pay out-of-pocket for brand-name drugs, seek international sources, or stop therapy altogether.

Safety Concerns Driving Enforcement

Part of the FDA's motivation stems from growing concerns about safety.[2] Reports of adverse events associated with compounded semaglutide and tirzepatide have surfaced, ranging from gastrointestinal side effects to overdosing, injection site reactions, and even hospitalization. Some issues stemmed from compounding errors, inconsistent active pharmaceutical ingredient (API) forms (e.g., semaglutide sodium vs. base), or inadequate quality controls.

As of mid-2025, the FDA and other public health agencies have reported over 1,000 adverse events linked to compounded GLP-1 formulations. Though most did not result in long-term harm, the Agency cites these incidents as justification for strict enforcement of compounding regulations.[1,2,3]

Although this figure may seem concerning on its own, it should be viewed in context. FDA-approved products like Wegovy, Ozempic, and Mounjaro are also linked to thousands of adverse events reported each year. Many involve well-known side effects like nausea, vomiting, diarrhea, and gallbladder problems. According to the 2023 FDA Adverse Event Reporting System Public Dashboard, semaglutide-containing products alone were associated with over 8,000 adverse events in the US. (https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. (Accessed 6/1/2025)

What sets apart the adverse events reported with compounded versions is the concern over manufacturing variability and dosing inconsistency, not necessarily a higher number of events, but the increased uncertainty in product quality and composition. This distinction supports the FDA's increased scrutiny and emphasizes its focus on sterility assurance, potency validation, and API integrity in compounded medications.

Advantages of 503B Outsourcing Facilities

Among the most trusted providers of compounded medications are FDA-registered 503B outsourcing facilities. Unlike traditional 503A pharmacies, which compound per individual prescription, 503B facilities are authorized to produce medications in bulk for healthcare office use and are subject to FDA inspections, current Good Manufacturing Practice (cGMP) requirements, and strict quality control standards, just as traditional pharmaceutical companies are.

503B facilities offer a higher level of regulatory oversight, providing several benefits, including validated sterile processes, dedicated cleanroom

environments, comprehensive environmental monitoring programs, and lot-specific release testing for potency, sterility, and endotoxins. These requirements help reduce the risk of contamination or subpotent formulations, ensuring greater consistency and safety.

Throughout the GLP-1 shortage period, 503B facilities played a crucial role in supplying healthcare systems and clinics with compounded versions that met current Good Manufacturing Practice (cGMP) expectations. While not immune to FDA scrutiny, these outsourcing facilities have often provided a safer and more scalable alternative than less-regulated sources, particularly when treating high-risk patient populations.

For physicians, especially those treating patients for whom commercial products are still too expensive, FDA-regulated 503B outsourcing facilities serve as an essential and trustworthy resource. Collaborating with these facilities gives prescribers confidence in the quality of care and helps expand access to effective therapies.

Legal Boundaries and Clinical Discretion

FDA policy prohibits the compounding of drugs that are "essentially a copy" of a commercially available product. However, clinical exemptions do exist. Suppose a provider can document that a compounded version includes a significant difference for a specific patient, for example, the addition of another ingredient, a modified dosage strength, or a preservative-free formulation. In that case, compounding may still be permitted.

This provision has led some compounders to explore formulations that include additives such as glycine, levocarnitine, pyridoxine, and cyanocobalamin or that offer concentrations not currently marketed by manufacturers. These alterations must be clinically justified and carefully documented to remain compliant.

Given these exemptions, prescribers must recognize the critical role compounded alternatives continue to play in bridging the affordability and accessibility gap. Especially when working with reputable 503B outsourcing facilities, compounded medications provide a clinically sound and regulatory-compliant pathway to ensure patients receive the treatment they need. Embracing these options, when justified and appropriate, strengthens the continuum of care and supports health equity in an increasingly cost-constrained environment.

Impact on Patients and Access

The consequences for patients are not theoretical. The compounded formulations often cost between $250 and $400 per month, which is less than half the out-of-pocket price for many commercial GLP-1 products. For the uninsured, underinsured, or those denied coverage based on therapeutic indication, compounded medications are the only realistic option.

Now, many patients are facing difficult choices. Some are stretching doses, skipping injections, or turning to non-regulated online sources and international pharmacies. Others have stopped therapy despite documented benefits in weight reduction, glycemic control, and overall quality of life.

Legal Challenges and Industry Pushback

Compounding organizations and industry groups have pushed back against these efforts. The Outsourcing Facilities Association (OFA) has criticized the FDA's actions as overly broad and insufficiently supported by data.[4] Some compounders have challenged enforcement in federal courts, arguing that their formulations are legally distinct and medically necessary.

A Need for Balanced Solutions

The dilemma reflects broader tensions in the US healthcare system: how to ensure patient safety without stifling access to affordable treatments. Compounded GLP-1s served a role during a time of acute need. As supply stabilizes, the regulatory focus has understandably shifted to safety and compliance, but with real-world consequences for patients.

Policymakers and payors must recognize this gap. Solutions could include expanded insurance coverage for GLP-1 medications, including for obesity-related indications, which would reduce financial incentives to seek compounded alternatives. Patient assistance programs from manufacturers could be expanded to reach a broader range of low-income patients.

From a regulatory standpoint, clarity is key. FDA guidance should help distinguish between noncompliant and clinically justified compounded formulations, supporting prescribers who have legitimate reasons for seeking tailored options.

Conclusion A Time for Perspective

The public health need for safe, effective, and affordable obesity treatment has never been more apparent. GLP-1 receptor agonists are transforming the medical landscape and making major improvements in population health—but only if patients can access them.

As the regulatory window narrows on compounded formulations, stakeholders must resist polarized responses. This is not a binary debate between safety and access but a challenge to achieve both through thoughtful policy, responsible compounding, and equitable healthcare reform. Patients deserve nothing less. **MM**



Sex Industry Patients: A Primary Care Perspective

by Mary Elizabeth Sutherland, MD, Kristine Jennings, MD, Gerrit Seymour, DO & Daniel Armounfelder, MD

Introduction

In medicine every new encounter presents a unique situation and circumstance, but each has a similar goal: healing. In addition to treating the individual patient, each physician promises through an oath to be "ever vigilant in aiding the general welfare of the community."[1] These principles are essential while extending care for a growing and particularly vulnerable population, those involved in sex work.

For the purposes of this article, "sex work" or "sex trade" refers to sexual acts or content that are compensated by money, goods, or other advantages. This may be further categorized as "direct physical contact," such as in personal sexual engagement with a client, and "titillation" which includes online, print, and phone services.[2] The variety and breadth of the sex industry, from online subscription services, sexting, or direct physical sexual acts, and the profit potential, recently has led to a substantial increase in people, mostly women and girls, involved.

To illustrate, OnlyFans, a popular online subscription service famous for creators showing adult pornographic content, reports approximately 500,000 new sign-ups and 10,000 new creators joining each day. It boasts over 100 million users globally. For the 300,000 content creators monetizing content, there is over $2 billion of annual earnings.[3,4] A *Wall Street Journal* article (7/1/25) indicated OnlyFans was for sale at an asking price of $9 billion.

As a single aspect of the sex industry, albeit a significant one, it is easy to use these data to understand the magnitude of the industry. This is particularly relevant to those in the Midwest, as even prior to the advent of online sexual content, our area has been called a "hub for sex trafficking" given its central location, extensive roadway systems, and hundreds of truck and road stops.[5]



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There is not a commonly agreed upon or validated approach for sexual history for those in high-risk sex work, however, you can utilize the Center for Disease Control's recommended "Five P's".

Ask patients about:
Partners
Practices
Protection from sexually transmitted infections (STIs)
Past STIs
Pregnancy intention

Acknowledging that sex trafficking is a separate and distinct issue, the conditions remain similarly supportive of the sex industry. With the meteoric rise of the internet, cell phones, and online traffic, online sex is pervasive. What used to be limited to physical location now extends beyond state and national borders. With the increased usage and virtually everywhere availability, it has become more common for physicians to encounter patients involved in sex work in clinical practice.

Medical Implications

Patients involved in sex work have elevated risk for sexual- and trauma-related health pathologies, but are less likely to seek primary care and if they do, may not be identified by taking a routine sexual history. Barriers to patient disclosure include stigma and fear of judgment. Providers may facilitate health information sharing by creating psychologically safe clinic spaces.[6–9] There is not a commonly agreed upon or validated approach for sexual history for those in high-risk sex work, however, using the Center for Disease Control's (CDCs) recommended "Fives P's" may be reasonable as an initial approach.[6,10] These include asking patients about partners, practices, protection from sexually transmitted infections (STIs), past STIs, and pregnancy intention. While gathering a routine sexual history, the American College of Obstetrics and Gynecology (ACOG) suggests using cues, such as current drug use or multiple sexual partners in the last month, to initiate a more thorough history.[11] While obtaining detailed information may be necessary to appropriately screen and treat, requesting permission to ask more invasive questions and respecting patient autonomy are key to building trust.[7,9]

Routine screening and preventative care should universally be offered including appropriate vaccinations. Given sex workers frequently encounter clients of unknown vaccination status, Tdap, Hepatitis A, Hepatitis B, measles-mumps-rubella (MMR), meningococcal, influenza, COVID, and human papilloma virus (HPV) vaccines should be offered.[8] Patients with a cervix should be screened for cervical cancer per the usual screening schedule. Men and transgender females who have sex with men should receive routine anal exams if they are engaging in receptive anal intercourse.[8]

The incidence of STIs for those in sex work is higher than the general public. In one study in Northern California, sex workers were more likely to have multiple sexual partners, multiple previous sexual partners, and recent anal sex. They also were more likely to be victims of unwanted vaginal and anal intercourse.[12] This same study highlighted factors that contribute to decreased condom adherence, further exacerbating STI risk. These included being offered more money to not use condoms, client refusal of condoms, and client force.[12] Given these risks, regular screening for STIs including gonorrhea, chlamydia, hepatitis C and B, syphilis, and trichomoniasis should be incorporated into care. Cadence of testing depends on sexual risk such as condom use.

Table 1. Three major legal frameworks discussed worldwide

Criminalization	Most common. Buying and selling sex are illegal. Critiqued for punishing sex workers rather than giving them better options.
Decriminalization	Not illegal, but neither is it state-sanctioned. May apply only to selling of sex, or may also apply to buying. Decriminalization is backed by the World Health Organization and Amnesty International due to removing barriers for sex workers to seek help if/when they need it.
Legalization	Government regulation of the sex industry, ie. state-sanctioned brothels.

For those without consistent condom usage, screening every three to four months is a reasonable approach. For those with consistent condom use, screening every six to 12 months seems to be sufficient.[13] Distinguishing the type of sexual contact (oral, anal, vaginal) is imperative as swabbing the anatomic area potentially exposed to an infection can lead to more accurate identification of infection.[14] New research has demonstrated decreased risk of gonorrhea and chlamydia when doxycycline postexposure prophylaxis is utilized in men who have sex with men (MSM) and transgender women at high risk of STI.[15] More studies are needed to extrapolate to other sex worker populations.

Globally, female sex workers are 30 times more likely to be living with HIV than other women of reproductive age. This requires specific attention to testing, prevention, and treatment.[16] Cost and stigma are the two biggest barriers to testing and must be addressed.[17] HIV self-testing kits (HIVST) have been shown to increase screening rates and identification in select populations.[18] Given the high risk of HIV acquisition, the CDC and World Health Organization (WHO) recommend offering pre-exposure prophylaxis regimens with tenofovir-emtricitabine or tenofovir-lamivudine.[8]

Although the exact numbers are unknown, several studies suggest that unintended pregnancy among women sex workers is also high. Often this may result in unsafe abortion practices when alternatives are not available. Dual contraception with a long-acting reversible agent and condoms is recommended to prevent unintended pregnancy.[8,19,20] Additionally, making emergency contraception options readily available can aid in prevention.[8]

Sex workers have reported high levels of childhood trauma and abuse and often have higher comorbid depression, post-traumatic stress disorder (PTSD), anxiety, suicidal ideation and attempts as a result. Being victims of violence, drug use, inconsistent condom use, and HIV/STI infections are also associated with increased mental health morbidity.[21] In addition to utilizing a trauma informed approach to care, sex workers should be routinely screened for anxiety and depression.[21,22] A comprehensive treatment strategy, including counseling and medication, is often necessary to treat the complex mental health concerns that arise.

Ethical Concerns

While caring for patients working in the sex industry, inevitably questions of ethics and the law will arise. Foremost may be the concern of when or if to make reports to law enforcement. While this paper primarily addresses sex work engaged in voluntarily by a consenting adult, it is worth noting that all 50 states and the District of Columbia mandate that physicians report suspected or confirmed child abuse, including images of child sexual abuse posted online.[23] For patients who are not minors, reporting laws become more complicated. They can be divided into two main categories: mandated reporting and permissive reporting.[23] Mandated reporting is, as implied, required. Permissive reporting, in contrast, refers to laws that allow for good-faith reporting without risk of punishment. For at-risk adults, generally defined as adults who one could arguably not have decisional capacity, most states have at least permissive reporting.[23] For adults who do have decisional capacity, reporting should not be done without consent. These are the situations in which the ethical and legal discussion becomes especially complex and extends beyond the exam room. Table 1 outlines the three major legal frameworks discussed worldwide.[24]

Another concern when discussing the ethics of decriminalizing sex work is whether or not people who are voluntarily working in the sex industry have true autonomy. This is raised in the context of Beauchamp and Childress's Four Principles of Biomedical Ethics: autonomy, beneficence, non-maleficence, and justice. One argument is that people are not freely choosing sex work if they are engaging in it out of financial necessity.[25] A counterargument is that a similar point could be made about any work that is remunerated.[26,27] Regardless of one's philosophical position on the matter, the role of the physician is to partner with the patient to work towards beneficence while simultaneously respecting autonomy in the issue at hand.[28]

Conclusion

Patient involvement in the sex trade increases health risks and limits access to care. By building rapport, providing non-judgmental evaluation, and offering individualized treatment, physicians may decrease health disparities. Ethical, legal, and cultural challenges remain in this area causing potential conflict for a physician, but this does not diminish the duty to provide excellent medical care in a safe environment.

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Addressing Physician Shortages by Broadening of Licensure Pathways for International Medical Graduates

by Fariha Shafi, MD, Sandeep Yanamala, BS, Umar Iqbal, MD, Harshini Kumaresan, BA, Madhumathi Vijayalingam, MD & Seth Baligod, MD

Streamlining and incentivizing IMGs to come work in the United States, especially in the underserved and primary care setting, is a worthy goal.

Introduction

The United States (US) population is aging rapidly, and within a decade, nearly 22% will be 65 or older.[1] This demographic shift, in addition to increased life expectancy, prevalence of chronic diseases, increased health literacy, integration of healthcare data (e.g. from wearable devices) and availability of newer therapeutic options, will significantly increase healthcare associated stress on societal resources. Of these, the availability of physicians is arguably the most critical.

The Association of American Medical Colleges (AAMC) has attempted to quantify this physician shortage and has arrived at an estimate of the US being possibly short of up to 86,000 physicians by 2036.[2] Moreover, current physicians are faced with a litany of challenges, delays in care due to non-availability of appointments, hospital beds, lab tests, radiology, and consults. These obstacles span the entire spectrum of healthcare from primary to sub-specialty care.

Efforts to address this physician shortage by expanding the roles of Nurse Practitioners (NPs) and Physician Assistants (PAs) have made some impact, but they have not fully resolved the issue, especially in high-need areas.[3] Although a significant increase in the number of PAs and NPs graduates has been observed, only a fraction practice in rural and underserved settings.[4]

According to recent data, only 25% of new NPs have chosen to work in rural areas, and just 9% of Advanced Practice Registered Nurses (APRNs) from the Centers for Medicare & Medicaid Services-funded programs practice in federally qualified health centers.[3] An Oregon Center for Nursing study found that only 25% of NPs remain in primary care, others opting instead for higher-paying specialty roles.[5] Another study found that a majority of NPs left for subspecialty care despite the vast majority undergoing primary care training.[6]

Problems Associated With Using NPs and PAs to Address Physician Shortages

Further complicating the gaps in care provided by physicians versus mid-level providers is the difference in training between NPs, PAs, and fully licensed physicians. While NPs and PAs are well-trained in patient care, they often lack meaningful exposure to complex medical cases.[7] This limitation becomes especially evident in underserved areas, where patients frequently present with multiple chronic and untreated conditions that require the comprehensive medical knowledge of a physician. Physicians at Hattiesburg clinic in southern Mississippi analyzed the cost data from the Centers for Medicare and Medicaid Services



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and found that care by non-physician providers was more expensive than care delivered by physicians.[5] They discovered that healthcare spending was higher for Medicare patients (excluding those in nursing homes or with end-stage renal disease) if their health provider was a non-physician clinician rather than a physician. After risk adjustment for patient complexity, an even larger difference translating to an additional spending cost of $28.5 million annually was found.[5] The stark contrast in healthcare spending was attributed to ordering more tests, an increased number of referrals to specialists, and a greater emergency department utilization. This higher cost is evidence that PAs and NPs alone cannot provide the same quality care as that of physicians.

Addressing the Physician Shortages by Using International Medical Graduates

Multiple efforts are currently underway to mitigate physician shortages. This includes increasing the size and number of medical schools and residencies, telemedicine expansion, adoption of artificial intelligence, and streamlining the process for International Medical Graduates (IMGs) to practice in the US.[7] For the purposes of this article, we will focus on the current status of IMGs in US healthcare, traditional pathways for IMGs to practice in the US, and recent attempts to develop alternative routes to licensure for IMGs.

Currently, nearly 25% of all active physicians in the US are IMGs. The representation is even larger in primary care fields such as internal medicine (40%).[8] International graduates have an outsized effect in specialties that are considered less attractive by US graduates. Many underserved areas in the US are disproportionally staffed by IMGs. Hence, they are a critical component of the our health care system. In summary, foreign trained physicians have been an invaluable resource to the US healthcare system and society at large.[9,10]

For most IMGs the pathway to practice in the US has meant a very rigorous selection process to obtain residency training. In turn, this generally attracts the most competitive applicants from across the world, enriching the US medical and training milieu. Residency ensures parity between all trainees whether local or foreign trained including medico-social and cultural. This model has been mostly effective and occasional exceptions have been made by local licensing authorities on a case-by-case basis for IMGs. However, it does provoke some thought about efficiency. Namely, physicians who have completed residency or even advanced fellowship training in other countries have to repeat the training here, generating redundancies and unnecessary expenses. The looming physician shortage crisis has incentivized many states to try and develop licensure pathways for IMGs who have already trained in a residency program outside of the US. Tennessee passed the first legislation to enable foreign residency trained physicians to bypass the general requirement of US based residency training before independent licensure in April 2023.[11] Even before the Tennessee law could come into effect, Iowa, Virginia, Florida, Wisconsin, and Idaho created similar pathways and more states are following suit. Alabama's Physician Workforce Act enables eligible IMGs to reduce residency time from three years to two in specific shortage areas.[12] These state-led initiatives represent proactive steps to address the physician shortage at the local level, especially as the crisis grows. By creating flexible pathways for IMGs to practice in underserved areas, states are ensuring that their healthcare systems can adapt to meet the needs of diverse, geographically disparate populations. The urgency with which the legislatures are acting, in a largely bipartisan way, underscores the realization that their constituents are hurting and unable to see a physician when needed.

The intention of the Tennessee Senate Bill 1451 and similar legislation is to fill the care gaps and help people get better and faster physician access. If qualified physicians can be incentivized to practice in rural Tennessee, it will help address widespread shortages found in these areas. Tennessee currently is forty-second in healthcare.[11,13,14] Timely access to physicians is likely to improve overall healthcare associated costs as well, limiting worsening of conditions due to delay in care. Additionally, many IMGs in training have physician partners who are trainees in their home countries. They are often saddled with the difficult decisions about what path to take while trying to pass their board examinations and having to split their families. A path towards allowing them to participate in the US physician work force would help alleviate their conundrum and help reduce physician shortages.

The above narrative might suggest that the Tennessee Senate Bill 1451 is a very timely and ideal piece of legislation. This comes with its own share of pitfalls and concerns. The most pressing issue is the differences in evaluation and standards of quality of training across the globe. Specialty training is heavily influenced by the prevalence of local pathologies and availability of resources.[15] This provides valuable perspective and diversity, but the primary standard of care must be met first.

It should be noted that the current bills require monitored practice for two years before license for independent practice is given but the details of enforcement of patient safety and oversight are lacking.[11] There are other unintended consequences as well, e.g. there may be reduced impetus for exceptional candidates to pursue US residency training as they have an alternate pathway. This may greatly affect the current self-selection of the best and the brightest from across the globe to come and train here. While the intention is to expand the primary care in underserved areas, we might end up with more specialists driven by monetary incentives to relocate rather than facilitating primary care. While there are ethical considerations regarding the effects of brain drain on resource poor countries, this issue is outside the scope of this paper.

Indeed, some of the concerns shared in the preceding paragraph have also been identified by members of the Tennessee Board of Medical Examiners, expressing strong concerns about the inability to assess applicants' competence, questions about mechanisms to check the qualifications and potential for patient harm as reasons for the stonewalling the execution of the bill.[16]

Building a resilient, inclusive healthcare system requires recognizing the value of IMGs and removing barriers to their practice. By doing so, these physicians may offer hope in addressing the worsening primary care and physician shortages, in general. Expanding programs like the Conrad 30 Waiver Program, enacting of the Healthcare Workforce Resilience Act, and implementing initiatives such as Assistant Physician programs could create more accessible pathways for IMGs to practice medicine.[5,14]

Conclusion

We recognize the impending crisis in healthcare resources (principally physician availability). We agree that innovative thinking is needed to prevent it and that our patients deserve physician-led care irrespective of the geographical area they inhabit. We agree that streamlining and incentivizing IMGs to come work in the United States, especially in the underserved and primary care setting, is a worthy goal. However, we must remain cognizant of the fact that any missteps that erode public trust must be avoided. With the variability in physician training word wide, it is imperative that there be a system of checks in place, prior to allowing independent licenses to such physicians. Acclimatizing to a different healthcare system and a different "culture" of medicine is important and takes time. It is essential for our healthcare workforce and our patients to have confidence in these measures. Ideally, no stakeholder should be surprised by legislative action, a consensus must be built first or we risk a serious blowback. This is the authors' perspective, and we welcome debate and discussion on this sensitive and critical issue.

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Carbon Monoxide Poisoning: Never a Bad Time to Refresh Your Knowledge

by Rebecca L. Tominack, MD

Unintentional exposures to CO are easily missed or misdiagnosed.

One can imagine that shortly after early humans tamed fire, they suffered its stealth attacks that could slay entire groups overnight. Carbon monoxide (CO) continues to cause tens of thousands of unintentional, non-fire-related exposures and approximately 500 deaths in the United States (US) every year. Intentional self-poisoning causes another 500 deaths.[1,2] Some 20-30% who need medical treatment after exposure show neurologic sequelae that can last for months and sometimes longer.[3] It is never a bad time to brush up on how to recognize CO poisoning and treat it.

Sources

Carbon monoxide forms during incomplete combustion of any carbon-containing substance in the presence of oxygen. If the combustion of the fuel molecule is complete, carbon dioxide (CO_2) is formed instead of carbon monoxide (CO).

Odorless, colorless, and tasteless, its presence is not detected without a special air monitor. Many people are at risk simply because they do not know the common situations in which CO can form, collect, and poison them. House fires are notorious for producing CO as well as cyanide, both potent asphyxiant toxins. Other common, non-fire sources of CO include camp stoves and lanterns; charcoal grills; gasoline-powered engines in cars, trucks and boats, and equipment (e.g., generators and power washers); and natural gas furnaces, water heaters, and ovens. Winter, with its snow, ice, and power outages, brings the risk of CO poisoning to its peak as people turn to unsafe options to heat their homes. In fact, most cases occur in homes with faulty furnaces during the colder months.[4]

It is also helpful to appreciate that CO poisoning can occur not only from a high air concentration over a short period of time but also from a low air concentration over a longer period of time.[5]



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Pathophysiology

Carbon monoxide is readily absorbed after inhalation, having ideal solubility to cross cell membranes. The most familiar toxic mechanism is displacement of oxygen from its binding sites on hemoglobin, so that less oxyhemoglobin arrives at the tissues. Furthermore, the presence of carboxyhemoglobin (COHb) shifts the oxygen-hemoglobin dissociation curve to the left, so that even if oxygen is delivered, it is less likely to unload in the tissues.[6] This naturally gives the impression that tissue hypoxia is responsible for the adverse effects of CO, and the faster that oxygenation is restored, the better the patient's chances to avoid tissue injury.

It turns out that the activity of CO in the body is far more complex. CO also binds to mitochondrial cytochrome oxidase where it interferes with cellular energy production. It generates reactive oxygen molecules that induce damaging lipid peroxidation of membrane lipids in a self-perpetuating chain-reaction. The accumulated cell damage, also known as oxidative stress, incites reactive inflammation. The brain, being an organ with a vast membrane-lipid content, can suffer heavily from cell damage due to lipid peroxidation and the resulting neuroinflammation.

Therefore, there are more pathological problems than tissue hypoxia at play.[7]

To be fair, the role of CO in the body is extensive and beneficial. Carbon monoxide is a gasotransmitter, an endogenous signaling molecule. It enables vasodilation, increased tissue perfusion, and cell protection during ischemia. When delivered by a CO-releasing molecular carrier, it shows multi-faceted therapeutic properties including anti-inflammatory, immune modulation, and apoptosis management. It has potential roles in organ transplantation and cancer therapy.[8] CO is indeed a mixed bag.

Clinical Manifestations of Carbon Monoxide Poisoning

Early symptoms in acute CO exposure are non-specific and include pounding headache, nausea, and dizziness. In the absence of a suspicious exposure scenario, the patient may be misdiagnosed as having a viral syndrome or some other self-limiting minor illness. CO-exposed patients may complain of decreased exercise tolerance, chest pain, and shortness of breath and may have EKG or biochemical evidence of myocardial ischemia or impaired cardiac function. This directs the workup along a cardiopulmonary route. Sometimes the patient presents because of a fall that was precipitated by a significant CO exposure, and Emergency Department attention is directed to injury assessment and the common reasons for a fall. In severe CO exposure the patient may present obtunded or comatose, which initiates a multi-pronged workup including intracerebral events. Carbon monoxide poisoning should have a place on the differential diagnosis for common, non-specific complaints of any severity.[9]

Laboratory Diagnosis

The most useful diagnostic test is the carboxyhemoglobin (COHb) level in the blood obtained in the lab by co-oximetry analysis of an arterial, capillary, or venous sample.[10] It is reported as a percentage of total hemoglobin. However, other etiologies for elevated COHb levels must be kept in mind. Normal ranges for nonsmokers are typically 0-3%, with people who smoke one pack-per-day having a COHb of 6% to 10%, depending on when the last cigarette was smoked. Water pipe/hookah smoking can raise COHb levels to 30%.[11] Infants can have falsely higher COHb levels due to interference of fetal hemoglobin with analyzer equipment.[12] Patients with hemolytic anemia can have higher levels of COHb because CO is a natural byproduct that results from the breakdown of protoporphyrin to bilirubin.[13]

Of note, typical pulse oximetry is usually normal even if there is markedly elevated COHb because oxyhemoglobin and COHb read at approximately the same wavelength.[14] Specialized pulse co-oximeters that non-invasively read COHb have been available for 20 years. According to a 2023 meta-analysis of studies evaluating accuracy, they have a relatively high false positive and false negative rate, which makes their routine use unreliable to rule-in or rule-out CO poisoning.[15]

The carboxyhemoglobin level does not always correlate well with the clinical signs and symptoms of poisoning. For example, symptomatic patients can have lower COHb concentrations than asymptomatic patients, based on their overall medical fragility or pre-existing conditions, especially anemia, heart disease, and lung disease. Severely-affected patients may have marginally elevated COHb by the time they present to the Emergency Department if a long period of time has elapsed since their exposure. This is because decline of COHb proceeds spontaneously as soon as exposure ceases.

Treatment: Supportive Care and Oxygen

The first goal of immediate treatment is survival of the patient, and the second is mitigation of delayed manifestations of tissue damage, primarily neuropsychiatric symptoms such as brain fog, headache, depression, anxiety, tremor, or other movement abnormalities.

Currently, in addition to supportive care, the mainstay of specific treatment is high-concentration supplemental oxygen, which accelerates the dissociation of CO from hemoglobin and its elimination through the lungs.[16] The average half-life of COHb on room air is five hours

MISSOURI POISON CENTER

The Missouri Poison Center provides no-cost assistance with drug overdoses and toxic exposures to the general public and healthcare professionals in Missouri 24 hours a day. The clinical specialists are highly-trained nurses and pharmacists (Certified Specialists in Poison Information) who are supervised by a dedicated physician Medical Toxicologist.

Each year the center manages nearly 60,000 cases, split between health care practitioners (20%) and the general public (80%). More than 92% of cases originating from the public are kept at home by advice to the caregiver, close observation, and follow-up.

Drug overdose and critical poisoning cases admitted to health care facilities are given individualized, evidence-based management recommendations as the clinical course of the patient evolves.



Residential carbon monoxide poisoning can be prevented by using a carbon monoxide detector.

The Missouri Poison Center is not-for-profit and is funded by the Missouri Hospital Association, the State of Missouri, SSM Health Cardinal Glennon Children's Hospital, and a federal grant from the Health Resources & Services Administration.

MISSOURI
POISON CENTER
1-800-222-1222
A Program of SSM Health Cardinal Glennon

Dr. Tominack is board certified in Internal Medicine and Medical Toxicology. She has been the Medical Director of the Missouri Poison Center for 11 years and was Assistant Medical Director for 16 years prior to that. She was the residency director for Occupational and Environmental Medicine at Saint Louis University for six years and also taught two master's levels courses in Toxicology and Environmental Toxicology at the School of Public Health at Saint Louis University. Dr. Tominack has special expertise in industrial, occupational, and environmental toxicology and has consulted for a number of private and governmental organizations over her career.

and decreases to about one hour on 100% oxygen. Although practices vary, a reasonable end point of oxygen treatment is reduction of COHb levels to <5%. The time this takes depends on the half-life and how high the COHb level was at the time the oxygen therapy was started. If the starting level is 40% COHb, it will take three half-lives to fall to 5% or lower, (i.e., 15 hours in room air or three hours on 100% oxygen). Pregnant women are routinely placed on oxygen for a longer period of time to treat the fetus. Fetal hemoglobin has a higher affinity for CO and supplemental oxygen is less efficient in dislodging it.[17]

High-concentration oxygen (nominally 100%) should be given as soon as possible by nonrebreather mask, or by intubation and ventilation if needed.

Hyperbaric Oxygen Therapy Is Not Standard of Care

There are many who believe Hyperbaric Oxygen (HBO) treatment should be given to patients with significant CO exposures. [18] Oxygen at three atmospheres of pressure in a specialized chamber lowers the average half-life of COHb to 20-30 minutes and increases the total amount of dissolved

oxygen in the blood. Restoration of oxygenation to the tissues as fast as possible has intuitive appeal, but it has not yet translated into demonstrably better clinical outcomes. HBO does not solve the problems of pathologic lipid peroxidation and subsequent inflammation to which delayed neuropsychiatric effects are more likely tied.[19]

The superiority of HBO over 100% normobaric oxygen in reducing the incidence of delayed effects has not been unequivocally demonstrated clinically as trials have had conflicting results. A recent commentary outlines the flaws in the two studies usually referenced to show better outcomes after HBO.[20] Most hospitals do not have immediate access to hyperbaric facilities and transferring a patient can take so long that the theoretical benefit evaporates. Similarly favorable outcomes can be achieved with 100% oxygen by non-rebreather mask. Regardless, HBO is considered safe and can be used for serious CO poisoning when the facility is readily available.

Looking to the future, current investigational approaches to decrease incidence of delayed neurologic sequalae from CO poisoning include dexamethasone, other agents intended to target the oxygen radical damage and inflammatory aftermath, and as direct CO-scavenging molecules.[21]

Conclusion

Unintentional exposures to CO are easily missed or misdiagnosed. The current mainstay of treatment in CO poisoning is good supportive care and 100% oxygen to accelerate the elimination of COHb. Hyperbaric oxygen is not considered standard of care and is not widely available for emergency therapy, but nonetheless may be considered in severe exposures.

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Community Health: Health Forward Foundation, REACH Healthcare Foundation, and Missouri Foundation for Health

by Charles W. Van Way, III, MD

Health Forward FOUNDATION

Achieve health equity and secure a fair and just region through leadership, advocacy, and resources.

Mission Statement of the Health Forward Foundation[1]

REACH healthcare foundation

To advance health equity through coverage and care for underserved people in our region.

Mission Statement of the REACH Healthcare Foundation[2]

Missouri Foundation for Health

We are a resource for the region, working with communities and nonprofits to generate and accelerate positive changes in health.

Purpose Statement of the Missouri Foundation for Health[3]

Community health is an increasingly important part of the effort to improve health. We tend to view patients as individuals or as members of a family, because that's how we encounter and treat them. But each individual and family is surrounded and supported by the community in which they live and depend on the resources available in that community. Viewing the health system as an integral part of society, and not just as a separate system, leads to a similar emphasis on the communities of which people are a part. We speak of such things as social determinants of health, social influences on health, community resources, and culture. All of these are aspects of community health. Perhaps the best working definition of community health is anything which affects the social determinants of health.

Most physicians would endorse the importance of community health, but few of us are aware of the extensive resources available to support it. There are three foundations in Missouri which exist to promote community health and health care. Health Forward is based in Kansas City, Missouri. It covers Kansas City, Jackson, Cass, and Lafayette counties in Missouri, and Johnson, Wyandotte, and Cass County in Kansas. REACH Foundation is based in Overland Park, Kansas, and covers the same area. The Missouri Foundation for Health is based in St. Louis and covers 84 counties in the northeast, east, and south of the state. In all, these foundations cover 87 of 114 counties in Missouri. Their combined assets amount to $3 billion (estimated). This money provides grants to a wide variety of community and healthcare groups.

A lot of physicians around Kansas City worked at Health Midwest, a health system that encompassed hospitals throughout eastern Kansas and western Missouri. It was bought by Hospital Corporation of



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Figure 1. Research Medical Center, now a part of Health Corporation of America.



Figure 2. Bridget McCandless, MD, shown with then-Governor Jay Nixon. Governor Nixon presided over the formation of the Missouri Foundation for Health Care, as well.

America (HCA) in 2003 (Figure 1). That purchase left a permanent legacy for Kansas City in the form of two healthcare foundations which support community health care to this day.

The Health Forward Foundation[1] and the REACH Healthcare Foundation[2] were formed as part of the buyout of Health Midwest by HCA. Both are non-profit foundations, active in promoting health care for the public in general and for underserved populations in particular. Because Health Midwest had hospitals and activities on both sides of the state line, there were two foundations Both support activities in the six counties including and around Kansas City. The larger of the two was in Missouri and has become the Health Forward Foundation.[1] The Kansas foundation is now called the REACH Foundation.[4] While smaller than Health Forward, it provides similar grant support to community health-related activities.

How the Foundations Were Formed

When HCA bought Health Midwest, it was a case of a for-profit entity buying a non-profit hospital group. The total buyout was worth $1.125 billion. But Health Midwest had paid much less in taxes as a not-for-profit entity than it would have as a for-profit corporation. The justification for this tax break is that it contributed to the health care of the community through charity care and community health programs. When it was bought out, the for-profit purchaser became obligated to carry out these sorts of programs.

In the buyout agreement, HCA agreed to fund foundations in Missouri and Kansas to support community health. Initial funding for Health Forward was around $410 million. At the same time, HCA agreed to take over some community activities, including charity care, and to improve existing hospitals through capital expenditures. The agreement about capital expenditures placed serious financial obligations on HCA.

At this time, Bridget McCandless, MD, (Figure 2) led the Missouri foundation. Its main legal advisor was Mark Flaherty. They are important to the next part of the story. Dr. McCandless is a graduate of the University of Missouri - Columbia, and trained in internal medicine at the University of Virginia. She holds a MBA from Rockhurst University. She was the first President and CEO of the Health Forward Foundation. She led the foundation during the next few critical years. Now retired from the foundation, she serves on the Independence City Council.

Governor Jay Nixon appointed Mark Flaherty to be on the foundation board (Figure 3). Acting as general counsel for the foundation, he discovered that Hospital Corporation of America (HCA) was in breach of its obligations to make $300 million in capital improvements and to maintain charitable care. He enlisted Seyferth Blumental & Harris law firm in a case against HCA. The Foundation sued HCA in 2009. The Kansas Foundation (now REACH) did not join the lawsuit. In January 2013, the trial team obtained an award of $162 million on behalf of the Health Forward Foundation. The trial court also ordered an accounting. Following the accounting and an appeal to the Missouri Court of Appeals, HCA settled the lawsuit

in February 2017. HCA paid the Health Forward Foundation $203 million,[4] adding substantially to is funding. The Health Forward Foundation is now worth $960 million, as of 2023.[5] The REACH Foundation was worth $141 million as of 2022.[6]

Both Foundations use the income generated to promote community health. Both emphasize underserved populations and health equity. The boards of directors of both include physicians, lawyers, administrators, and community representatives (Figure 4). Each has one representative named by their respective state, Kansas for REACH and Missouri for Health Forward.

The Missouri Foundation renamed itself the Health Forward Foundation in 2018. As of 2024, it has dispensed $400 million in grants over the last 21 years.[1] In 2024, $24 million in grants supported such varied areas as a voter registration drive, publication of a Kansas City voters' guide, support for Missouri Amendment 3 and Proposition A, a guide to the Missouri legislative agenda, an agency providing down payment assistance, minor home repair support, and home ownership counseling, and organizations dedicated to ensuring equitable access to high-quality medical, oral, and behavioral health care. The Foundation held a Food as Medicine Summit on the nutritional components of health care. There were grants to many other initiatives relating to community health and health equity.[1]



Figure 3. The late Mark Flaherty, shown while speaking to the Kaufman Foundation. He was general counsel for the Health Forward Foundation during the years of the lawsuit against HCA.

The REACH Healthcare Foundation disbursed similar grants. It directs funding to three goals: bridge the coverage divide, close the health equity gap, and strengthen the safety net. They have funded the Kansas Assistance Network, which assists people to obtain insurance coverage, and other community advocacy groups. They have funded direct health care in such areas as primary care, mental health, and oral health.[2]

The Missouri Foundation for Health (MFH), based in St. Louis, originated in another conversion of a not-for-profit entity to a for-profit entity. In this case, Blue Cross Blue Shield of St. Louis (BCBSSL) converted to for-profit in 1996. As a result of that, the new foundation was formed in 2000. Interestingly, this foundation began during the tenure of Jay Nixon as Governor of Missouri.

Their coverage area mirrors that of the original BCBSSL, 84 counties in Missouri, excepting the 30 counties in the west and northwest (Figure 5). The current value of the MFH endowment was $1.8 billion in 2024 (estimated). They fund such activities as



Figure 4. Board of Directors of the REACH Healthcare Foundation. Like the other two foundations, there are physicians, other health care professionals, lawyers, administrators, and representatives of the public and of the state.



Figure 5. Service area of the Missouri Foundation for Health. Based in St. Louis, it covers the former coverage area of Blue Cross Blue Shield of St. Louis.

Missouri Foundation for Health

MoCAP, a program to help Missouri based nonprofits to submit grant applications and a program to help organizations raise funds. They fund translation and interpretation services and direct health care to underserved populations. They build the healthcare workforce, especially in underserved areas. There are grants to improve women's healthcare and reduce infant mortality. Indeed, the list of grants covers a wide range of health-related activities.[3]

Health Forward, Missouri Foundation for Health, and REACH are broadly-based organizations. All three have boards of directors which include physicians, nurses, lawyers, administrators, and community representatives (Figure 4). Intentionally, these foundations were set up to be able to consider and support a wide variety of activities under the broad heading of community health. Importantly, neither foundation carries out many activities itself. Rather, both give grants to organizations which carry out activities. In general, they see their roles as providing funding and support and in being reliable sources of information.

These foundations exhibit commitment to community health. This is less intuitive than simply supporting, say, dental clinics or primary care. Community health depends on a matrix of factors, including healthy nutrition, adequate housing, availability of health care and health insurance, and income. Supporting these factors may mean moving into the political arena. For example, health status tends to correlate with income. Therefore, supporting Proposition A to increase the minimum wage may well improve community health. Unfortunately, this can be controversial. Very few people will argue with providing primary care to underserved populations. Many people might feel that regulating the minimum wage is beyond the scope of a foundation dedicated to community health. But today, aspects of the health care system are controversial. Even childhood vaccinations against infectious disease, a generally-recognized public health benefit, have become controversial.

The debate around the scope of community health has been going on for the last two decades. For the most part, health care organizations accept that many things outside of health care should be considered as determinants of health. Community health has been the justification for such policies as supporting gun control, opposing restrictions on transgender care, and supporting health care for undocumented immigrants. All of these are politically sensitive. But it is important to realize that these three foundations are not just physician organizations, or even just health care organizations. They are truly community service foundations, and all three of them emphasize the need to improve care in underserved populations.

To conclude, Missouri is fortunate to have these foundations. All three are legacies of the conversion of a not-for-profit to a for-profit entity. They continue to fulfill their missions to enhance community health in our region.

Acknowledgment

Thanks to Bridget McCandless, MD, for her insight into the history of these foundations. She was the founding director of what is now Health Forward and provided great insight into the foundations in Missouri and Kansas which support community health.

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MM

Inactive, Reactive, or Proactive?

by Brian D. Biggers, MD

Recently, I had the pleasure of attending the American Medical Association (AMA) meeting as President of the Missouri State Medical Association and as an Alternate Delegate. I know many of us, including myself, have had difficulties with the AMA and some of the policies. It has only been the past few years where I have come back into the fold. Many of us would like to think that the body of medicine is an easy place to navigate; it is not. I tell my medical students that it takes all of us to make medicine work. It truly does.

As I sat in the reference committee meetings and the body of the House of Delegates, I listened to all points of view. Did I agree with every resolution or what was said? I did not. At times, I felt people were trying to push a personal agenda and not looking at medicine. As physicians we tend to focus on issues that are important to us and the patients that we treat. This is human nature and a little self-preservation. Unfortunately, it is these small points that have divided the body of medicine and that some of our members tend to focus on.

I was invited by a fellow breast surgeon to dinner with physicians from all specialties from all over the country. The meal and company were amazing. What I learned is that many of us have similar concerns with the current practice of medicine. We worry about Medicare reform and how we can survive unless we get appropriate reimbursement that is sustainable. We have concerns about the scope of practice and how we combat this. Pre-certification remains a national problem.



Brian D. Biggers, MD, FACS, is a breast surgical oncologist and general surgeon with CoxHealth in Springfield, Missouri, USA, and the 2025-2026 MSMA President.

We have reached a crossroads. Physicians, for the most part, are calm, and want to help and please their patients. This is a strength, but it can also be a weakness. Many of the problems we face are self-inflicted wounds. We have allowed the scope of the problem to develop. We need to fix Medicare reimbursements, but we ask for more to be covered by Medicare. It has been mentioned in legislature that we keep asking for more, and yet still complain about payments. There are finite dollars available for coverage. If the legislature covers more, then why are we asking for an increase in payments? In their eyes they already gave us something.

At the state level we need to be intentional in delivering healthcare for Missouri. We need to increase our membership in MSMA. I recall a story about a physician who became upset when he recently received an invitation letter to join MSMA along with an attached invoice. The physician contacted MSMA and claimed that the term invoice was meant for services rendered.

The reality is that services have been rendered to every non-MSMA member of this state. Your state organization is going to battle at the state Capitol to help every physician of this state regardless of being a paying member, as well as improving the care of every patient in this state.

Sometimes, people leave organizations with small disagreements. Just as I did not agree with every point made at that AMA meeting; it holds true for our own state. Perhaps we all should be looking at the larger picture.

We need to be masters of our own destiny not only at the state, but at the national level as well. Legislators have said if the physicians of this state were united in the organization as the attorneys are we would have unlimited lobbying power. In my inauguration speech I made the comment ... "in life we can be one of three things: inactive, reactive, or proactive. We have been inactive and reactive for way too long. It's time for proactive change." **MM**

Outmanned, Outgunned & Running Out of Time

Protecting the Practice of Medicine: Why Physician Advocacy Must Be Backed by Physician Action

by Jacob R. Scott, MA

Missouri physicians are facing a defining moment. Our role as leaders in patient care is being challenged—not by science, not even by technology, but by politics.

Just as if you were in the operating room faced with the challenge to provide a precise and a prudent level of care to a patient, we need that same level of moxie as we approach the legislative and political process here in Jefferson City. You would do anything to save your patient—now it's time to try and save our state.

Your lobbyists at MSMA are the tip of the spear, a constant fixture at the Capitol, but we are not a substitute for what you bring to the operation. The insurance lobby, the hospital lobby, and the mid-level medical professional lobby have been gaining ground for several years in the halls of our state capitol, at the expense of physician-led care and the practice of medicine as a whole. We are outmanned, outgunned, and running out of time.

Each legislative session brings a new wave of "scope of practice" expansion bills. These proposals, often well-intentioned on the surface, aim to allow non-physician providers to practice medicine independently, with far less training and oversight. While collaboration among healthcare professionals is essential, physician-led care remains the gold standard for patient safety and clinical outcomes.



Jacob Scott, MA, is MSMA's Director of Legislative Affairs.

Last year, optometrists[1] were able to successfully garner a vote for a major scope expansion bill in the House that would allow them to perform certain surgical procedures on the eye. They achieved this even though the Speaker of the Missouri House is a physician. This doesn't bode well for the future of medicine, unless we take action to reverse the course.

Another new scope-creep proposal popped up this session relating to the authority pharmacists have to fill prescriptions. Under this new proposal,[2] pharmacists would be allowed to fill a script for 90 days for ANY medication, so long as they believe that in their professional judgment it is permissible. They do have to attempt to notify the physician, but it is only required after the fact. There is NO limitation on the number of times this can happen in a calendar year. A similar version of this proposal was just introduced as an executive order[3] by Governor Kehoe this spring.

This isn't about turf. It's about standards. It's about the difference between years of medical education and training versus abbreviated certification programs. It's about protecting patients from a system that prioritizes speed over quality, and efficiency over expertise.

We are not powerless—but we must be proactive. The political process responds to those who participate in it. That means physicians must be visible, vocal, and unified in our advocacy. And most importantly, we must be willing to invest in it with our time and our money.

That's the mission of the Missouri Medical Political Action Committee (MMPAC)—to be the organized, political arm of physician advocacy in the political arena. MMPAC exists to support candidates who understand and respect the value of physician-led care and to oppose those who do not.

Too often, physicians hesitate to get involved in politics. We assume our credentials and commitment speak for themselves. But in Jefferson City, what speaks

loudest is engagement—and resources. Campaigns are won with support, not silence. Policy is shaped by those in power, and MMPAC plays a role in that important determinative process.

If we want a healthcare system built on quality, not shortcuts, we must act. That means contributing to MMPAC—not as a donation, but as an investment in the integrity of our profession.

MMPAC exists as your opportunity to respond in kind to all that threatens the profession. We have made it easy and rewarding to give. If just 100 physicians who read these words to join our exclusive 1850 Society, we will turn heads at the Capitol and organized medicine will be better for it. Yes, I am talking to you. I firmly believe you won't miss the contribution; instead, you will wish you had given sooner.

The threats to medicine are real. The decisions made at the Capitol affect how you practice, how you're reimbursed, and how patients receive care. We cannot afford to be observers.

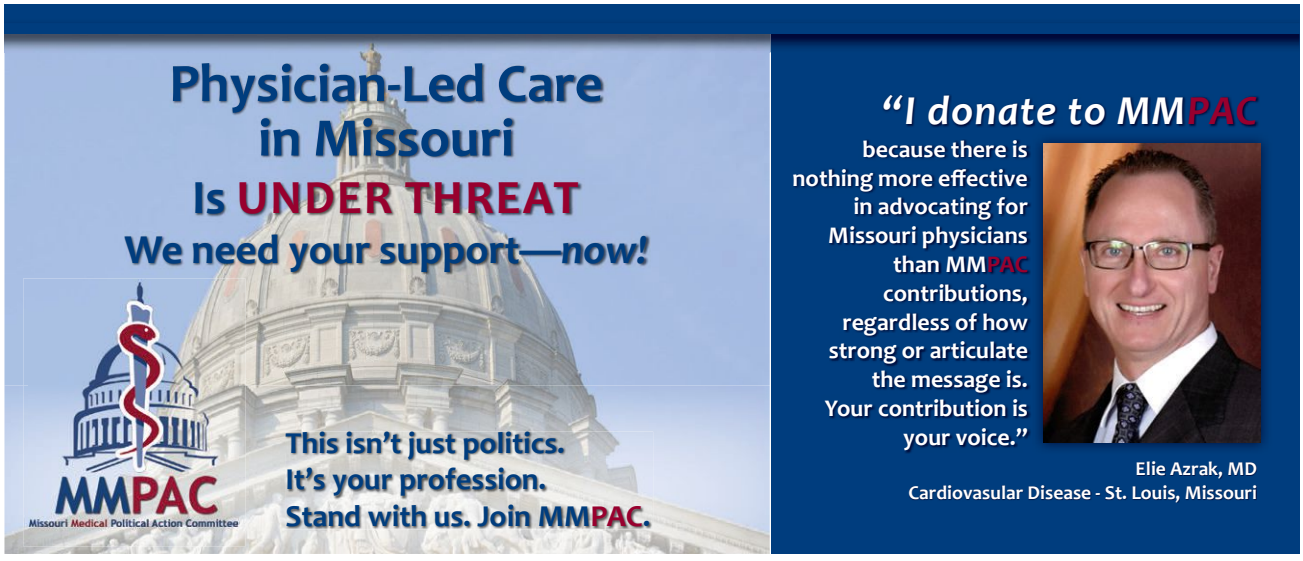
We must be advocates—with our voices, with our votes, and yes, with our dollars.

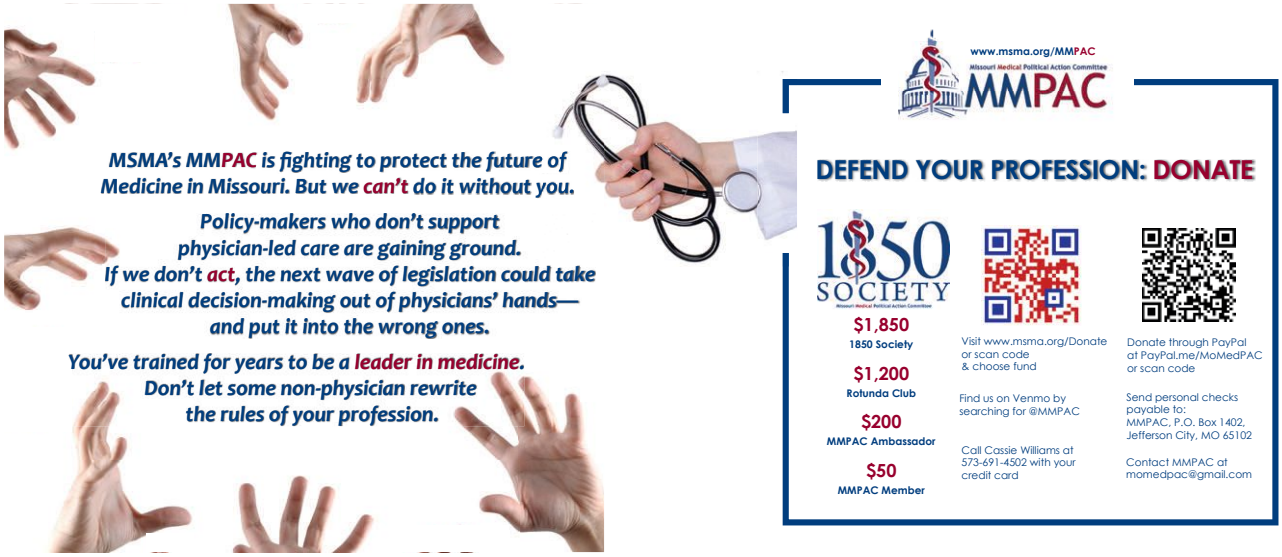
This is far from over! Join the fight, financially. Donate today. www.msma.org/mmpac or contact Cassie Williams at cwilliams@msma.org or call 573-691-4510.

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Report of the American Medical Association Annual Meeting

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

The American Medical Association (AMA) House of Delegates (HOD) held its 2025 Annual Meeting in Chicago, June 6-11. The HOD is a policy-making body, so the Annual Meeting considers a variety of issues. These include new policies to promote public health, reports on previous concerns, calls for new legislation, and initiatives for regulatory issues. The meeting also included inauguration of the new President and elections for President-Elect, Board of Trustees (BOT), Councils, and the Speaker and Vice-Speaker. The HOD has 733 delegates, of whom more than 90% attended the meetings.

The meeting of the Organization of State Medical Association Presidents (OSMAP), took place the afternoon before the AMA's opening session on June 6. Robert Seligman reported on the activities of the Physicians' Foundation, including the physician survey and other activities supporting physicians. Bruce Scott, MD, President, Michael Suk, MD, Chair of the Board of Trustees, and Todd Askew, Senior Vice President for Advocacy, held a panel discussion on the current political climate. Over the past 20 years, the AMA has increasingly aligned with the Democratic party. With the Republicans currently in power, AMA priorities often receive an unenthusiastic reception. Dr. Scott noted that all new Presidents bring new challenges. The AMA must maintain the long game, speaking consistently on behalf of physicians and patients. Mr. Askew said that there is increased tension between the executive authority of the President and the legislative authority of Congress and that the AMA is not willing to compromise on any changes to Medicaid or to research funding. Dr. Scott noted that there are attacks on science and established practices. Which battles should the AMA fight? Mr. Askew said that progress comes from the confluence of opportunity and priority. Focus depends partly on which opportunities occur. Yet, the priorities of reimbursement, preservation of Medicaid, control of prior authorization, and physician autonomy remain important.

Outgoing President, Bruce Scott, MD, spoke at the opening session of the HOD. He spoke as an "Angry Person." The dysfunction in our health care system reflects dysfunction in Congress. We continue to take pay cuts even while health insurance companies make record profits. We must argue with faceless bureaucrats to fund necessary care for our patients. Congress threatens to cut Medicaid funding for millions of people. Proposed changes in the student loan program will discourage future doctors. Doctors are closing their practices and retiring early. We must turn our anger into action. Reform of prior authorization has bipartisan support at the federal level, and at the state level. We are suing insurance plans for suppressing out-of-network reimbursement. He asks: Are we finally angry enough that we will not take it anymore?

James Madara, MD, outgoing Executive Director, highlighted his 14-year tenure. The AMA has prospered under his leadership, and membership has begun to grow again. He credited outstanding mentors, both from above and below. Principles are important. Luck is important. Family is important. All of these contributed to his success in the position. His successor will be John White, MD, who was a leader at WebMD, overseeing its significant growth.



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, USA.



MSMA physicians attending the AMA Annual Meeting in Chicago. Front row, L-R: Joe Corrado, Brian Biggers, Ed Cabbabe, Charles Van Way, Elie Azrak, Mildred Olivier, Joanne Loethen, Jay Devineni, and Deepu Sudhakaran. Back row: L-R: Ravi Johar, Kelly Schmidt, Lacey Raper, Betty Drees, Mason Tuttle, and Druv Bhagavan. Not pictured: George Hruza.



Drs. Joanne Loethen, Marc Mendelsohn, Kelly Schmidt, and Elie Azrak.

Bobby Mukkamala, MD, is the 180th president of the AMA. In his inaugural address, he called for a sustainable, equitable, and accessible health care system. Dr. Mukkamala lives and practices otolaryngology in Flint, Michigan, a once-thriving city which has fallen on hard times. He knows the impact that Medicaid cuts will have on the underprivileged. He deplored the cuts to biomedical research, health-related agencies, and immigration. We have too few physicians, they are stretched too thin, and are under too much pressure. Limiting legal immigration further restricts the physician supply He remains optimistic but calls on physicians to unite and to fight for a better health care system.

Willie Underwood, III, MD, MSc, MPH, is the new President-Elect of the AMA. Lisa Egbert, MD, was re-elected as Speaker of the HOD. John Armstrong, MD, was re-elected as Vice-Speaker. Sheila Rege, MD, and Marta Van Beek, MD, were elected to the Board of Trustees (BOT). There were additional elections for the Councils.

Turning to HOD actions, resolutions are submitted by Delegates to propose policy changes or actions. The BOT or one of the Councils may submit a report which contains recommendations for policy or actions. Both resolutions and reports may be adopted, modified, or rejected. This year, the HOD considered 245 reports and resolutions. These items are split among eight reference committees, each of which conducted both virtual and in-person hearings and prepared a report on each item to the HOD.

In an environment of radical disruptive change, threats to evidence-based medicine and public health spurred strong calls for the protection of health care infrastructure and biomedical research, including funding and access for state Medicaid programs, the independence of the National Institutes of Health, and life-saving vaccine programs.

On June 9, all 23 members of the CDC Advisory Committee on Immunization Practices were terminated by HHS. In response, the HOD passed an emergency resolution calling for reinstatement of the panel and calling for letters to HHS and to the Senate Committee on Health, Education, Labor, and Pensions.

There was great concern over proposed changes in Medicaid, including eligibility, funding, work requirements, and provider taxes. Many resolutions (205, 207, 221, 223, 231, 238) were directed to preserving aspects of Medicaid and Medicare, largely defending existing funding. While there is general recognition that both programs have serious flaws, recommendations for improvement have been limited to reform of physician reimbursement.

Improving the reimbursement of physicians remains an ongoing effort. An outline of current efforts is at https://fixmedicarenow.org. Resolution 233 called for periodic reports on the ongoing status of these efforts. Physician payment cuts have totaled 30% over the last 25 years. We need relief urgently.

The current Congressional appropriations bill ties future reimbursement to inflation, a small but critical step towards Medicare reform. But this is not yet enough.

In light of government staff reductions, the AMA will work to offer a method for physicians to report CMS payment delays and other obstacles to timely receipt of reimbursements. The information collected will inform advocacy efforts to protect physicians from unreasonable CMS payment delays.

The AMA has long opposed provider taxes to fund Medicaid, preferring a more secure funding base. But current proposals to end or modify such taxes will reduce Medicaid funding. Resolution 211 called for support of provider taxes, while still opposing taxes on physicians. This is a reversal of existing policy and may make it more difficult for the AMA to oppose provider taxes applied to physicians. Missouri funds its Medicaid program with approximately $4 billion in provider taxes.

There was concern over the closure or defunding of several government health-related agencies. Resolution 502 opposed limiting medical research by lowering total funding and putting a cap on indirect costs. Overwhelming sentiment favored maintaining our present system of grant-funded research. Resolution 239 called for preservation of access to the resources of the CDC. Resolution 242 called for protecting public trust in biomedical research, public health, vaccine safety, and evidence-based medicine.

The HOD continues to focus on reducing administrative burdens and improving healthcare delivery. Recommendations included ensuring access to opioid pain medication post-discharge and supporting medication continuity during insurance transitions. There were recommendations to enhance transparency in Medicare Advantage plans, standardize insurer communications to physicians, and improve public reporting of hospital complaints. The AMA opposes requiring prior authorization for in-person visits with a physician, promotes federal and state legislation to minimize the impact of prior authorization requirements, and develops best practices for ensuring continuity for patients across different insurance plans and health care systems.

Resolution 704 called for the AMA to collect data on prior authorization to evaluate a class action lawsuit. Many physicians feel strongly that a class action suit will be the only way to rein in the abuses related to prior authorization. This resolution is the first step in that direction.



Drs. Joanne Loethen and Betty Drees.



Jay Devineni, MD, and Lacy Raper, Mason Tuttle, Medical Students.

There were resolutions asking for medical insurance coverage for a variety of things. Resolution 230 asked for mandated coverage of anti-obesity drugs GIP and GLP-1 as well as lowered burden of prior authorization. Other resolutions called for coverage for nutritional counseling, consulting on firearm use and storage, and childhood vaccinations.

In an important effort to curb pharmacy practices of denying some prescriptions, claiming that they are out of the prescribing physician's scope or specialty, the AMA will study the national prevalence and patterns



Charles Van Way, III, MD, was elected President of the Organization of State Medical Association Presidents.

of these pharmacy practices, and will work with state medical boards, pharmacy boards, and appropriate federal agencies to protect the authority of plenary licensed physicians to prescribe all legal medications in accordance with their training and medical judgment.

Medical education is an ongoing interest of the AMA. Resolution 229 expressed support for accreditation bodies, ACGME, COCA, and LCME, to maintain standards of diversity, equity, and inclusion. Resolution 241 called for support of schools which accept international students and opposed decertification of students in the Student Exchange Visitor Program (F-1 visas).

Our residency programs have a substantial number of international medical graduates (IMGs). Travel bans by the current administration will affect those applying for J-1 Visas or awaiting their visa interviews. Delays or denials of interviews may seriously disrupt patient care. More significantly, processing for new J-1 visas has been suspended. Resolution 237 advocated restoring J-1 visa processing, at least for physicians. The AMA will send communications to Congress, the Department of Homeland Security, the Department of State, and other relevant agencies, calling for the immediate resumption of J-1 Visa processing for IMGs.

The AMA defines AI as "augmented intelligence" rather than the more commonly used "artificial intelligence." It's an AMA thing. BOT Report 24 discussed the formation and activities of a Task Force on AI, Digital Health, and Informatics. This body is intended to respond to the increasing impact of these technologies within the health care system. The report serves as a progress report after the first year of activity.

BOT Report 18 recommended that the AMA oppose legal or civic prosecution of physicians who carry out physician-assisted suicide, especially in the states which have legalized it. That said, the HOD voted to maintain AMA opposition to physician-assisted suicide in both AMA policy and code of ethics.

Resolution 714 called for a root cause analysis of the decline in private practice. There was extensive discussion, reflecting the importance of this issue. Resolution 225 expressed support for private practicing physicians in the community. The continuing decline in private practice is closely related to the decline in physician reimbursement and the increasing administrative burdens. The AMA continues to address both of these issues.

Physicians from Missouri continue to serve in leadership roles. **David Barbe, MD**, is Past President of the AMA. **Edmond Cabbabe, MD**, serves on the Council for Long Range Planning and Development. **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**, serves on the Council on Science and Public Health. **Charles Van Way, III, MD**, is President of OSMAP, the Organization of State Medical Association Presidents. Jeff Howell, JD, our Executive Vice President, serves on the Board of Directors for ASMAC, the American Society for Medical Association Counsel.

This meeting considered over 245 reports and resolutions. This summary is necessarily incomplete. The proceedings of the meeting, as well as summaries of addresses at the meeting and the texts of all resolutions and reports, are available on the AMA website. Highlights from the meeting can be found at https://www.ama-assn.org/House-delegates/annual-meeting/highlights-2025-ama-annual-meeting. The Interim Meeting of the HOD is scheduled to take place in National Harbor, Maryland, November 8-12, 2025. **MM**

Finding the Levers to Make Change

by Betty M. Drees, MD

Most of these stories are about events that may have seemed ordinary to me at the time but highlight the influence we have during the daily interactions with learners.

As I reflect on my professional career that began four decades ago after graduation from medical school, I can identify in retrospect those factors and influences that consistently drove my choices and resulted in the deep satisfaction I feel about my career. Those factors and influences can be summarized as 1) a love of both humanities and sciences; 2) a belief in human potential; and 3) an interest in making systems work to support the mission.



Figure 1. Betty Drees, MD, University of Kansas School of Medicine Class of 1984.

Growing up in Wellington, Kansas, I was an avid reader but also loved the outdoors and being in nature. This began my dual love of humanities and sciences. When I graduated from Wellington High School, I was undecided on majors and started college at the University of Kansas, Lawrence, Kansas, as an English major while also taking the premedical science classes. I knew that I loved the humanities and took multiple courses in literature, history, languages, and other humanities in the early college years. But as I took more science classes, I also felt drawn to the biomedical field from courses such as genetics, anatomy, and microbiology.

In the early 1970s when I started college, there were few women physicians as role models and at that point, I had never even met one. As an undergraduate student, I was married and had a family and was unsure that a career in medicine was a realistic choice. At a critical point when I was considering my career options, I was fortunate to have a college advisor who encouraged me to pursue my aspirations in medicine. It was a routine advising session for that person but had a profound impact on my decision to go forward with applying to medical school. It was an early lesson in the influence we all may have on others to reach their potential without even realizing it. Later when I was in medical school, I joined the student chapter of the American Medical Women's Association where a number of local women physicians attended our meetings. Meeting them and hearing their stories about their career journeys and how they balanced their personal and professional lives gave me the confidence that I had made the right choice. Again, they were probably unaware of their impact just by being present in what would seem unremarkable circumstances to them at the time.

I went to medical school at the University of Kansas in Lawrence, Kansas, (Figure 1), where I also completed an internal medicine residency and a fellowship in endocrinology and metabolism. I chose endocrinology as a specialty due to inspiring mentors, including Drs. Neil Schimke, Joe Kyner, Barbara Lukert, and James Kennedy. Endocrinology was appealing for three major reasons. First, the applied physiology of endocrinology fits my inclination toward systems and logic. Second, the care of individuals



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Left, Dr. Drees returning to practice endocrinology as physician researcher at University Health and Dean Emerita at University of Missouri-Kansas City, 2014-2025.



Figure 2. Early career as an Endocrinologist at the Kansas City Veterans Affairs Medical Center and Assistant Professor at the University of Kansas, 1989-1998.



Figure 3 . White Coat Ceremony as Dean (Dr. Drees, center) with University of Missouri-Kansas City School of Medicine Docents. The docents welcome the students who join their teams at the White Coat Ceremony. At Commencement, the Docents hood the graduating seniors.

with a chronic condition such as diabetes mellitus is very satisfying because each person has a compelling life story of living with diabetes that invokes my humanities background and love of narrative. And third, I had the opportunity to take a position in an endocrine-related research laboratory at the Kansas City Veterans Affairs (VA) Medical Center as part of the VA Career Development program after fellowship (Figure 2). This additional training was essential for developing research skills for a career in academic medicine. I worked on parathyroid gland projects in the laboratory of James Hamilton, PhD.

It was while I was at the VA working as an endocrinologist, researcher, and member of the faculty of the University of Kansas School of Medicine that I began taking on administrative roles in education and clinical care. I participated in the curriculum renewal work for the medical school that introduced me to the pedagogy of medical education, as well as regional and national leaders in that field. I worked on a number of hospital committees in research, quality improvement, and management, and served as the Acting Chief of Medicine and Program Director for Specialty Care Services.

Administration was certainly not among my early career goals, but I took on these roles so that I could have an impact on things that were important to me in patient care and education. In an interview with the *New York Times* in 2009, Supreme Court Justice Ruth Bader Ginsburg said, "If you're going to change things, you have to be with the people who hold the levers." This rationale was why I took on administrative roles; I wanted to be in positions where I could participate in the work that build the systems to make it easier for people to succeed and reach their potential in their roles as physicians, researchers, students, etc. And highly functioning clinical systems reduce medical errors and improve patient outcomes.

It was a privilege to care for veterans and to work at the VA during a time of innovation in systems of quality improvement and clinical data capture in the 1990s. But after a decade at the VA, I moved to the University of Missouri-Kansas City (UMKC) School of Medicine to take a position as docent and as the Associate Dean for Academic Affairs. As a docent, I had a team of a dozen medical students ranging from years three through six in the six-year, combined BA/MD program. I had a weekly general internal medicine clinic with them and an annual inpatient internal medicine rotation at University Health of Kansas City (formerly Truman Medical Center). This close longitudinal relationship between the docent and students, and between junior and senior students within the team, is an example of a system that is designed to provide continuous mentoring for the benefit of students' personal and clinical development (Figure 3). I felt academically at home in this innovative



Figure 4. Left, Dean of the University of Missouri-Kansas City School of Medicine, 2001-2014. Right, With Previous Deans: Dr. Drees, Marjorie Sirridge, MD (5th Dean), Harry Jonas, MD (2nd Dean), Richardson Noback, MD (Founding Dean), and James Mongan, MD (3rd Dean).

education, and I felt clinically at home working as an endocrinologist at University Health where clinical care and education are both highly valued.

After two years at UMKC, I was appointed as the seventh Dean of the medical school by Chancellor Martha Gilliland (Figure 4). This is a position I held for 13 years before transitioning back to the faculty in 2014. My goals as Dean were to support the learning environment for medical students and residents, to support and celebrate the innovative UMKC curriculum for medical students, to improve the infrastructure for academic success of the faculty members, and to strengthen the relationship with the community to improve health. UMKC is affiliated with excellent teaching hospitals (in Kansas City, MO: University Health of Kansas City, St. Luke's Hospital of Kansas City, the Center for Behavioral Health, Children's Mercy Hospital, the Kansas City VA Medical Center, Research Medical Center; and in St. Joseph, MO: Mosaic Life Care), which foster strong clinical education and support the development of the physician workforce in the region.

Some examples of projects while I was Dean include 1) founding the Department of Biomedical and Health Informatics to develop a faculty body and graduate programs that support clinical research; 2) developing a formal consortium for quality improvement and patient safety with our affiliated hospitals; and 3) establishing residency programs and new graduate education programs for anesthesiology assistants and physician assistants to address workforce needs in Missouri.

The faculty role in mentoring students, residents, fellows, and junior faculty in clinical, research, and leadership skills may be underappreciated. For this reason, I endowed annual awards to recognize faculty mentors who are nominated by their mentees. Recognition of 18 excellent mentors from the faculty over the past decade highlights these individuals' efforts and their impact on the careers of others. And it sets these faculty forward as role models to mentor the next generation of scholars. From a personal perspective, the teaching awards I have received from residents and fellows are very meaningful, as is the American College of Physicians, Elizabeth and Emily Blackwell Award for Outstanding Contributions to Advancing the Careers of Women in Medicine awarded to me by the American College of Physicians in 2022. However, the personal stories from students, residents, and fellows that something I said or did that had a positive impact on them are the most memorable. And most of these stories are about events that may have seemed ordinary to me at the time but again highlight the influence we have during the daily interactions with learners. Being recognized as a positive influence on others is as good as it gets as an educator.

After leaving the Dean's role and returning to the faculty, I wanted to continue making an impact on health in our community, as well as return to my roots as a physician researcher. I chose to focus my research on metabolic health through clinical trials that address lifestyle interventions for metabolic syndrome and diabetes prevention. Community outreach activities include participating in forming a regional shared learning network in diabetes in partnership with the Missouri Hospital



Figure 5. President of the Graduate School of the Stowers Institute for Medical Research, 2018-2024. At graduation in 2019 with founding dean, R. Scoot Hawley, PhD.



Figure 6. Our family photo with my husband, Bill Drees, children (Jessica Lundin, Matt Drees, and Alex Drees), and granddaughter Sorah at my retirement reception as dean in 2014.

Association and serving as a facilitator for the Show-Me Diabetes ECHO (Extension for Community Health Outcomes) sponsored by Missouri Telehealth Network. This virtual program provides subspecialty support and education for primary care clinicians throughout the state. To further support diabetes and endocrine care in the region, I was the founding program director for the UMKC Fellowship in Endocrinology, Diabetes, and Metabolism in 2016. To date, two-thirds of our graduates have remained in the region to practice. I currently work part-time at UMKC and University Health as a Professor and Dean Emerita.

In 2018, I took on an additional role in education as President of the Graduate School of the Stowers Institute for Medical Research (GSSIMR) in Kansas City, Missouri (Figure 5). The Stowers Institute for Medical Research was founded by Jim and Virginia Stowers and opened its first research labs in 2000. The Graduate School accepted its first doctoral students in 2012 and awarded the first PhD in biology in 2016. The development of the doctoral biomedical education program was led by founding dean R. Scott Hawley, PhD. It is an innovative education program designed to maximize the potential of emerging biomedical scientists with limited, but focused classroom work and an emphasis on experiential learning in laboratories mentored by world-renowned scientists. When I joined as President, the school was early in the process of regional accreditation by the Higher Learning Commission, which was awarded in 2021. My previous experience with academic administration and accreditation as a medical school dean provided background to help put in place the systems of faculty appointments, learning assessments, program evaluations, and the learning environment required for accreditation. I retired from GSSIMR in 2024 and am now President Emerita.

I participated in organized medicine at the local, regional, and national level throughout my career because this is one of the ways to "be with the people who hold the levers." I served as President of the Kansas City Medical Society (2020), chaired the Governing Council for the Academic Physicians Section (formerly Section on Medical Schools) of the American Medical Association (2009-2-10), served as Missouri State Medical Association (MSMA) Councilor for District 7 (2015-2024), was a Contributing Editor for MSMA's journal *Missouri Medicine* (2015-2024), and am currently a Delegate to the American Medical Association for MSMA. Advocacy for the practice of medicine and healthcare are essential to support and maintain the systems, policies, and legal framework that impact effective and safe healthcare, high quality medical education, and cutting-edge biomedical research. This infrastructure should serve the clinicians, learners, researchers, and patients for all to reach their full potential.

My professional path was driven by love of science and humanities, a belief in human potential, and an interest in systems. But it was supported by many mentors, advisors, and friends along the way and by a loving family. My parents set an example of hard work and strong values when I was growing up in rural Kansas, and I could not have pursued my passion for medicine without the unwavering support of my husband, Bill, my three children (Matt, Jessica, and Alex) and their partners, and my four grandchildren (Figure 6). They are an essential part of the narrative of my life and career. **MM**

CORRESPONDENCE

Inspiring Lives

Congratulations to *Missouri Medicine* for receiving the highest rating among state medical journals. I believe the three artificial intelligence services got it right. Together with managing editor Lizabeth Fleenor and others, you have brought *Missouri Medicine* to a well-deserved place of national prominence. As a longtime member of MSMA, I can state it hasn't always been the case thus making this achievement even more remarkable.

Lastly thanks for the honor of having my biography published. It was beautifully done. I believe MSMA is fortunate to have you as the editor-in-chief. As a proud military veteran, I sincerely thank you for your USAF service.

Richard Hellman, MD
Endocrinology, North Kansas City, Missouri

Voted #1

With pride, I note that *Missouri Medicine* has been voted #1 by three leading artificial intelligence programs. I'm not surprised. I have been a *Missouri Medicine* contributing editor for many years. Even longer than the 25 years you (John C. Hagan, III, MD) have been the Editor. In the distant past, our journal was far from the best before you became Editor. This singular honor reflects on the hard work and creativity of you as editor, and Lizabeth Fleenor as Managing Editor. Kudos also to MSMA that has sponsored our Journal over a century, since 1904. You have made it what it is today—one of the best medical society journals in the country.

Arthur Gale, MD
Associate Clinical Professor Emeritus, Washington University, School of Medicine
Contributing Editor, Missouri Medicine
St. Louis, Missouri

Compounding Pharmacies for 0.5% Timolol Nasal Spray for Acute Migraine

As outlined in the editorial by Missouri Medicine Editor John C. Hagan, III, MD, (March/April 2025; 122:76-80), physicians should be aware of the ways compounding pharmacists (CPs) can uniquely contribute to better patient care. This is especially relevant when FDA approved medications are unavailable, unaffordable or require changes in dosage, unique combinations of medications or delivery method.

Compound pharmacies are present in most large cities and in many mid-sized ones. Accredited compounding pharmacies (which may be located using the search tool of the Alliance for Pharmacy Compounding—https://a4pc.org/find-a-compounder) can mail special medications within specified states throughout the US. Ideally, physicians would have a working relationship with a CP. These compounding pharmacies should be licensed to dispense or ship to your state or residence.

Local CPs should be able to formulate the 0.5% timolol nasal spray for acute migraines that Dr. Hagan and other researchers have found useful. See publication in The International Journal of Pharmacy Compounding (https://ijpc.com/Abstracts/Abstract.cfm?ABS=5349).

Thomas C. Kupiec, PhD
President and Managing Editor
International Journal of Pharmaceutical Compounding
Edmond, Oklahoma

Fake Science

I admire the recent article on "Fake Science" published in the May/June 2025 issue of *Missouri Medicine* (pages 162-168). The integrity of scientific research is under attack. The damage is at a critical level and increasing exponentially as artificial intelligence evolves. The insights provided by Dr. Jian and L.H. Yaeger are both enlightening and timely.

The article aligns with statistics noted in the *Wall Street Journal* of June 14, 2025, which reported "The number of articles published in medical journals grew 47% between 2016 and

CORRESPONDENCE

2022, from 1.92 million to 2.8 million." This suggests a troubling trend where the proliferation of published research is not entirely an increase in credible and reliable studies. Sadly, most of the rise comprises low-quality, misleading, biased, or largely fabricated research papers.

This article underscores the importance of vigilance and discernment in both the publication and distribution of trustworthy and valid scientific literature. It serves as a crucial reminder to both healthcare professionals and the public to critically evaluate the sources and quality of medical research.

Thank you, authors and Missouri Medicine, for bringing attention to this critical issue. We must address it promptly or risk losing the respect and confidence of both the public and honest researchers.

Randy T. Jackson, MD
Ophthalmology, Sedalia, Missouri

Aging Well

I have just read the March/April 2025 *Missouri Medicine* with our department's theme issue "The Science of Aging Well." It is a fantastic compilation of papers that address important health care topics for our older Missourians. We are fortunate to have the great expertise of so many physicians across the state of Missouri who are committed to the health of our aging population. When thoughtfully implemented, the guidance offered by these authors can enhance the care and well-being of our older patients.

The faculty of Saint Louis University School of Medicine, Division of Geriatric Medicine greatly enjoyed the collaboration with *Missouri Medicine.*

Julie K. Gammack, MD
Professor of Medicine
Saint Louis University School of Medicine
Division of Geriatric Medicine

MM

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Anxiety and Depression in Today's Youth: A Current Look into Assessment and Treatment

by Meredith Scafe, PhD, Meghan Kanya, PhD, Meaghan Flynn, PhD & Ram Chettiar, DO

Children's Mercy

Approximately 16% of primary care visits include addressing a mental health concern, highlighting the urgent need for primary care providers to address the rising rates of adolescent depression and anxiety



Meredith Scafe, PhD, (pictured), is a Clinical Assistant Professor of Pediatrics at University of Missouri-Kansas City School of Medicine, Children's Mercy Hospital, Kansas City, Missouri, USA. Meghan Kanya, PhD, is a Clinical Psychologist at University of Missouri-Kansas City School of Medicine, Children's Mercy Hospital, Kansas City, Missouri, USA. Meaghan Flynn, PhD, is a Clinical Child Psychologist at University of Missouri-Kansas City School of Medicine, Children's Mercy Hospital, Kansas City, Missouri, USA. Ram Chettiar, DO, is Medical Director, Depression and Anxiety in Youth Clinic; Medical Director, Pediatric Care Network for Behavioral Health; Clinical Associate Professor of Pediatrics at University of Missouri-Kansas City School of Medicine, Children's Mercy Hospital, Kansas City, Missouri, USA.

Abstract

Following the COVID-19 pandemic, the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry, and the Children's Hospital Association declared a national emergency in child and adolescent mental health. Rates of anxiety and depression in youth continue at unprecedented levels, contributing to rising numbers of suicide attempts and lowered school attendance. Though many medical providers are trained to assess and provide recommendations for anxiety and depression, many report feeling ill-equipped to address these concerns in a timely, feasible, and effective manner. We review the existing literature on screening for anxiety and depression in the medical setting and provide evidence-based tools for providers to support patients, with acknowledgments of special populations. Additionally, we review multi-disciplinary models of treatment, such as one used by the Depression and Anxiety in Youth (DAY) program at Children's Mercy Kansas City.

Prevalence of Anxiety and Depression in Youth

The prevalence of youth with clinically-elevated depression and anxiety has been increasing. In 2015, worldwide estimates indicated 7% of youth had clinically elevated symptoms of anxiety and 7.5% reported elevated symptoms of depression.[1,2] In 2021, Racine and colleagues estimated a staggering 20.5% of youth experienced elevated symptoms of anxiety, and 25.2% of youth reported elevated symptoms of depression globally.[2] Meta-analyses demonstrate that depression is associated with numerous negative outcomes, including academic underachievement, unemployment, early parenthood, suicidal behavior, and substance use.[3] Similarly, anxiety disorders in adolescence are predictive of future mental health symptoms, substance use, physical health problems, self-harm, employment difficulties, and negative financial outcomes.[4] Depressive disorders are typically considered when youth experience suicidal ideation, with nearly 30% of youth with major depressive disorder having reported suicidal ideation within the past year and over 10% having reported a suicide attempt.[1] Surprising to some, 9% of adolescents with anxiety disorders

have also contemplated suicide, while 6% have made suicide attempts.[5]

Youth with adverse childhood experiences,[6] those with lower socioeconomic status (SES),[7,8] and youth who identify with minority groups report increased rates of depression, anxiety, and suicide. For example, 67% of youth who identify as lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual or aromantic, or with other sexual orientations and gender identities (LGBTQIA+) report symptoms of anxiety, 54% report symptoms of depression, and LGBTQIA+ youth are more likely to die by suicide than those who do not identify as LGBTQIA+.[9] Further, although the proportion of Black and Hispanic youth who report clinically-elevated anxiety or depression symptoms is lower than that of White peers, rates of suicide have been steadily increasing for Black and Hispanic youth (ages 10-24) over time, with estimates indicating Black children (ages five to 12) are twice as likely to die by suicide as their White peers.[10-14] Additionally, Black, Indigenous, and people of color (BIPOC) youth are directly and indirectly, and negatively impacted by racism and intersectionality with other marginalized identities. For example, youth who identify as both Black and LGBTQIA+ are more at risk due to intersecting identities.[15,16]

Barriers to Accessing Mental Health Treatment

Despite high rates of depression and anxiety, more than 50% of youth do not receive needed behavioral health treatment.[11,17] This disparity is even more pronounced for youth who identify with racial/ethnic minority groups, those with low SES,[11,18] or those who identify as LGBTQIA+.[19] Hoffmann and colleagues' (2022) review demonstrates that Black and Hispanic youth are less likely to be seen by a behavioral health provider than other racial/ethnic groups, have fewer visits, and are less likely to receive evidence-based behavioral health treatments or psychotropic medications.[11] The literature indicates that many complex systemic factors prevent youth from accessing needed behavioral health services.[20]

Behavioral Health Care in Medical Settings

Barriers to accessing traditional behavioral health services contribute to approximately 16% of primary care visits addressing a mental health concern.[21] To meet patients' mental health needs, integrated behavioral health care (IBHC) models have been developed and implemented to improve the identification and treatment of behavioral health symptoms in medical settings.[22,23] IBHC models broadly integrate medical and behavioral health providers into collaborative teams to coordinate patient care and address behavioral health symptoms.[24] In this model, medical providers address anxiety and depression symptoms via medication, while behavioral health providers use behavioral or cognitive approaches to assist patients in reducing symptoms. Empirical findings support the effectiveness of IBHC models in treating adolescent anxiety and depression.[25] Essential to addressing youth behavioral health symptoms within medical settings are evidence-based screening and treatment practices.

Screening for Youth Anxiety and Depression in Medical Settings

The United States Preventive Services Task Force (USPSTF) recommends that health care providers screen youth ages eight to 18 years for anxiety and youth ages 12 to 18 years for major depressive disorder.[26] Screening for behavioral health symptoms in medical settings is positively associated with identifying symptoms, referring to services, and following up with medical providers.[27-29] Screening includes the administration of standardized questionnaires during routine or specialty care visits by medical or behavioral health providers. According to the USPSTF,[26] best practices for youth depression screening include caregivers completing the nine-item Patient Health Questionnaire (PHQ-9)[30] or youth completing the PHQ modified for adolescents (PHQ-A).[31] These questionnaires include one item that assesses for suicidal ideation. However, one study found that depression screeners alone failed to detect one-third of youth at risk for suicide.[32] Therefore, the AAP recommends providers complete a suicide screening measure, (e.g., The Ask Suicide-Screening Questions), in addition to depression screening. The USPSTF also recommends using standardized questionnaires, including the Screen for Child Anxiety-Related Disorders (SCARED), to assess symptoms of anxiety.[33] Another brief measure used to screen for symptoms of generalized anxiety

disorder (GAD) is the GAD-7.[34] These questionnaires provide clinical cutoff scores that indicate the severity of youths' symptoms, which can inform providers' clinical decision-making. Most (92.1%) caregivers support routine mental health screening in primary care, preferring to review results with a professional. They also report feeling more comfortable completing caregiver-report questionnaires than having their child completing self-report measures.[35]

Treatment of Anxiety and Depression in Medical Settings

Once a youth is screened for mental health symptoms, providers should be prepared to provide treatment recommendations based on the youth's presenting concerns and screening results. Treatment for major depressive disorder and anxiety disorders may include pharmacotherapy, psychotherapy, collaborative care, psychosocial support interventions, and complementary and alternative medicine approaches.[1] To determine the best course of treatment, stepped-based care models, in addition to providers' clinical judgment, should be used to determine which interventions are least resource-intensive and most beneficial for youth.[36] The literature commonly describes two-stepped care models. The progressive model indicates patients benefit when they receive brief behavioral health interventions regardless of symptom severity[37,38] Whereas the stratified model triages youth into the appropriate level of care based on their symptom severity and functional impairment.[36] Treatment recommendations within the stratified model can include watchful waiting, self-help, clinician-guided self-help, brief interventions, individualized therapies, and specialist and inpatient services.[39] [37,38]

Pharmacotherapy for Depressive Disorders in Youth

The Treatment for Adolescents with Depression Study (TADS), published in 2004, is an often-cited multicenter randomized controlled trial examining the effectiveness of fluoxetine and cognitive behavioral therapy (CBT) in treating depression in adolescents.[40] The study concluded that treatment with fluoxetine only, CBT only, as well as the combination of fluoxetine and CBT led to significant improvement in depression symptoms, but the combination treatment had the best response and resulted in better functioning and quality of life.

Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of pharmacotherapy in the treatment of depression in youth. Within this class of medication, fluoxetine is approved by the US Food and Drug Administration (FDA) for use in the treatment of major depressive disorder in children eight years and older, while escitalopram is approved in adolescents 12 years and older.[41,42] Providers may prescribe other medications to address depression in children and adolescents, and off-label prescribing within this population is common and consistent with general practice. A notable exception to this is the SSRI medication paroxetine, which carries a higher risk of suicidal thinking and behavior in adolescents when compared to other medications in this class, and therefore is not a recommended treatment option for this population.[43]

About 60% of children and adolescents will respond to initial treatment with SSRI medication. Of those who do not initially respond, another 55% will respond to another SSRI medication or a serotonin and norepinephrine reuptake inhibitor (SNRI) medication along with CBT.[44] Currently no definitive empirical guidelines exist regarding how to switch from one medication to another, but providers use two common approaches. The most conservative approach consists of tapering the initial medication until it is discontinued prior to starting the second medication. Of note, fluoxetine does not require tapering, considering its extended half-life and unlikelihood of withdrawal symptoms. The other approach to switching medications is to cross-taper, where one medication is tapered gradually while the second medication is started and optimized over weeks to months. This approach minimizes the risk of clinical decompensation and is less time-consuming. However, this approach also increases the potential interactions and associated side effect burden with two medications being taken at the same time.[45] Once a pharmacotherapeutic approach is determined to be successful through the resolution of depressive symptoms, youth and their caregivers may be interested in coming off their medication. The risk of symptom relapse may be elevated when treatment is discontinued and therefore it is recommended that youth remain on their medication for at least six to

nine months once they have experienced a resolution of their depression. Based on the timeline and severity of depressive symptoms, the provider may choose to slowly lower the dose of the medication and monitor the patient's mood closely over the following several months, or choose to discontinue the medication completely.[46]

SSRI medications are generally well tolerated, though mild side effects are common and may include dry mouth, nausea, diarrhea, heartburn, headache, somnolence, insomnia, dizziness, change in appetite, weight loss or gain, fatigue, nervousness, tremors, bruxism, or diaphoresis. Serious side effects are rare but have been reported, including suicidal thinking and behaviors, behavioral activation, hypomania or mania, sexual dysfunction, seizures, abnormal bleeding, or serotonin syndrome. All medications that treat depression, including SSRIs, carry a black box warning for suicidal thoughts and behaviors in adolescents and young adults up to age 24. This warning was implemented in 2004 and unsurprisingly has led to alarm for many prescribers and patients. It is important to note that no suicide deaths were reported in the cases that were studied. Additionally, meta-analysis determined that suicidal thoughts and behaviors increased by 3% in adolescents and young adults on antidepressant medications, while they also increased by 2% in those on a placebo pill.[47,48] A troubling trend that has been observed since the FDA implemented its black-box warning on antidepressants is that the prescribing of these medications decreased, leaving many patients with depressive symptoms untreated. It is clear that untreated depression carries a much greater risk for suicidal behaviors than the risk associated with antidepressant medications. The morbidity and mortality risk of utilizing medication to treat depressive symptoms is further mitigated with close monitoring of treatment response and tolerability by a prescribing provider.[49]

Pharmacotherapy for Anxiety Disorders in Youth

The Child/Adolescent Anxiety Multimodal Study (CAMS) published in 2010 was a large multicenter randomized controlled trial that showed that both CBT and sertraline treatment for anxiety in children and adolescents ages seven to 17 significantly reduced the severity of anxiety symptoms. However, similar to TADS, the combination of psychotherapy and pharmacotherapy proved to be the most beneficial.[50]

Several disorders are classified under the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) anxiety umbrella. SSRI medications are considered safe and effective in the treatment of generalized anxiety disorder, social anxiety disorder, separation anxiety disorder, and panic disorder in children and adolescents. This class of medications would be considered the first-line pharmacologic option for youth with anxiety disorders, with escitalopram receiving FDA approval for the treatment of generalized anxiety disorder for children aged seven to 17 years. SNRI medications have also been shown to improve primary anxiety symptoms. Within this class, duloxetine also has FDA approval for the treatment of generalized anxiety disorder for children aged seven to 17 years. As with the treatment of depression, providers may prescribe other medications to address anxiety symptoms in children and adolescents, and off-label prescribing within this population is common and consistent with general practice.[42]

SNRI medications tend to be well tolerated, like SSRIs, but as a class, they have an elevated risk for side effects when compared to SSRIs. Common side effects may include dry mouth, nausea, diarrhea, headache, tremor, insomnia, somnolence, appetite changes, weight gain or weight loss, and diaphoresis. Due to their impact on norepinephrine, SNRIs are also associated with risk for elevated blood pressure and heart rate. Similar to SSRIs, SNRIs carry a black box warning for suicidal thinking and behavior in adolescents and young adults. Venlafaxine has been linked to higher rates of discontinuation syndrome and elevated suicidal thinking and behavior in this population when compared to other SNRIs.[51]

Behavioral Treatments for Depression and Anxiety in Youth

CBT has consistently demonstrated positive effects in decreasing youth anxiety and depressive symptoms.[52,53] Indeed, a meta-analysis of 42 RCTs found that CBT proved to be a possibly efficacious treatment for childhood depression and a well-established treatment for adolescent depression.[54] For anxiety, individual CBT therapy and several other modalities, (e.g., exposure-based treatments), are

well-established treatments for adolescents.[55] CBT interventions for youth are typically short-term and focus on teaching youth and their parents specific skills based on how youths' cognitions, feelings, and behaviors influence each other.[56] CBT interventions have also been adapted to be delivered to groups, as abbreviated behavioral health interventions, via electronic resources, or as phone applications.[57] Acceptance and Commitment Therapy (ACT) and Interpersonal Psychotherapy for Adolescents (IPT-A) have been shown to have positive effects in treating anxiety and depression in youth.[58,59] In sum, medical providers should seek to refer youth to resources that reference these modalities.

Case Example: Depression and Anxiety in Youth Clinic

To demonstrate how these recommendations support youth in outpatient settings, we will look at a new multidisciplinary outpatient clinic at Children's Mercy Hospital designed to offer short-term, evidence-based treatment to youth ages 12-17. For context, Children's Mercy Hospital is located in the Kansas City, Missouri, metro area and serves youth from a variety of socioeconomic and cultural backgrounds across Kansas and Missouri. Upon referral to the clinic, potential patients are verbally screened for anxiety and depression symptoms, as well as common comorbid conditions that may lead to differences in treatment model needs, e.g., autism spectrum disorder. As a treatment team, representatives from medical and therapy disciplines discuss the "fit" of potential patients within the clinic treatment model, as well as identify recommendations for the best treatment course, (e.g., medication first), then therapy once at a therapeutic level of medication.

Screening measures, i.e., GAD-7 and PHQ-9, are first administered at the intake appointment to assess baseline levels of anxiety and depression in youth. These measures are repeated minimally every two months, in addition to clinical information and observation within the sessions, to assess response to treatment and adjust individualized treatment program for youths as needed. Additionally, following the intake appointment, further screening for other conditions that may be either comorbid with anxiety and depression or underlying anxiety and depression is considered and completed when appropriate. For example, the Child and Adolescent Trauma Screen[60] or the UCLA PTSD Reaction Index[61] may be administered to assess symptoms of trauma, while the Vanderbilt[62] or Conners-4[63] may be used to assess for symptoms of attention deficit hyperactivity disorder.

Based on a patient's wants, needs, and goals identified collaboratively with the family and treatment team, a treatment plan is identified, which may include medication management, e.g., initiation of SSRI, individual therapy (using CBT or ACT frameworks, with additional Dialectical Behavior Therapy, exposure therapy, executive functioning skills, and mindfulness skills), and skills-based group therapy. Given the treatment plan identified, as well as other factors, such as time of year entering the program, patients participate in simultaneous services, when possible, though adjustments may be made to the timeline for clinical reasons. For example, for youth and families who want to complete a combination treatment of medication and therapy, a course of treatment may be recommended that begins with medication and then starts therapy approximately six to eight weeks later, to better align benefits from medication with momentum in therapy. Additionally, some youth or families may enter the DAY Clinic, preferring to start with just one modality of treatment, i.e., therapy or medication, and later, with the support of their treatment team, decide to include a second modality of treatment.

Additional Considerations for Depression and Anxiety Treatment

In addition to the evidence-based outpatient treatments discussed, many other interventions should be considered by medical providers who do not have access to multidisciplinary outpatient programs. For primary care providers, the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) toolkit is highly recommended as it outlines specific collaborative care practices, (e.g., imbedded behavioral health providers), and treatment recommendations, (e.g., patient monitoring), based on symptom severity.[64] Additionally, evidence supports the positive treatment effects of single-session interventions (SSIs; i.e., interventions that include one visit or encounter with a clinic, provider, or program) on youth depression and anxiety.[65,66] SSIs take many forms and can include brief behavioral health visits or digital

Table 1: Resources Quick Reference Guide

Resource Type	Resource Name	Accessibility
Symptom Screeners		
Depression Screener	Patient Health Questionnaire Modified for Adolescents - 9 (PHQ-A-9)	American Academy of Child and Adolescent Psychiatry
Generalized Anxiety Screener	Generalized Anxiety Disorder – 7 (GAD-7)	Anxiety and Depression Association of America
Global Anxiety Screener	Screen for Child Anxiety Related Emotional Disorders (SCARED)	American Academy of Child and Adolescent Psychiatry
Suicide Screener	Ask Suicide-Screening Questions (ASQ)	National Institute of Mental Health - Ask Suicide-Screening Questions (ASQ) Toolkit
Provider Treatment Resources		
Pharmacotherapy guidelines	American Medical Association Pharmacotherapy Guidelines	American Medical Association Pharmacotherapy Guidelines
Guidelines for Addressing Adolescent Depression	Guidelines for Adolescent Depression in Primary Care	The Reach Institute – GLAD-PC
Practice Guidelines: Anxiety	AACAP Anxiety Resource Center	AACAP Anxiety Resource Center
Practice Guidelines: Depression	AACAP Depression Resource Center	AACAP Depression Resource Center
Anxiety and Depression Psychoeducation	Seattle Children's Anxiety FAST Resource	Seattle Children's Anxiety FAST Resource
Behavioral Health Tools: Primary Care	American Academy of Family Physicians – Six 5 minute tools	American Academy of Family Physicians
Brief Mental Health Interventions	Orygen – The National Center of Excellence for Youth Mental Health	Orygen – The National Center of Excellence for Youth Mental Health
Parenting Resources		
Parent Anxiety Medication Guide	AACAP: Anxiety Disorders: Parents' Medication Guide	American Academy of Child and Adolescent Psychiatry
Parent Depression Medication Guide	AACAP: Depression: Parents' Medication Guide	American Academy of Child and Adolescent Psychiatry
Self-Help Resources		
Crisis Hotline	988 text/call hotline	Suicide and Crisis Lifeline Missouri
Mental Health App Guide	Mobile Health Index and Navigation Database (MIND)	Mobile Health Index and Navigation Database (MIND)
Psychotherapy Referral Resources		
Search for Behavioral Health providers	Psychology Today	Psychology Today
Certified Community Behavioral Health Centers	Missouri Behavioral Health Council – Find a Provider	Missouri Behavioral Health Council Find a Provider

mental health interventions, e.g., phone applications.[67] These interventions can increase access to care by eliminating barriers, (e.g., transportation issues), that prevent families from receiving care or are good options for patients who do not need more intensive outpatient therapy.

Conclusion

Approximately 16% of primary care visits include addressing a mental health concern, highlighting the urgent need for primary care providers to address the rising rates of adolescent depression and anxiety.[21] Medical providers can support the behavioral health needs of youth by screening for anxiety and depression routinely, providing referrals to behavioral or mental health professionals, consulting with specialty providers, (e.g., psychiatrists), and providing evidence-based pharmacotherapy or behavioral therapy interventions within medical clinics. See Table 1 for a quick reference guide of clinical resources to use in practice.

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Disclosure

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Psychosocial Supports for the Physical and Mental Health of Youth with Autism and Other Neurodevelopmental Disabilities

by Melissa Campbell, PsyD, Elizabeth Hastings, MD, Paige McArdle, PhD, Daren Olsen, PhD, Kate Benton, PhD & Cy Nadler, PhD

Children's Mercy

Providers should not lose sight of the patient themselves, always seeking opportunities to support self-advocacy, health literacy, and self-determination.



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Abstract

One in six youth has a neurodevelopmental disability (NDD), and autism diagnostic rates continue to rise. Before and after a diagnosis, families need trusted sources of guidance to navigate co-occurring medical and psychological conditions, and to manage unique stressors including transition to adulthood. However, medical professionals from all specialty areas struggle to identify resources to support the complex psychosocial and healthcare needs of these patients and their families. This primer on psychosocial supports for youth with autism will explore the major mental and physical health stressors faced by affected youth and families, and discuss opportunities for primary care and other providers to provide resources and empower their patients. Through awareness of key challenges and resources, non-specialist providers can integrate autism-specific supports into their regular practice. These same approaches will also allow providers to offer more holistic care for the broader NDD patient community as well.

Introduction

Over 20 years ago, the Centers for Disease Control and Prevention estimated that one in 150 youth had autism; most recently, that estimate is 1 in 31.[1] Perhaps even more notably, more than one in six youth are now estimated to have some type of neurodevelopmental disability (NDD), a broad category that includes diagnoses like autism, intellectual disability, learning disability, and other developmental conditions.[2]

While research and supports for people with autism have also increased over the last 20 years, the landscape for physical and mental health remains discouraging. Youth on the autism spectrum with and without co-occurring intellectual disability face significant unmet healthcare needs.[3] Despite having increased risk for co-occurring mental health conditions, autistic youth and their families struggle to connect with providers who are willing and able to serve them.[4] Autistic youth from underrepresented racial and ethnic groups as well as low-income families face even more significant barriers to care.[5] To support medical professionals from all specialty areas, this resource will explore the

complex mental and physical health stressors faced by autistic youth and their families, as well as discuss opportunities for primary care and other providers to empower their patients.

Medical Complexity

Up to 60% of youth with autism are medically complex, and even more notably, about 40% of all medically complex youth have autism.[6] Co-occurring medical conditions may manifest as behavioral symptoms, (e.g., aggression, self-injurious behaviors, anxiety, inattention and hyperactivity), and treatment of these conditions can improve quality of life for both child and family.[7] Medical providers are well-positioned to help patients and families identify possible autism, including inheritability, given family recurrence rates of approximately 20%,[8] as well as to ensure that emerging medical challenges are not dismissed due to the presence of a known developmental diagnosis (a phenomenon called diagnostic overshadowing).[9] For instance, people with autism face increased risk for epilepsy,[10,11] yet those symptoms may be overlooked or falsely attributed to autism.

While certainly present in neurotypical children, common medical challenges that commonly present along with autism may require special attention. For instance, sleep disorders impact between 50-80% of children and adolescents on the spectrum.[7,12] Common symptoms include bedtime resistance, sleep onset insomnia, and night-time awakenings. Though the etiology is unclear, youth with autism experience higher rates of gastrointestinal symptoms than their typically developing peers, including constipation, diarrhea, and abdominal pain.[7,13] Finally, medical professionals should also attend to significantly higher injury risk for autistic youth. These risks range from increased rates of wandering and elopement in young children[14] to higher rates of suicidal ideation and self-injury for adolescents and adults.[15] Youth with autism face increased risk for maltreatment,[16,17] including medical trauma, e.g., including increased rates of physical restraint during hospitalizations.[18]

Psychosocial Complexity

Neurodiversity

Medical providers need not be experts in autism or other neurodevelopmental disabilities to recognize and provide support for the psychosocial needs of their patients. To aid in this goal, it is important to develop an understanding of the growing neurodiversity movement, an extension of the broader disability rights movement.[19] Neurodiversity refers to the idea that all human brains develop differently and are therefore different from each other. Acknowledging and embracing neurodiversity does not deny differences, or even that some differences may be disabling; rather, a focus shift towards promoting strengths and providing accommodations helps facilitate acceptance and inclusion.[20]

Co-Occurring Mental Health

Up to 78% of youth diagnosed with autism also have one (or more) mental health conditions, compared to 14.1% of youth without autism.[21] The actual prevalence of mental health diagnoses in youth with autism could be even higher.[22] The most common co-occurring mental health conditions for youth with autism are behavior and conduct problems, anxiety, attention deficit/hyperactivity disorder (ADHD), and depression. Challenging behaviors, (e.g. tantrums, aggression, self-injury), are often the presenting problem that get autistic youth "in the door" to mental health services.[22] As with physical health conditions, providers should guard against diagnostic overshadowing for mental health conditions, (e.g., attributing behavior problems to "just the autism"), which may delay access to important treatments and other support.

Caregiver Burnout

Caregivers of individuals with autism face higher levels of stress, anxiety, depression, and feelings of caregiver burnout.[23,24] Parents report challenges finding social support, childcare, and babysitters/respite care providers. We urge clinicians to consider the needs of the whole family when supporting youth with autism and other NDDs.

Autism and Developmentally-Focused Psychosocial Supports

Individuals with neurodevelopmental differences benefit from evidence-based treatments (EBTs) targeted to their specific needs. This may involve domain-specific intervention, (e.g., speech-language therapy, occupational therapy), or a broader range of developmental skills, (e.g., naturalistic developmental behavioral interventions) that support joint attention and social engagement. Regardless of the intervention target or modality, providers should advocate for

strengths-based approaches, e.g., building on a child's areas of strength, rather than just focusing on areas of weakness. Moreover, providers can emphasize neurodiversity-affirming clinical practice, which means respecting individual and family preference for the terms and language used to describe disability.[25] As discussed above, many people see disability as an integral part of their own self-identify and community, so providers can partner with youth and families to ensure that medical and mental health care is provided in an accessible way and aligns with their values.[26,27]

Applied behavior analysis (ABA) has a strong empirical base for teaching and supporting a wide variety of skills and reducing challenging behaviors, regardless of diagnosis. However, insurance companies generally require a medical diagnosis of autism to provide coverage. Often described non-specifically as "ABA therapy" in community settings, these approaches use close observation and individualized programming to support behavior change. In response to the neurodiversity movement, there is a widespread movement in the field of ABA to adopt "neurodiversity-affirming" care practices that aims to "optimize the lives of an autistic individual without sacrificing their unique autistic self."[28]

Many supports do not require a diagnosis and thus may be accessed before or during referral for diagnostic evaluation. For youth from birth to three years of age, medical providers can refer for a developmental evaluation through their state's early intervention (EI) system, such as Missouri First Steps.[29] Youth who meet the state's criteria for a delay in one or more areas of development may qualify for therapies provided in their natural environment, e.g., home, childcare setting, and in partnership with the child's family. Services may be billed to a family's insurance, with a possible copay, or provided free of charge.

Families of youth who do not qualify for EI but demonstrate concerns that warrant intervention may need additional referrals. Many states offer parenting programs, such as Parents as Teachers,[30] which serves low-income households, for youth up to age five. For youth with emotional or behavioral concerns, behavioral parent training programs, such as Parent-Child Interaction Therapy,[31,32] can help parents/caregivers increase positive interactions and manage challenging behavior. Other parent-mediated interventions, (e.g. mindfulness-based, cognitive behavioral, acceptance and commitment therapy), combined with parent education and behavior management training are shown to reduce stress and increase self-efficacy in parents.[24] Some primary care practices offer integrated behavioral health services, which increases treatment access and improves mental health outcomes.[34] For school-age children and adolescents, social skills programming may also be beneficial. These services tend to be private pay, unless provided in the school setting.

Treatment of Medical and Psychosocial Complexities

Medical treatments are beyond the scope of the present review. However, significant guidance exists for clinicians on how to tailor medical and medication interventions for youth with autism and other NDDs.[35] Here, we focus on psychosocial supports and key referrals in the assessment and management of co-occurring conditions.

Sleep

For sleep disorders in youth, behavioral interventions are often the first line of treatment, including parental education regarding sleep hygiene, environment, and bedtime routine and working towards planned ignoring, i.e., extinction[12,36]. Increasing daytime physical activity can also improve sleep in youth with autism.[37] Treatment with melatonin can be considered if behavioral interventions are insufficient[37] Symptoms of obstructive sleep apnea (heavy, loud-mouth breathing, loud snoring) warrant referral to a medical sleep specialist. Symptoms of restless leg syndrome (intense need to move legs to get comfortable, moving frequently during sleep) warrant evaluation for iron deficiency, which can be common in picky eaters.

Gastrointestinal

Routine monitoring of gastro-intestinal symptoms is important as these symptoms can manifest as behavioral challenges, e.g., aggression, self-injurious behavior. Some contributing factors may include restricted diets (especially if entire food groups are avoided), feeding challenges, and consumption of inedible items (pica) that are common in this population. Physicians should consider nutritional evaluation and/or referral to specialty feeding clinics when concerns warrant additional evaluation, as well as evaluating for and treating constipation.

Mental Health

Youth with autism need regular screening for mental health/behavioral symptoms starting in the preschool years.[21] Again, providers should guard against diagnostic overshadowing that might lead to untreated co-occurring conditions. For youth with co-occurring mental health

concerns, referrals for psychological services may also be appropriate. EBTs for anxiety and mood concerns include cognitive behavioral therapy (CBT), behavioral and exposure-based therapies, and acceptance and commitment therapy (ACT) or other mindfulness-based interventions tailored to youth. These EBTs may require modification for youth with autism due to differences in language, social skills, cognitive, or executive functioning skills. However, PCPs should not shy away from referring to or advocating for mental health treatments simply because a child also has autism. Children with autism should not be excluded due to their diagnosis.

Caregiver Support

Caregivers may experience feelings of guilt or other barriers to asking for help—so be proactive in asking them what they need. We recommend providing information on parent support groups and community organizations geared toward parents of autistic/neurodivergent youth, such as your local chapter of the Autism Society.[38] Each state has at least one Parent Training and Information Center and/or Community Parent Resource Center.[39] In Missouri, the Missouri Parents Act (MPACT)[40] provides free information and advocates to help families navigate their child's educational needs protected by the Individuals with Disabilities Education Act.[41]

Educational and Government Supports

Individuals ages three to age 21 may qualify for an Individualized Education Program (IEP) through their local school district, which does not require a medical diagnosis. Families should request an evaluation in writing and provide written consent to start the evaluation process. Youth who are not found eligible for an IEP may receive fewer intensive supports through other school-based programming, such as a multi-tiered system of supports. Students who have a medical diagnosis may also receive supports and accommodations through a 504 Plan.[42]

Families may also access additional support through their state's developmental disability office. Local or regional disability offices may provide a list of parent resources, and many state programs offer family services and/or financial support. Some states offer funding for respite care by a trained provider or individual selected by the family, e.g., extended family member. In Missouri, regional disability offices are run by the Missouri Department of Mental Health[43] and offer funding to support individuals with autism and their families through the Missouri Autism Projects.[44]

Transition Considerations

Often referred to as the "services cliff," autistic youth and their families face significant challenges in identifying appropriate supports during and after the transition to adulthood.[44] Identifying appropriate adult medical care requires proactive collaboration between the patient and family as well as existing primary care and subspecialty providers.[46] Health insurance coverage itself may add complexity, though many private health plans will allow parents to maintain an adult on their employer insurance well past the age of 18 years. However, it is important to secure Medicaid as a primary or secondary insurance provider to access other state services, e.g., Medicaid Waivers for adult services. Parents need to balance the pros and cons of keeping private insurance which can be expensive but would offer more options for doctors and specialists.

Parents and caregivers of youth with higher support needs will need to consider guardianship and/or conservatorship of their child at the age of 18, or make other legal arrangements to allow for ongoing involvement in healthcare and other aspects of life. Legal guardianship encompasses the power to make decisions for another person around topics such as personal care, welfare, living, health, and safety. However, depending on the individual, full and even partial guardianship can be limiting and restrictive. Alternatives such as Supported Decision-Making (SDM) should be considered in light of these restrictions.[47] SDM is a legal process in which the person maintains a greater level of autonomy compared to full guardianship. In an SDM arraignment, the individual retains the right to make decisions for themselves while receiving necessary support from trusted individuals they select. Each state has different laws, requirements, and procedures for obtaining guardianship and SDM, but these processes require documentation delineating the needs and capabilities of the individual, including medical evaluations, psychological assessments, and legal forms specific to the state.[48]

The transition to adulthood also requires navigating complex changes encompassing school district, county, and state systems. Typically, these changes are most robust during the ages of 18-21. During this time, young people may remain eligible

for a school educational plan (IEP), though services shift in focus from special education to community integration, vocational and/or life-skill training, and planning for post-secondary years. Students with lower support needs may have the option to attend formal post-secondary programs, such as community college or vocational/trade schools with varying levels of support from the school district.

For students with higher needs, the focus for the transition years is likely to be more practical, (e.g., life skills or job training), with the goal of transitioning these young adults to community programs after the age of 21. Most school district transition programs have staff who will work closely with parents to provide education/resources and write goals that address important tasks in the form of a long-term life plan. However, many responsibilities will ultimately fall to parents, and a proactive approach is critical. Medical professionals can support families by directing them to key transition planning resources, including through groups like Autism Speaks[49] and Charting the Life Course.[50]

A crucial step for youth as well as adults with disabilities involves applying for benefits and Medicaid eligibility, typically through the state's designated disability office. This can be done as soon as a disability is identified; however, services may be limited until a child reaches adulthood. The process for approval has multiple steps and requires some assessment and documentation.[51] Once eligible, families will work with a service coordinator to develop an Individual Support Plan (ISP) that outlines needs as well as services being requested, such as vocational services (job coaching/training), day program, life skill training, behavioral support, therapies, respite care, and personal assistant hours. Transportation needs should be included as this can be a barrier for adults accessing services and jobs in the community. As part of a service plan, families need to consider both present and future living arrangements. This can range from independent living, supported living, group home living, cooperative living arrangements, to a full residential center depending on the needs of the adult. Because higher levels of care are very expensive, they can take time to secure (and may require significant documentation and justification). Many states prefer families to maintain adults in their home with support for as long as possible. While this arrangement has advantages, it can place a significant burden on parents as they begin to age and are not as equipped to provide daily care and support. Another challenge is the possibility of wait lists for different waivers, which can significantly delay services. Providers should encourage families to investigate financial supports through the Social Security Administration[52] both before and after an individual with autism reaches legal adulthood.

Conclusion

Medical, psychiatric, and allied health providers need not specialize in autism or other NDDs to offer compassionate, timely, and responsive care to their patients. However, as with all clinical relationships, the best outcomes are achieved through committed partnerships and teamwork. In many cases, providers may have to expand who is on the team by seeking out consultation. Providers may need to adapt their care by partnering closely with guardians and community advocates of their adult patients. Most importantly, providers should not lose sight of the patient themselves, always seeking opportunities to support self-advocacy, health literacy, and self-determination. By leveraging resources and engaging with those who do have disability-related expertise (including parents, caregivers, and individuals themselves), providers can help patients with autism and other NDDs thrive.

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Screens Are Not the Enemy: Recommendations for Developing Healthy Digital Habits in Youth

by Megan B. Bolch, PhD, Rachel M. Moore, PhD, Gail C. Robertson, PhD, Meredith J. Scafe, PhD & Libby Matile Milkovich, MD

Children's Mercy

Guidance on youth digital media use should prioritize the individual characteristics of the child and family, as well as digital media quality, rather than focusing primarily on screen time.



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Abstract

With the rapid and ever-evolving growth of both digital media platforms and mental health concerns in youth, parents and practitioners are faced with the challenge of critically evaluating the effects of digital media use on youth development.[1] Despite popular culture's narrow focus on the risks, research has established both positive and negative effects of youth digital media use.[2,3] In contrast to interventions primarily focused on screen time limits, the goal of this article is to propose a framework for healthy digital habits rooted in a social-ecological model, called the Multisystemic Model of Digital Habits. This framework considers the intersection of the digital environment, family environment, and individual factors when examining digital media use by youth. Using this framework, practical recommendations are offered, including strategies to evaluate media use and guidance on encouraging healthy digital habits with consideration for unique family and individual needs.

The Current State of Youth Digital Media Use

Almost 90% of youth aged 11 or younger interact with digital media[4], including television, radio, social media, mobile apps, video games, and streaming platforms.[3] Youth aged eight to 12 spend around five and a half hours daily on digital media, while youth aged 13 to 18 spend about eight and a half hours.[5] With ubiquitous digital media access among youth, approximately 60% of parents report concerns about how digital media use affects their children's development.[6] About 60% of parents of a child under the age 12 also seek parenting digital media advice from doctors or other parents.[7]

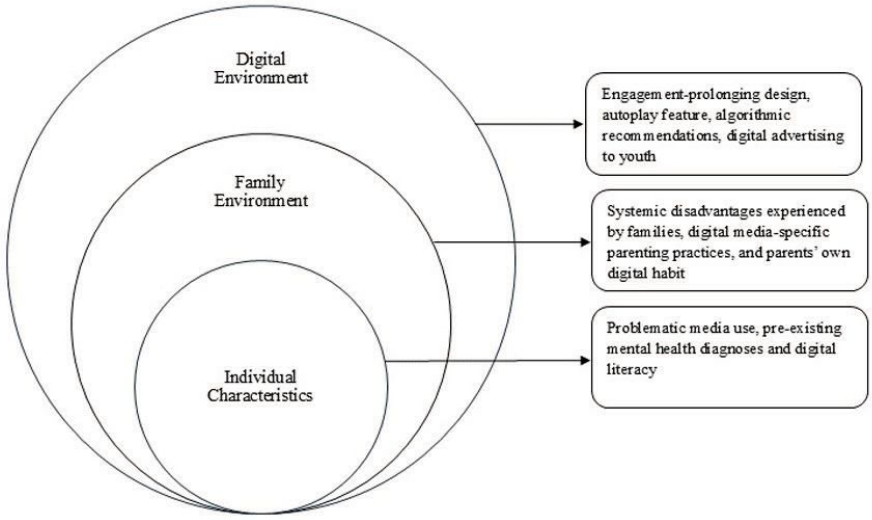
Digital Media Use and Youth Outcomes

Mainstream media predominantly focuses on sharing the negative effects of youth digital media use. Negative effects of youth digital media use include traumatic experiences from being exposed to inappropriate or explicit content, development of sleep problems, attention and cognitive difficulties, mental health problems, and poor academic performance.[8,9] While the potential negative effects should not be underestimated, several

factors can moderate harmful developmental outcomes associated with digital media use. These factors include type of digital media exposure and engagement (active versus passive),[8] quality of parent-child relationship,[10] and excessive or problematic media use (PMU), with associated impairment in various areas of functioning.[11]

Digital media is not exclusively linked to negative youth outcomes. Multiple positive effects have also been associated with youth digital media use including increased accessibility to novel information (e.g., current events), early learning opportunities (e.g., alphabet/counting apps, Sesame Street), social connections (e.g., forming social relationships with other students), and health information (e.g., access to information about medical conditions).[5] A review of 131 articles indicated that other benefits of digital media use include positive cognitive and social-emotional development.[12] Further, digital interventions such as care via telehealth platforms have been leveraged to promote favorable reductions in symptoms of depression and anxiety for adolescents.[13]

Figure 1. The Multisystemic Model of Digital Habits



Gaps in Current Recommendations

While parenting guidance has predominantly focused on screen time limits, a narrow focus on screen time alone overlooks the broader context of moderators of digital media harm.[14] According to the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry (AACAP), guidance on youth digital media use should prioritize the individual characteristics of the child and family, as well as digital media quality, rather than focusing primarily on screen time.[15] Mitigators of harm may include factors such as decreasing access to distressing content, and promoters of benefit, such as fostering opportunities for social connection digitally. A new framework is needed that integrates digital media use within the context of the whole child, moving beyond screen time limitations.

A New Framework for Healthy Digital Habits

We propose a framework, called the Multisystemic Model of Digital Habits, that de-emphasizes screen time by providing context of youth outcomes associated with digital media. This social-ecological systems model acknowledges the interaction of factors at different levels—such as the digital environment at the macro-level, the family environment at the meso-level, and individual factors at the micro-level—in influencing outcomes. Within this framework, youth digital media use and its associated outcomes are considered (Figure 1). We offer recommendations pediatric providers can consider integrating into their professional practice outside and within their clinics at each level.

Macro-Level: Digital Media Environment

At the broadest level in the Multisystemic Model of Digital Habits framework, digital environments are designed by technology companies without sufficient consideration for the unique developmental needs of youth.[16] Digital environments include autoplay, algorithmic content recommendations, and digital advertising to increase youth engagement.[17] The more users engage on the platform, the more revenue companies generate. One design technique to prolong engagement is autoplay, which streaming platforms like Netflix and YouTube use to automatically play

the next video after the initial video is complete, making consumers feel a loss of self-agency.[18] Users feel a similar lack of self-agency with another design technique, algorithmic recommendations, which platforms like TikTok and Facebook use to suggest tailored content to increase the likelihood of prolonging engagement.[19] These algorithms promote extreme, emotionally arousing, or high-pleasure trending content to increase users' engagement. For these algorithms to work, platforms constantly collect data from their consumers through customer-created content and customers' patterns of use.[20] Youth's unique vulnerability to advertising means the collection of their data is of particular concern.[16] Digital marketing embeds advertising in platforms that are trusted by youth, some of which can be harmful.[16] The rapid uptake of digital media, including generative artificial intelligence (AI), is particularly concerning in a profit-centered digital environment that often overlooks the unique needs of youth, who are typically early adopters.

Recommendation 1: Advocate for Policy Change Aimed at the Digital Media Environment

Advocacy is essential to shift the digital media environment to a child-centered design as the default. Experts have already started advocating for such policy changes. For example, in June 2024, the US Surgeon General called for a warning label on social media platforms.[21] This proposed measure was a plea for legislation to improve awareness and behavior change. Similarly, in 2023, the American Psychological Association issued the Health Advisory on Social Media Use in Adolescence, encouraging changes to the digital environment to protect youth from possible harms of social media platforms.[22]

Continued advocacy efforts should focus on supporting federal regulations that require the technology industry to adapt apps to suit the developmental needs of youth. For example, apps and platforms should limit autoplay functions, advertising, promotion of inappropriate content, data collection, and other features that are linked to previously discussed adverse youth outcomes. Medical providers can participate in advocacy efforts by joining health care advocacy groups like those offered by the American Medical Association or staying up to date on legislative efforts by joining special interest groups such as the AAP's Council on Communications and Media, which provide information about advocacy efforts at the national level. Additionally, providers can contact their regional and national representatives regarding specific legislation.

Recommendation 2: Encourage Families to Modify or Tailor Their Child's Digital Environment

Router and device-level settings may be implemented to avoid some manipulative design features. Apple iOS and Android platforms provide screen time controls at the operating system level, allowing users to restrict access to specific websites or apps and limit usage time based on customized settings. Implementing these restrictions can create friction and slow down the automatic impulse to access digital media that captures users' attention and prolongs engagement. Third-party monitoring options such as Circle and Boomerang have also been recommended by online safety experts and offer additional features like more robust content monitoring.[23] Reducing harmful content such as illegal or maladaptive behaviors may serve to change behavior and reduce risks based on individual vulnerabilities.[24] Websites, such as commonsensemedia.org and childrenandscreens.org, offer recommendations on router and device-level settings.

Meso-Level: Family Environment

In addition to the broader digital environment, mesosystem-level factors within the Multisystemic Model of Digital Habits framework include systemic disadvantages experienced by families, digital media-specific parenting practices, and parents' own digital habits.

Sociodemographic characteristics like single parent households, belonging to a marginalized race or ethnic group, and parents with less education attainment have been associated with higher digital media exposure and digital media use.[25] Youth in families with lower income tend to have more access to devices in their bedroom.[25] Higher parent-reported stress and chaos (e.g., confusion, disorganization) within the home are associated with more time spent on devices.[26] These findings likely represent systemic disadvantages experienced by families, such as limited access to childcare and after-school activities, which may require a greater reliance on digital media to occupy youth.

The overall family digital media culture, including parent media use habits, affects youth digital media use.[21] Higher levels of parent digital media use are associated with higher levels of youth digital media use.[28-30] In addition to total screen time usage, researchers have introduced the concept of "technoference," defined as everyday interruptions in interpersonal interactions due to digital media.[31] Such interruptions may occur during face-to-face conversations or during daily routines, such as meals, playtime, or bedtime. Interruptions may lead to feelings of intrusion when another person interacts with digital media during planned time together.[32] Higher parent digital media use is associated with fewer parent-child interactions, lower responsivity to child bids, and parent hostility in response to children's bids for attention,[32] all of which affect youth social-emotional health and the quality of parent-child relationship. These parent-child interactions are likely bidirectional, as parents who have youth with more problem behaviors may become more stressed, which may lead to greater technoference, such as withdrawal from parenting duties with digital media use, which in turn may contribute to more child problem behaviors and parent-child relationship difficulties.[33] Consequently, this cycle of stress and withdrawal can exacerbate existing issues, creating a feedback loop that intensifies both the child's and the parent's problematic behaviors. This may also be why parents with problematic media use are almost 10 times more likely to have youth with problematic media use.[30]

Poorer quality of parent-child relationships is associated with increased digital media use in youth.[28,29] Digital health recommendations for youth often include recommendations for parents to moderate their children's access to digital media. Examples of digital media-specific parenting practices include setting digital media content restrictions and screen time. Digital media-specific parenting practices, whether strict and lenient, have shown inconsistent associations with healthy digital habits in youth.[34] The parenting style and quality of parent-child relationships, two key factors in child development outcomes, may mediate the impact of digital media-specific parenting practices.[11] For example, authoritative parenting, the style of parenting that combines warmth, sensitivity, and clear boundaries, is associated with healthy digital habits and positive parent-child relationships.[11,35]

Recommendation 3: Encourage Families to Develop a Household Culture of Healthy Digital Media Habits

Family digital health guidance should shift from emphasizing youth's screen time and content limitations to fostering open conversations about the family's digital media culture. This includes examining parents' own digital media use and the quality of parent-child relationship. The AAP's Family Media Use Plan is a valuable tool for encouraging open conversations within families about media use.[36] Media plans should be reviewed frequently and adjusted based on factors such as age and developmental level of the child. It includes prompts tailored to different age groups, which can be customized with family responses. Prompts such as "Screen-Free Times or Zones," "Communicating about Media," and "Using Media Together" help foster communication and strengthen parent-child relationships around digital health. This tool enables families to thoughtfully shape their digital media culture in a way that aligns with their values. For instance, establishing family agreements on screen-free zones, such as the dinner table, and screen-free times, like before bed, can encourage face-to-face interactions to reduce technoference. This approach is more likely to be accepted if the entire family agrees with the household expectations.

Recommendation 4: Provide Guidance on the Effect of Parents' Own Digital Media Use on Youth Outcomes and Digital Media Habits

Raising awareness about the impact of parents' digital media use on youth outcomes and digital habits is crucial. Pediatric providers can facilitate this by discussing the topic as part of anticipatory guidance, starting as early as infant well-checks. Direct education about how parents' digital habits can influence the quality of the relationship with their child and their child's digital use is key.

Given that parents often turn to digital media to cope with parenting stress, recommendations to reduce parent digital media use should be accompanied by alternative strategies. For example, pediatric providers may help parents identify triggers of stress and alternative coping strategies such as

talking with a friend or co-viewing digital media with their child. When parents use digital media in the presence of their children, the explanation of the purpose and context of their usage to their child can help youth learn appropriate digital media use and reduce feelings of being ignored. The parents' explanations of their own digital media use can be foundational in building digital literacy skills or the understanding of healthy digital media use in their children. This transparency fosters a healthier digital media culture at home and promotes mutual understanding within the family.

Recommendation 5: Provide Education About Parenting Strategies Related to Healthy Digital Use

In response to parents' questions on digital specific topics such as screen time limitations, pediatric providers may shift guidance to encourage high quality parent-child communication about digital media. Consistent with the AAP and research outcomes, providers could recommend that parents use digital media to connect, co-view, and create.[32] Education on online etiquette, empathy, ethics, digital media safety, personal boundaries, and how to regulate digital media habits may be helpful in conversations with youth.[32, 37]

Micro-Level: Individual Characteristics

Lastly, at the micro-system level within the Multisystemic Model of Healthy Digital Habits Framework, there are individual factors like PMU, pre-existing mental health diagnoses, and digital literacy that can be considered.

PMU, also known as problematic internet use or internet dependency, lacks a universal definition, but often is characterized by excessive, impulsive, or risky behavior.[38] PMU is positively linked to psychological outcomes such as depressed mood, anxiety, sleep disturbance, attention problems, and behavioral concerns.[39] The prevalence of PMU is estimated to be between 5% and 10% of youth using media.[39]

Youth with mental health disorders, such as depression and attention-deficit/hyperactivity disorder (ADHD), are at increased risk of harm from digital media due to the higher prevalence of PMU among these individuals.[39] Youth with PMU engage in more risky, excessive, and impulsive social media engagement, increasing their risk of encountering distressing content,[40] which may result in emotional distress. Exposure to distressing content, particularly cyberbullying, has been associated with elevated levels of anxiety and depression.[41] The ubiquity of access to digital media allows it to become an easy distraction during times of emotional distress, reinforcing social media engagement. A recent study found that most 11-17-year-olds "sometimes" or "often" use their phones to escape from negative emotions[42] and many used media to relax before bed. However, using the digital media excessively to distract from emotional distress has been linked with worsening self-regulation abilities over time, as it may reduce youth's opportunities to learn these skills.[43, 44] Youth experiencing PMU, anxiety, or depression, are particularly vulnerable to diminished self-regulation skills.[44] In turn, lack of self-regulation strategies exacerbates feelings of anxiety and depression, creating a cycle of emotional distress.

Recommendation 6: Screen for Problematic Media Use

Pediatric providers can screen for PMU using validated tools such as the parent-report measure, Problematic Media Use Measure (PMUM),[45] or the youth-report measure, Problematic and Risky Internet Use Screening Scale (PRIUSS).[46] If screening indicates PMU, pediatric providers should initiate referrals for evidence-based treatment. Treatment may include psychological interventions like cognitive behavioral therapy aimed at directly addressing digital media use.[47] Given the high rate of mental health disorders associated with PMU, pediatric providers should also consider screening for mental health comorbidities such as ADHD, anxiety, and depression. Improving the co-morbid mental health disorders can improve PMU.[48]

Recommendation 7: Promote Digital Literacy for all Youth

Digital literacy has been proposed as a tool to mitigate harm for vulnerable individuals. The American Library Association's Digital Literacy Task Force asserts that digital literacy is "the ability to use information and communication technologies to find, evaluate, create, and communicate information, requiring both cognitive and technical skills."[49] Digital literacy can be a protective factor when it comes to reducing negative impacts of digital media use. Encouraging engagement in joint critical thinking with children about viewed

content is foundational to building digital literacy skills. Promoting youth digital literacy by teaching skills such as the use of security features and responsible online actions is critical.

Recommendation 8: Tailor Digital Media Use Recommendations to Youth's Unique Needs

Pediatric providers should take a child-centered approach with digital media guidance which focuses on delivering recommendations and interventions to families, children, and adolescents based on the patient's individual needs as opposed to taking a one-size fits all approach. Individual factors such as developmental needs and psychological vulnerabilities (e.g., mental health conditions) are specific nuances to consider when examining media use and healthy digital habits. The AAP's Center of Excellence on Social Media and Youth Mental Health 5 C's (Child, Content, Calm, Crowding Out, and Communication) framework may help providers customize guidance for the individual youth.[51] This approach allows for focused attention on the individual child, the quality of the content, use of appropriate coping strategies, assessing if media use is "crowding out" other enjoyable family activities, and highlights the need for continued communication about this topic.[51]

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Constantly Connected: What Healthcare Providers Need to Know About Vicarious Trauma in an Evolving Digitally Connected Global Community

by Meghan Kanya, PhD, Patricia Davis, LSCSW & Gail C. Robertson, PhD

Children's Mercy

There is a growing awareness that our youth and adults are experiencing stress responses to vicarious exposure to local, national, and international events due to current levels of access to information and interaction via electronic devices and social media.



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Abstract

Easy access to streaming news and sensational headlines has transformed society's exposure to traumatic narratives. From personal stories on social media platforms to news articles about violence in communities, patients and their caregivers may not recognize their exposure as traumatic nor recognize their psychological sequalae as unhealthy. In addition, youth with trauma-related mental health symptoms are not consistently identified in pediatric primary care clinics. Due to the increase in proximity to traumatic stories, healthcare providers working with youth require additional skills designed to engage patients and families in conversations about exposure to violence via technology and symptoms of vicarious trauma. This article aims to summarize current understanding of vicarious trauma via technology, the impact of vicarious trauma on youth, and provide best practices to improve providers' ability to disseminate evidence-based guidance.

The Case for Vicarious Trauma

This week I met with a friend, who was beside herself after learning a friend's teenage son died by suicide the night before. She had known this teenager since he was five years old. He was best friends with her grandson, and they had grown up together. This teen appeared to have everything going for him. He had a loving two-parent, financially-sufficient, family home, an active and stable social life, and a safe academic atmosphere where he received good grades.

What went wrong? How did no one know he was suffering? His family shared that, although he openly talked about social worries and concerns, these were common discussions among his peers. There had been a mass shooting at a sports rally killing one bystander, injuring many, and traumatizing hundreds, as well as current domestic and foreign political divisiveness, but he wasn't directly connected to those situations. Or was he?

These types of stressful, even traumatic, events are not new in the world. Could this teen have felt more connected and closer to these events due to technology and social media than what many of us are

used to when hearing about social, political, economic unrest and violence? Historically, connection to community and world unrest looked and felt different for many. Families would huddle together to watch the evening news, balking at the awful scenes on television, even that of war, riots, and terrorism on both foreign and local soil. They would talk as a family about the scary, disturbing events and their ways to maintain safety. Then they might say some prayers and turn off the television. All went to bed and their brains processed and reprocessed the news, eventually allowing their stress response systems to return to baseline. They had a good night's sleep and awoke the next day to tackle new things, both good and bad.

This does not seem to be the case for young people today. They are seeing horrific events, not only on television during the news hours, but also watching repetitively on the 24-hour news cycle. They can read opinions via blogs on their phones and never miss the late-breaking updates. They can view live updates from individuals in war zones or from within schools during an active shooter event. What used to be far away horrors, buffered by adult monitoring and scheduled depictions of news, are now impacting our children's day-to-day lives more and more.

Trauma Defined

The diagnosis of Post-Traumatic Stress Disorder (PTSD) was first included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) in its third edition,[1] published in 1980. With its inclusion, there was an acknowledgement that traumatic events can impact human experience, mental health challenges can result from experiences outside of oneself (i.e., not just a character flaw), and that traumatic events impact the brain and body differently than "normal stressors." In the current edition of the DSM (DSM-5), PTSD as a diagnosis is defined by the following:[2] A) Exposure to actual or threatened death, serious injury, or sexual violence via directly experiencing the event, witnessing in person the event as it occurred to others, learning that the event occurred to a close family member or close friend, or experiencing repeated or extreme exposure to aversive details of the event (e.g., first responders and emergency response professionals); B) Presence of at least one intrusion symptom associated with the event (e.g., intrusive memories, recurrent dreams/nightmares, dissociative re-experiencing); C) Presence of at least one form of avoidance toward stimuli associated with the event (e.g., avoiding memories of event, avoiding external reminders of event); D) Presence of at least two changes in cognition and mood associated with the event (e.g., difficulties remembering parts of the event, negative cognitive beliefs, blaming of self for the event, feeling detached from relationships); E) Presence of at least two changes in arousal/reactivity associated with the event (e.g., irritability, self-destructive behavior, hypervigilance); F) Duration of disturbances is more than one month; G) Disturbances causes significant distress or impairment; and H) Disturbances not attributable to other conditions or substance use/abuse.

Since the 1990s, there has been an increased awareness that the DSM definition of traumatic events and associated trauma-related symptoms and diagnoses may not properly represent alternate forms of trauma, such as instances of prolonged, repeated interpersonal violence, vicarious trauma (i.e., that experienced through watching/hearing of traumatic events on electronic devices/platforms), or complex developmental trauma, which significantly impact functioning in similar and different ways than that demonstrated in "traditional PTSD."[3]

Within the DSM-5, there is a specific note that exposure to a traumatic event cannot include exposure via electronic media, television, movies, or pictures, unless the exposure is work related.[2] In effect, what this means, is that an individual presenting with trauma-related symptoms in response to watching non-stop coverage of a recent mass shooting would not meet criteria, may not receive appropriate support and intervention, and may not even be identified as having trauma-related symptoms due to lack of screening. This issue is especially salient for youth due to differences in presentation of trauma-related symptoms in younger populations, developmental shifts in cognitive and emotional processing, and social media use.

Technology Advances in Entertainment, Connections, and Media

Advances in and access to technology have significantly changed our lives in the past 25 years.

In 2000, only 50% of households in the US had one or more computers, and fewer than 7% of individuals around the world were online.[4-5] In 2011, 35% of the US population had a mobile phone. Today, 98% own a cellphone with over 90% owning a smartphone. Most of the world's population now has access to the internet. There are more cellphones in existence than there are people in the world. [4-6]

With expansions in access to technology, choice on where and how to connect with others has also increased. Social media was first on the horizon in early 2000s with less than one million connected to MySpace.[4] Today, Facebook has nearly three billion active users each month.[7] There are numerous social media platforms from which to choose and many teens report using social media daily.[6] Dixon reports that the average internet user is spending 2.5 hours per day on social media, which is up from 40 minutes per day nine years ago.[7] Online connections have shown benefits for teens, including increased felt social connection with others who share similar identities and interests.[8] However, online connections can also mean increased awareness of events negatively impacting friends, loved ones, and even complete strangers, causing increased emotional distress and fear.[9]

Technological advances have also expanded access and choice of news. A 2015 Pew Research study showed that nearly 70% of the those in the US who access internet via their smartphones, follow "breaking news" on their phone and report forwarding pictures and videos depicting news events.[9] For our youth, the Pew Research Center found that almost half do not trust national news sources.[10] Studies show that over half of teens aged 14-18 obtain their news from social media rather than traditional news media. In fact, although television, print, and radio continue to be the preferred news sources for older groups, Instagram and TikTok are the most popular source for news among younger people.[12-13] Algorithms in social media applications are designed to increase frequency of content users engage with. When there is a tragic news story that a teen has investigated, it is likely they will be bombarded with similar stressful and traumatic content, potentially without the tools or resources to properly cope and process information.[14]

Social Media and Trauma Exposure

Researchers have made a clear case that access to social media can be both helpful and dangerous for teens. Dangers include decreased self-esteem/body image, and increased risk of bullying, emotional problems, and sexual violence.[15-16] Adolescents are at high risk for these effects due to their less mature abilities to manage peer pressure and emotional regulation.[16]

In addition, researchers have examined links between trauma exposure and emergence of trauma-related symptoms. Related to large scale disasters, a person's level of proximity to traumatic events and frequency of exposure to news coverage is relevant to their risk for developing trauma-related symptoms.[17] Though it is common to seek information following a large-scale disaster for safety purposes and to mitigate growing anxiety, studies show that viewing images with humans in life-threatening circumstances causes high emotional and physical reactivity.[18] Examples of these types of events in just these past few years have included the invasion of Ukraine, a massacre at an Israeli music festival with retaliation leading to tens of thousands of harmed children and families in Israel and Palestinian territory, mass shootings at public places, natural disasters across the globe, and severe child maltreatment. While television news has been studied to determine the effects of graphic news content on individuals, we have only limited research regarding the impact of news gathering via social media on youth and adults.[10]

Sequalae of Vicarious Trauma

Vicarious (or secondhand) trauma is conceptualized as a change or threat to one's beliefs, assumptions, and expectations about the self and/or the world that occurs due to exposure to stories, evidence of or disruption in one's safety, trust, esteem, independence, and frame of reference.[18] In essence, it is a fundamental shifting of what we know or believe to be true about the world, that distresses us and

creates fear, dread, and the symptoms of traumatic experience despite the trauma being non-personal.

This experience of vicarious traumatization has been observed in individuals working first-hand with eyewitness news media covering traumatic events,[19] citizens viewing COVID-19 pandemic media or bombings,[20] and in communities exposed to systemic or structural violence.[21] At this time, there are limited studies on the effects of media consumption and occurrence of vicarious trauma in children and adolescents. As reviewed above, we know there is a direct correlation between length of exposure to traumatic narratives, frequency of observation, intensity, and/or proximity to worldview-changing aspects of vicarious exposures to the occurrence of vicarious traumatization in individuals, which we can assume is similar in youth populations. Recognizing the symptoms, early unhealthy sequalae, and functional impairments is crucial in the primary care setting, as early identification and intervention can be invaluable. The symptoms are often very similar to those of PTSD, but do not have a crucial element of threat to self (at least not directly; first criterion). Figley identified three categorical effects including: 1) psychological distress or dysfunction, 2) cognitive shifts, and 3) relational disturbances.[22-23] These categories generally focus on impairment in typical functioning and shifts from baseline for the individual in question.

Behavioral effects can include: nightmares (usually about content or emotionally-related content to that which is observed), intrusive thoughts, disturbing imagery (often intrusive), avoidance of material, sleep disturbance, somatic complaints (stomachaches, headaches, dizziness, fatigue), physiological arousal (increased heart rate, breathing, jitters), disruption to interpersonal relationships, difficulty with school or work, and/or counterintuitive insistence of consuming more related content. Emotional effects can include: anger, sadness, anxiety, numbing, and/or low mood/depression. And finally, cognitive effects can include: change in worldview, paranoia/heightened sense of vulnerability, increase in distrust, increased dependency, sense of helplessness, and/or externalizing of locus of control.

In contrast to adult presentations of PTSD, it is essential to recognize that early trauma-related symptoms in children are often more nuanced. This has been recognized in the DSM-5 with subtypes for children six and younger and is largely recognized in the field as limiting when describing vicarious traumatization or stress. The symptoms listed above may combine, be more intense in one area over another, or be presented more by impairments in role or life than internalized experiences. For example, in children and adolescents, exposure to trauma, particularly in a repeated way, can create a youth who is more insecure in their safety in the world, wary of others, and generally more suspicious.[24] Motta highlights that children and adolescents' experience of trauma often presents as a "pervasive and persistent alteration of one's self-view and a wary take on their environment," suggesting that our youth may be forever changed by their experiences of trauma, regardless of intervention. [24]

What Can Providers Do?

Universal Screening

Add screening questions to capture social media trauma exposure and negative mental health sequelae. Provide explanation and choice of participation in screening questions to yield more engagement from patients.[25] This can be as simple as voicing: "I want to make sure my patients are safe and managing stress as best they can. We know that what young people see on screens, including things in the news or on social media pages, can be scary or disturbing. I'd like to assess your level of screen interaction, and any struggles related to this. You can choose to answer or not." Then asking: 1) Do you access news media, including social media sites like TikTok? 2) Are there times you feel bad, sad, or scared after viewing news about local, national, or international events? and 3) Have there been times someone has frightened or harmed you through social media (e.g., online bullying) recently or in the past?"

If they screen positive to questions #2 or #3, consider offering a PTSD symptom screener, such as the Adolescent Primary Care Traumatic Stress Screen (APCTSS*) below. [26]

In the past month, have you: 1) Had bad dreams about scary experiences or other bad

dreams? 2) Had upsetting thoughts, pictures or sounds of scary experiences come into your mind when you didn't want them to? 3) Tried not to think about or have feelings about scary experiences? 4) Been mad at yourself or someone else for making the scary experiences happen, not doing more to stop it, or to help after? 5) Felt jumpy or easily startled, like when you hear a loud noise or when something surprises you? (*Two or more positive responses on the APCTSS indicate concern for PTSD.)

If risk of PTSD or trauma-related symptomology are identified, there exist a number of evidence-based interventions that reduce trauma responses in youth and families, such as Trauma-Focused Cognitive Behavioral Therapy. Consider referral to a behavioral health clinician who treats PTSD.

Guidance During Times of Crisis in the News

For all patients seen in primary care settings and healthcare settings for youth, it is important to assess and provide education regarding exposure to trauma.[27-28] The following recommendations can be utilized both as prevention and in response to concerns expressed, whether screening is negative or positive.

Safety Check-Ins, Assess Reactions

Exposure to news during times of disaster can exacerbate feelings of hopelessness, anxiety or overwhelm. Assess thoughts of suicide, hurting self or others, or fear of dying. Ask what upsets or worries them about what is going on? How are they coping with their feelings? Validate their concerns when possible. "What is happening is awful. It's upsetting to see others going through this. Your reactions are understandable." Fact check if needed. Remind them that social media feeds are not always accurate information. Put into context. When appropriate, clarify they are not directly in harm's way. Remind caregivers and youth they can call 988 any time if concerns arise.

Empower

Help them focus on what they can control rather than on what they cannot control. Suggest finding ways they can provide positive impacts. Are they able to volunteer for organizations supporting their interests related to the event? The more individuals feel like they can make meaningful contributions to situations, the less likely they will experience negative stress responses.

Maintain Routines

Encourage returning to regular schedules. Structure can reduce perceptions of anxiety and unpredictability.

Limit Exposure

Recommend refraining from watching news 24/7. Turn off news notifications. Turn phone and news off at bedtime to allow stress response to return to baseline. Encourage social media breaks.

Engage Caregivers

Check-in with the caregiver. Do they have the resources they need? Youth take cues from caregivers and other adults around them. Encourage caregivers to model healthy technology use, coping with news, and coping with distress. If caregiver needs to vent or discuss further, suggest they do so with adult friends, family, or therapist rather than with their youth. Encourage healthy family connections and viewing material together with supervision, digestible dialogue, and support offered.

Future Directions

Thus far, much of the research and clinical decision-making processes related to trauma have focused on symptoms following traumatic events directly involving an individual or someone they know. However, there is a growing awareness that our youth and adults are experiencing stress responses to vicarious exposure to local, national, and international events due to current levels of access to information and interaction via electronic devices and social media. The following areas of research would expand our current understanding: the impact of different types of media on vicarious trauma symptoms; feasibility and acceptability of screening for vicarious trauma in medical clinics with patients/families; risk and protective factors for vicarious

trauma via electronic means; screening tools to assess for exposure to vicarious trauma and presence of vicarious trauma symptoms; treatment recommendations for vicarious trauma; and effective structural interventions for youth social media use (e.g., phone free zones).

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Call It When You See It: Major League Soccer Organization and Pediatric Hospital Team Up for Anti-Bullying Program

by Ram Chettiar, DO

Children's Mercy

Creating an anti-bullying culture, celebrating kindness in the schools, and providing bullying resources for our community partners to bring an awareness and hope that we can put an end to this longstanding problem.



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Abstract

Bullying remains a widespread social issue in the United States (US). Those who bully, are bullied, or witness bullying may experience negative emotional and physical consequences.[1] To address the gap in accessible youth bullying interventions, Children's Mercy Kansas City partnered with Sporting Kansas City to develop Red Card KC, a bullying awareness program focusing on the impact of bystanders in bullying situations. The program is delivered to school and community partners through interactive assemblies educating youth on recognizing bullying, managing bullying situations, and standing up against bullying. Red Card KC has also partnered with schools to recognize and celebrate students who show kindness within their schools and communities. By targeting bystanders in bullying situations, the Red Card KC program empowers youth to come together in the fight against bullying.

Bullying

Bullying is a term that is familiar to all of us and has been present in schools throughout history. However, the ways in which youth experience bullying have evolved over time, and no clear unified strategy to manage these concerns has emerged. The most accepted definition for bullying requires three criteria to be met: 1) unwanted aggressive behaviors with an intent to inflict harm on another person, 2) an observed or perceived imbalance of power; and 3) the behavior occurs repeatedly or is likely to be repeated.[2] This definition distinguishes bullying from teasing, where there is no intent to harm and everyone is having fun; conflict, where power is equally balanced; and a mean moment, which is an isolated incident unlikely to be repeated.

Types of bullying may fall into one of five categories.[3] Traditionally, bullying was only thought of as physical, verbal, or emotional in nature. Physical bullying may include actions such as hitting, kicking, pinching, or spitting. It may also include taking someone's things or rude

gestures.[3] Verbal bullying includes teasing, name-calling, taunting, or threatening.[3] Emotional bullying includes leaving someone out, spreading rumors, or purposefully embarrassing someone.[3] In recent years, bullying categories have broadened to include sexual bullying and cyberbullying. Sexual bullying includes inappropriate actions based on someone's sexuality or gender. This may involve sexual statements, inappropriate touching, or even sexual assault or rape.[3] Cyberbullying has gained prominence since the emergence of social media and includes posting or sharing negative, harmful, false, or mean content about someone through digital media, (e.g., social media, text, direct message, email).[3]

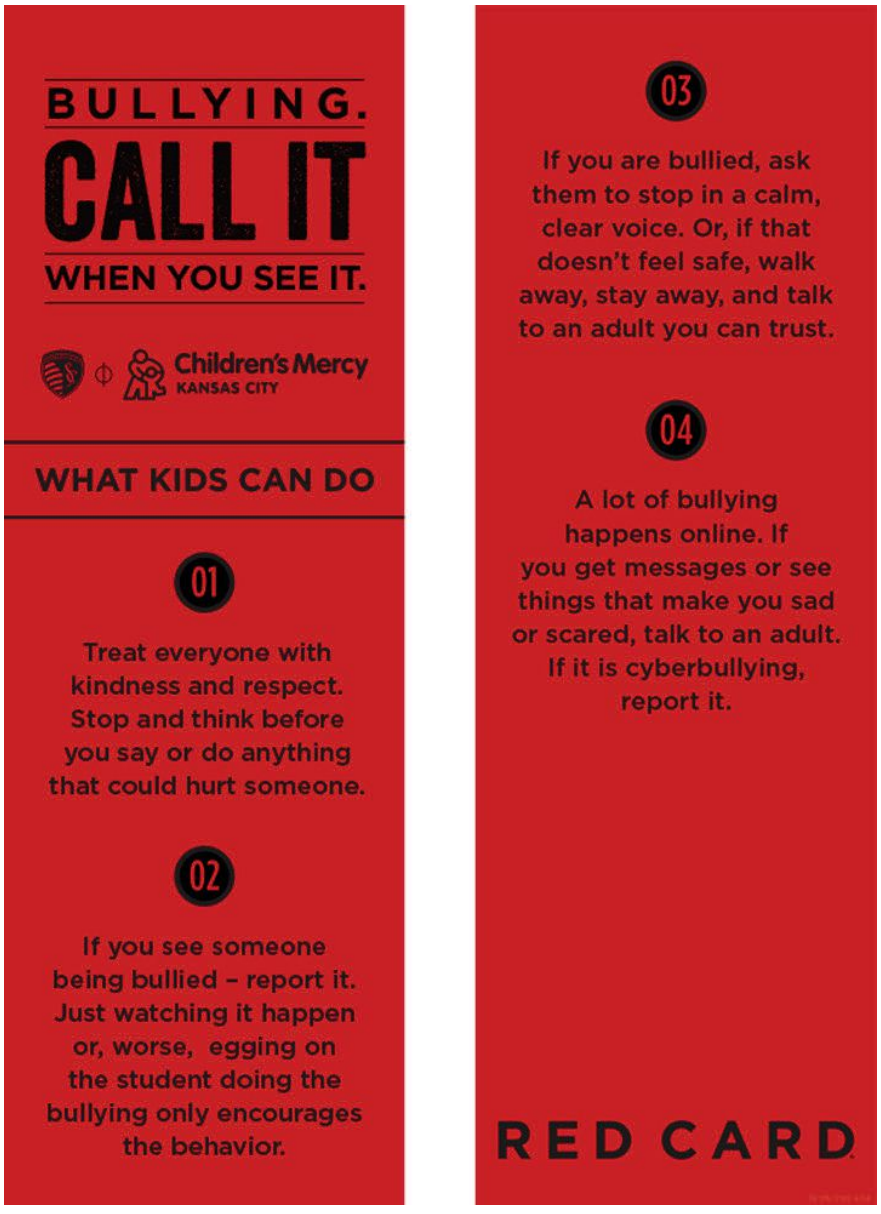
The Youth Risk Behavior Surveillance Survey (YRBSS) found that about one in five high school students reported being bullied on school property, and another one in six reported being cyberbullied in the last year.[4] Prevalence of bullying is highest in the middle school years (28%), followed by high school (16%), and primary school (9%).[5] Female students report being bullied at higher rates than male students (30% compared to 19% respectively).[4] Rates of those who are bullied rise to 40% in those who identify as lesbian, gay, or bisexual.[4] The Gay, Lesbian and Straight Education Network (GLSEN) collects data on gender and sexually diverse youth and reports that 60% of transgender youth have reported being harassed due to their gender expression.[6] Several other factors may contribute to certain youth being targeted for bullying including appearance, disabilities, race, religion, social skills development, and socioeconomic status.[7]

Bullying negatively impacts not only those who are bullied, but also the individuals who are bullying others. Immediate impacts of bullying include both physical injury and emotional distress. Studies have shown that those who are bullied are at higher risk for depression, anxiety, sleep difficulties, lower academic achievement, and dropping out of school.[8] On the other hand, youth who bully others are at increased risk of dropping out of school, physical violence, vandalism, early sexual activity, criminal convictions, and substance misuse.[8,9] The World Health Organization (WHO) recognizes the significant mental and physical health impacts of bullying on youth with longstanding effects well into adulthood, calling it a significant public health problem warranting urgent attention.[10]

The focus of bullying situations often lands on the person doing the bullying and the person being bullied. The role of bystanders in these scenarios are commonly overlooked. Bystanders are present in 85% of bullying situations and provide an audience, reinforcing the bullying.[11] Removal of the audience in bullying situations should not only mitigate the risk for bullying to occur, but will also reduce the negative impacts that bullying has on those who witness it, even when they are not direct participants.[12] Schools who implement bullying awareness programs that focus on a bystander intervention are likely to be more successful in eliminating bullying and peer victimization behavior.[13] Bystanders also have the ability to potentially intervene with the person doing the bullying to show that they do not agree with these actions and will not stand for it. Bystanders also have the opportunity to follow up with the person who was targeted to show that they care, do not support the bullying, and may assist in finding help, if necessary.

Between the years 1999 and 2015, anti-bullying legislation has been passed across the United States in all 50 states and the District of Columbia.[14] According to the United States Department of Education, Office of Civil Rights, schools are required to eliminate hostile environments and take steps to prevent harassment from reoccurring.[14] The impact of this legislation may not be clear as schools are not provided financial resources or guidance to improve school climate or security. School-based interventions around bullying have been tried in the United States and across the world with positive results in reducing bullying behavior and improving mental health outcomes in youth.[15] These interventions may include school-wide rules and sanctions, teacher training, classroom rules around peer victimization, conflict resolution training, as well as collaborative efforts with parents and caregivers.[16] Anti-bullying intervention has been shown to reduce peer victim perpetration by up to 23% and peer victimization by up to 20%.[17]

Figure 1. Example of a Bullying "Tip Card"



Red Card KC

Recognizing the gap in guidance for schools and the lack of resources that many schools have in regards the implementation of effective anti-bullying intervention, Red Card KC was developed to support schools in the Kansas City metropolitan area. The program is bringing awareness to bullying within the community and filling the gap that many schools face with a novel anti-bullying intervention to address this need (Figure 1).

Red Card KC is a bullying awareness program primarily targeting bystanders in bullying situations. In 2016, a partnership was formed between Children's Mercy Kansas City hospital system and the Major League Soccer (MLS) team, Sporting Kansas City. This union began with a naming rights agreement between the hospital system and the MLS team for Sporting Kansas City's home stadium, Children's Mercy Park. Through this partnership, the two organizations have been working together to create positive change in the health and wellbeing of the Kansas City community.[18] This collaboration has naturally emphasized focused on the health of youth. The need for a community-wide bullying awareness program was determined through a community needs assessment, discussions with community partners including schools and law enforcement, and valuable feedback from the Children's Mercy's Patient Family Advisory Council's Teen Advisory Board—a board made up of past and present Children's Mercy patients between the ages of 13 and 18, recommended by Children's Mercy staff members. The program operates under the Children's Mercy's Communications and Marketing department through their Brand Partnerships program along with Sporting Kansas City's Partnership Marketing

department. There are currently two medical advisors who oversee the educational content and curriculum for Red Card KC, who are faculty members of the Division of Developmental and Behavioral Health and within the section of Clinical Psychology and section of Child and Adolescent Psychiatry. The program currently has enrolled over 60 schools and community partners in the Kansas City area and continues to grow every year.

The campaign uses a "red card" as a visual tool to empower youth to exemplify its motto, "Call it when you see it," just as a soccer referee would show a "red card" to a player after a serious offense (ejecting that player from the game and leaving the team shorthanded for the remainder of the game). Soccer is a sport that is growing in popularity within the United States, and by virtue of being played around the world, provides a natural environment for athletes to come together from different backgrounds to compete as a part of a team. Athletes have served as role models for youth throughout history, dating back to Ancient Greece.[19] The Red Card KC campaign recognizes the power that professional athletes have in their influence on youth and was able to create a clear, simple, and strong message for youth to "Call it when you see it" at schools and within their communities around Kansas City. The perspectives of professional soccer players are valuable in the messaging of the campaign where they are effectively able to illustrate the analogy that just as a "red card offense" in soccer let's the whole team down, taking part in bullying behavior lets the school community down.

The program is delivered to school and community partners through resources educating youth on recognizing bullying, managing bullying situations, and standing up against bullying. It provides red "tip cards," printed in English and Spanish, to community partners with tips for kids, parents, teachers, and coaches to address bullying situations. It also provides scripts for public address (PA) announcements around bullying awareness for schools during October, Bullying Awareness Month. Red Card KC-branded posters depicting students overcoming diverse bullying situations (including body shaming, verbal abuse, cyberbullying, and discrimination) are provided to community partners to raise awareness and inspire students to stand up to bullying within the schools. A monthly newsletter called "Play Your Cards Right," is sent out to partners of the Red Card KC program and shares stories around acts of kindness and inspiration. Red Card KC-branded signage is provided for athletic fields and stadiums with rules for sportsmanship. The Children's Mercy Kansas City medical advisors for the Red Card KC program also serve as resources for community members or groups who would benefit from additional supports including providing educational talks and workshops.

"Call it when you see it" is a call to action for bystanders to stand up to bullying and show that it will not be tolerated in their communities. An important goal of this message is to teach students the values of kindness, empathy, and the importance of creating a strong, caring school community where the members look out for one another, just as teammates on a soccer field might do. Red Card KC puts on interactive assemblies in elementary and middle schools on both the Kansas and Missouri sides of the Kansas City metro during October. These assemblies are presented by a Children's Mercy mental health professional, a Sporting Kansas City professional soccer player, the official mascot for Sporting Kansas City ("Blue the Dog") and a school administrator. The assemblies provide a platform for the school administration to share the school's policies around bullying and that students are supported and safe within the school. The Children's Mercy mental health professional provides students education around the impact of bullying on mental health and what to do if someone finds themselves in a bullying situation or is a witness to a bullying situation. The professional soccer player shares his personal experiences overcoming bullying or feeling like an outsider. Blue the Dog brings joy, excitement, and comedic relief to an otherwise serious and important conversation. Considering the growing number of community partners and limited resources to provide in-person assemblies, Red Card KC has also developed a "virtual assembly" that is provided to schools who do not receive an in-person assembly, along with the educational

material and resources provided to all school and community partners. The program also recognizes and celebrates students who show kindness within their school and communities by presenting them as KITS Champions—standing for "Kindness In the Schools," where "kit" is another name for a soccer uniform. There are two students chosen per school based on a process of nomination by their peers and teachers. These students receive a letter recognizing their achievement, a Sporting Kansas City jersey, a commemorative Red Card KC and Sporting Kansas City-branded soccer scarf, and recognition on the field of a Sporting Kansas City match that year.

Conclusion

Children's Mercy Kansas City and Sporting Kansas City recognize the widespread negative social impacts of bullying in our community and nationally. In the midst of a youth mental health crisis in the United States, it is essential that we stand up to bullying and "Call it when you see it." Bystanders play a critical role in putting an end to bullying and are the primary targets of the Red Card KC campaign. Creating an anti-bullying culture, celebrating kindness in the schools, and providing bullying resources for our community partners to bring an awareness and hope that we can put an end to this longstanding problem.

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A Practice Primer and Update on Anti-Bacterial Resistance

by Pak Ho Au, MD, Mustafa Gandhi, MD, Kathryn Deere, PharmD, Jina Patel, PharmD & Hariharan Regunath, MD

This is a practice primer on antimicrobial resistance, new-found mechanisms and the spectrum of clinically important newer antibiotics.



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Abstract

Antibiotic resistance is driven by inappropriate antibiotic use. Multi-drug resistance is a rising concern in Gram-negative bacteria. Prompt recognition and appropriate antibiotics are needed for improving outcomes. This is a practice primer for clinicians in the management of resistant infections that summarizes mechanisms, treatment, updates and the spectrum of activity for newer antibiotics, most relevant to current clinical practice.

Introduction

Antibiotic resistance is primarily driven by the selective pressure from antibiotic use. Subtherapeutic doses improve growth rate, reproduction, and feed utilization in animals, serving as reservoirs.[1-3] Antibiotic resistant human infections increase hospitalization, cost, and long-term disabilities.[4,5] An understanding of the resistance patterns to relevant antibiotics, enables appropriate antibiotic use and thereby facilitating stewardship.[6,7] This is a practice primer on antimicrobial resistance, new-found mechanisms and the spectrum of clinically important newer antibiotics.

How to Determine Risk for Drug-Resistance for Empiric Therapy?

A detailed history and review of prior infections are vital.[8-10]

Recent Antimicrobial Use

Antibiotic use within the preceding six months fosters resistance, and it is even higher when within 30 days.[8,9,11] β-lactams and fluoroquinolones are associated with multi-drug resistant (MDR) infections.[8,12] Intravenous antibiotic use within the past 90 days is a risk for methicillin resistant *Staphylococcus aureus* (MRSA) and drug-resistant *P.aeruginosa* in hospital-acquired pneumonia.[13]

The Setting (Community/ Nosocomial/Travel/Contacts)

Vancomycin resistant *Enterococcus* (VRE), carbapenem-resistant *Acinetobacter* species and MDR *P.aeruginosa* are pathogens associated with nosocomial settings, whereas, MRSA and extended spectrum β-lactamase (ESBL) producing *Enterobacterales* have now become prevalent in the community.[5]

Prior Colonization/Infections

Colonization precedes infection, e.g., MDR Gram-negatives colonize the aero-

digestive tract of patients in long-term care facilities or intensive care units.[14,15] Empiric antibiotic spectrum must encompass a preceding infection within the previous six months. MRSA colonization or prior infection is a risk factor for invasive MRSA infection.[16,17]

Comorbidities

An underlying cerebrovascular accident is an independent risk factor for MDR *P.aeruginosa* infection while solid cancers are associated with a lower risk.[18] Cirrhosis, diabetes mellitus, cardiovascular disease, and neurogenic bladder are associated with quinolone resistant *E.coli* infections.[19]

Institutional Antibiogram

If the institutional antibiogram reveals <80% susceptibility (interpreted as >20% resistant) to an antibiotic, that agent may not be an efficacious empiric choice.[9]

What is New in Resistance Mechanisms?

The traditional mechanisms are 1) inactivation, 2) target-site modification, 3) uptake/penetration limitation, and 4) efflux. Intrinsic resistance is from innate (genetically mediated) structural changes in the outer-membrane, efflux pumps or other mechanisms e.g. glycopeptides (vancomycin) cannot enter the outer-membrane of Gram-negatives, aerobic bacteria inactive metronidazole, mycoplasma/ureaplasma lack cell wall rendering β-lactams ineffective, etc. Acquired resistance evolves from the selective pressure of antibiotic use, where resistance genes are acquired from other alive (transduction or conjugation) or dead bacteria (transformation), or spontaneous mutations.[20] New-found mechanisms include antibiotic tolerance and antibiotic persistence, both facilitated by antibiotic pressure.[21,22] Antibiotic tolerance is the ability of a bacterial population to survive brief duration of bactericidal antibiotic treatment, i.e., susceptible *in vitro*, but *in vivo*, they slow down the processes responsible for drug-killing. Antibiotic persistence denotes a heterogenous sub-population of persisting bacteria within the usually determined duration of treatment. There are no tests yet, to detect them, as they are exhibited *in vivo* only.[21]

Why Are Gram-Negative Bacteria Efficient in Their Resistance Mechanisms?

Gram-negatives have an outer-membrane beyond the cell wall, creating a periplasmic protected space to conserve β-lactamases, whereas, Gram-positives excrete them into their environment, and eventually diffuse away lowering their efficacy.[23] Table 1 summarizes the resistance mechanisms of Gram-positives.[24] Figure 1 displays the array of enzymatic and non-enzymatic mechanisms in Gram-negatives, of which, β-lactamases are the most common.[25-27] They are classified either by molecular/amino-acid structure (Ambler classes) or based on substrate and inhibitor profiles (Bush and Jacoby, more relevant to clinical practice). Resistance profile widens from penicillinases (resistant to penicillin, first and second generation cephalosporins) and cephalosporinases (AmpC) to extended spectrum β-lactamases (ESBL, resistant to third generation cephalosporins) and carbapenemases (Table 2).[26,27] The resistance genes are either constitutively present (AmpC) or acquired (including plasmid).[28] Other mechanisms include reducing the number of porin channels (carbapenems) in the cell wall or an extracellular biofilm, (e.g. *Pseudomonas*) that limits antimicrobial penetration and host-immune response.[29,30]

What is the Meaning for Susceptible, Resistant and Intermediate Results?

The Clinical and Laboratory Standards Institute (CLSI) and the Food and Drug Administration (FDA) publish specific minimum inhibitory concentration (MIC) breakpoints or cut-off values that differ between genera/species.[31] Susceptible (S) means a high probability and resistant (R) means a low probability of efficacy at the usual doses of that particular antibiotic for a pathogen. Before 2014, intermediate (I) meant that usual doses have a lower probability than S, but a higher-than-normal dose can still be efficacious for certain body sites where the drug is concentrated better. Later, the CLSI introduced the term "susceptible-dose-dependent" (SDD) for cefepime in *Enterobacterales* —where the maximum approved dose or frequency or both could be efficacious. By 2019, SDD categories were established for daptomycin and *E.faecium*, and ceftaroline and *S.aureus*. In 2020, "I" was re-

Table 1. Resistance Mechanisms in Clinically Important Gram-positive Pathogens

Pathogen and Resistance Strategy	Antibiotic resistance	Gene(s) Involved	Comments
Staphylococci			
Drug inactivation	β-lactams (penicillins with or without cefazolin[a])	*blaZ*	Plasmid-encoded β-lactamase, hydrolyzes penicillins; isoxazolyl penicillins (eg, nafcillin), cephalosporins,[a] and carbapenems are stable
Target replacement	β-lactams	*mecA*	PBP2a has low affinity for β-lactams (except ceftaroline and ceftobiprole)
	Vancomycin (VRSA)	*vanA* Gene cluster	Acquired from enterococci; rare isolates described
Target modification	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins *cfr*	Mutations in 23S rRNA genes are main mediators of resistance; *cfr* gene is the only transferable determinant of LNZ-R
	Ceftaroline	*pbp2a*	Mutations in *pbp2a* associated with high-level ceftaroline resistance (MIC >32 µg/mL)
Changes in cell surface adaptation	Vancomycin (VISA)	*vraRS, yycFG, graRS, rpoB*	Many genes involved in the resistance phenotype, most related to regulatory systems
	Daptomycin	*mprF, dlt, vraRS, yycFG, pgsA, cls*	Many genes involved in the resistant phenotype; main pathway seems to be repulsion of the antibiotic through an increase in the net positive charge of the cell envelope
Enterococci			
Drug inactivation	β-lactams (penicillins)	*blaZ*	Rare, found mostly in *E. faecalis*
Target replacement	Vancomycin	*van* Gene clusters	Several gene clusters described, most acquired on mobile elements; intrinsic low-level resistance seen in *E. gallinarium* and *E. casseliflavus* (VanC phenotype)
Target modification	β-lactams (penicillin and ampicillin)	*pbp5*[b]	PBP5-R differs from PBP5-S in only about 5% of amino acid sequence; certain amino acid substitutions have been directly implicated in ampicillin resistance (see text)
	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins, *cfr*	Rare, mutations in 23S rRNA and L3/L4 are similar to those found in staphylococci, as is the *cfr* gene
Changes in cell surface adaptation	Daptomycin	*liaFSR, yycGF, gdpD, cls*	Most frequent mutations found in daptomycin-resistant clinical isolates; many genes involved; resistance pathways differ between *E. faecalis* and *E. faecium*
Streptococci			
Target modification	β-lactams (penicillin)	PBPs (*pbp2x*, *pbp2b* in pneumococci), *murM*, *cpoA*, *pdgA*	PBP changes are the most important determinant of β-lactam resistance; mosaic PBPs are often found in penicillin-resistant isolates
	Linezolid	23S rRNA genes, L3/L4 ribosomal proteins, *cfr*	Rare
Unknown	Daptomycin	Unknown	Rapid development of daptomycin resistance in certain species of streptococci

Abbreviations: LNZ-R, linezolid resistance; MIC, minimum inhibitory concentration; PBP, penicillin-binding protein; rRNA, ribosomal RNA; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *S. aureus*. [a] The ability of certain types of staphylococcal β-lactamase to hydrolyze cefazolin may cause therapeutic failures. [b] PBP5 (encoded by *pbp5*) is part of the core genome of enterococci. Because of its decreased affinity for penicillin, it is responsible for the natural tolerance of these organisms to β-lactams. Reproduced with permission from reference 24

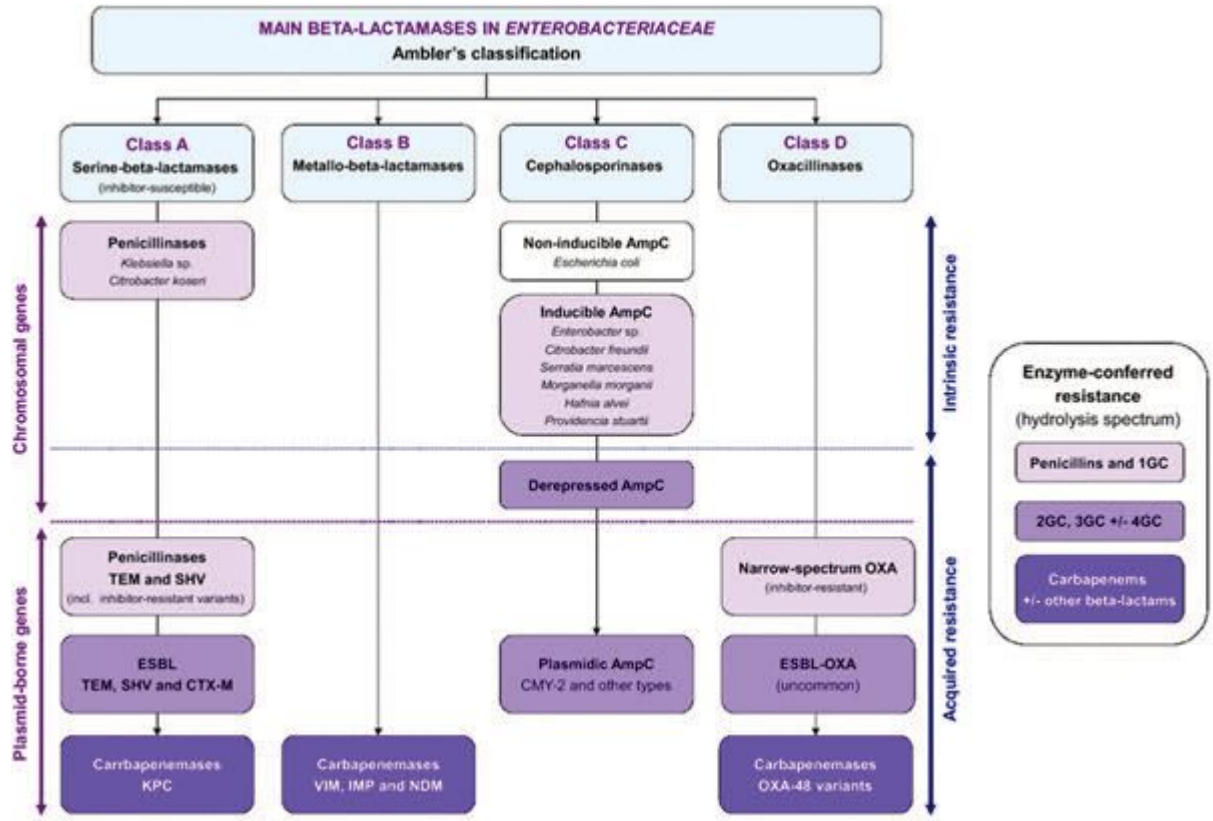
defined as antibiotics with a potential to concentrate at certain sites, e.g. urine, and the S category was eliminated for colistin/polymyxin B.[32]

What Are the Current Testing Methods and Limitations?

Phenotypic Methods

The Kirby-Bauer disk-diffusion method (qualitative) method, uses antibiotic disks on inoculated agar plates and incubated for 16 to 24 hours.[33] The diameter of inhibition (clearing) provides interpretation, but without the MIC value, automation and validation for fastidious and slow-growing bacteria.[34-36] The broth (macro- and micro-) dilution, and gradient methods (E-test) measure the MIC.[35] They precisely compare antibiotic effectiveness on specific pathogens, e.g., in viridans streptococci endocarditis, treatment differs by the penicillin MIC. Limitations are cost,

Figure 1 Gram-negative β—lactamases' classification
Source: Reproduced with permission from reference 25



labor, and longer time.[37] Micro-dilution has been miniaturized, automated, and commercialized as pre-prepared frozen or dried plastic trays containing 96 microwells with serial antibiotic dilutions (12 antibiotics in eight two-fold dilutions), saving space, reagent, and time to results, but the pre-fixed antibiotic choices is a limitation. There are four FDA-approved commercial systems that provide results within three to 24 hours, and are most widely used in US labs.[36,38]

Genotypic Methods

Several FDA approved polymerase chain reaction (PCR) and deoxyribonucleic acid (DNA) hybridization tests detect many resistance genes.[39] Advantages are the automation, objectivity, and rapid results from clinical or culture specimens.[40] Limitations are cost, low throughput and over-reporting, i.e., presence of the gene not necessarily meaning *in vivo* resistance. Useful, when for a single gene mediated resistance, and not for mechanisms involving multiple genes. Nevertheless, they're handy for stewardship, e.g. a negative nasal PCR for MRSA enables discontinuation of empiric vancomycin).

Mass spectrometry (matrix-assisted laser desorption/ionization—time of flight, MALDI-TOF) measure the mass-to-charge ratio of a sample and allows rapid detection of susceptibility-linked biomarker ions and thus allow for the indirect discovery of predominantly chromosomally encoded resistance genes.[41]

Presently there are no approved methods to determine biofilm, "antibiotic tolerance," or "antibiotic persistence."[21,42]

How Do You Recognize Resistant Pathogens in Day-To-Day Practice?

The detection of *mec* A in staphylococci or *van* genes in enterococci, from positive blood cultures or sputum samples, is one way (Table 1). This is unavailable for other tissue specimens.

Table 2. Resistance patterns of β-lactamases in Gram-negative pathogens

β-lactamases	1st GC	2nd GC	Cefoxitin	3rd GC	4th GC	Carbapenem	Aztreonam	Inhibition by β-lactamase inhibitors
Low Level AmpC								
High-level AmpC								
ESBL								
KPC								
NDM								

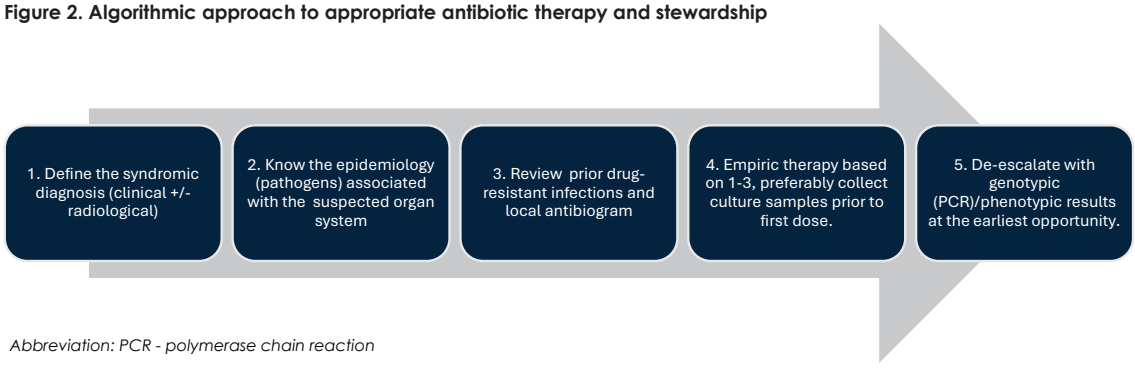
GC – generation of cephalosporins, ESBL – extended spectrum β-lactamase, KPC – Klebsiella pneumoniae carbapenemase, NDM – New Delhi Metalloproteinase, green - susceptible, yellow – variable, red – resistant.

Table 3. Classification of carbapenemases

Serine carbapenemases	Metallo-carbapenemases
KPC, IMI, SME, OXA-48, OXA-181, OXA-23, OXA-40, OXA-58	NDM, VIM, IMP

Abbreviations: IMI, imipenem-hydrolyzing β-lactamase; IMP, imipenemase metallo-β-lactamase; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillin carbapenemase/oxacillinase; SME, Serratia marcescens enzyme; VIM, Verona integron-encoded metallo-β-lactamase.

Figure 2. Algorithmic approach to appropriate antibiotic therapy and stewardship



Abbreviation: PCR - polymerase chain reaction

Gram-negative bacteria that harbor an inducible AmpC, are often abbreviated as SPACE/SPICE [*Serratia marcescens, Providencia stuartii, P aeruginosa, Acinetobacter*/Indole-positive *Proteus*, *Citrobacter* and *Enterobacter*].[26] The degree of gene expression (low-level or high-level, see Table 2) determines their susceptibility results. At low-level (gene-repressed), results will show resistance to first generation cephalosporin, but susceptibility to ceftriaxone. Using ceftriaxone will de-repress the gene, leading to emergence of ceftriaxone resistance *in vivo*, risking treatment failure. Cefepime is the only exception, a weak inducer and resists AmpC hydrolysis by forming a stable acyl enzyme complex.[26,43] There are no approved tests for AmpC detection and its inducibility. Acronyms have limitations, e.g., *C.freundii* has AmpC, but not *C.koseri*; and Indole-positive *Proteus* now include *Morganella morganii* (renamed), *Enterobacter aerogenes* is now called *Klebsiella aerogenes*, etc.[26] In recent years, the acronym HECK-Yes (*Hafnia alvei, Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes, Yersinia enterocolitica*) has replaced SPICE/SPACE among stewardship supporters to emphasize the limitations of acronyms to learners.[44] For ESBL testing, most labs incorporate sequential steps.[45] It is suspected with resistance to a third generation cephalosporins in non-AmpCs organisms or to cefepime among AmpC producers. Growth inhibition by the addition of clavulanate or by

Table 4. Clinical characteristics of ESKAPE pathogens

Species	Resistances	Clinical syndromes	Treatments	
			Serious Infections	Non-serious Infections
Vancomycin-resistant *Enterococcus*	Vancomycin, ampicillin, linezolid, teicoplanin, piperacillin, cephalosporins, multidrug resistant	Catheter-associated-UTI, vascular catheter-associated bacteremia, intra-abdominal and pelvic infection, endocarditis	Linezolid, daptomycin, high-dose ampicillin and sulbactam	Nitrofurantoin[b], doxycycline, fosfomycin, omadacycline
Methicillin-resistant *S. aureus*	Aminoglycosides, β-lactams, chloramphenicol, trimethoprim, macrolides, tetracycline, fluoroquinolones, multidrug resistant	Acute bacterial skin and skin structure infection, bacteremia, pneumonia, osteoarticular infection, endocarditis	Vancomycin, daptomycin, linezolid, tigecycline[a]	Clindamycin, Dalbavancin, lefamulin[μ], omadacycline, oritavancin, trimethoprim and sulfamethoxazole, tedizolid
K. pneumoniae	Polymyxins, carbapenems, fluoroquinolones, third-generation cephalosporins, aminoglycosides, tetracyclines, pandrug resistant	Pneumonia, pyogenic liver abscesses, necrotizing and soft tissue infection, bloodstream infection, meningitis, endophthalmitis, UTI	meropenem, meropenem-vaborbactam, ertapenem and meropenem, imipenem-cilastatin-relebactam, ceftazidime-avibactam, aminoglycosides*, polymyxin combination therapy*, tigecycline [a],	Plazomicin, eravacycline[£]
A. baumannii	Carbapenem, polymyxins, β-lactams, tigecycline, ceftazidime, fourth-generation cephalosporins, multidrug resistant	Ventilator-associated pneumonia, central line bloodstream infections, nosocomial meningitis, skin and soft tissue infection, catheter-associated UTI	Colistin, tigecycline, cefiderocol, eravacycline	
P. aeruginosa	First- and second-generation cephalosporins, piperacillin-tazobactam, aminoglycosides, quinolones, carbapenems, polymyxins, multidrug resistant	UTI, bloodstream infection, ventilator-associated pneumonia, chronic respiratory infection, skin and soft tissue infection, endocarditis	Piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime, meropenem, ciprofloxacin, ceftazidime-avibactam, cefiderocol, imipenem-cilastatin-relebactam	
Enterobacter species	Carbapenem, fourth-generation cephalosporins, fluoroquinolones, β-lactams, polymyxins, multidrug resistant, pan-drug resistant	UTI, bloodstream infection, neonatal pneumonia, skin and soft tissue infection, intra-abdominal infection, endocarditis, septic arthritis	Cefepime, ciprofloxacin, gentamicin, meropenem, piperacillin-tazobactam, imipenem-cilastatin-relebactam	Nitrofurantoin[b]

UTI – Urinary tract Infection

*[b]Nitrofurantoin is prescribed only for uncomplicated urinary tract infections. [a] Higher risk for mortality, use reserved for when no other alternate treatments are suitable. [μ] Limited clinical data on MRSA pneumonia. [£] Klebsiella pneumoniae can easily develop resistance to eravacycline due to mutations in the lon gene. *Significant toxicity and unfavourable pharmacokinetic/pharmacodynamics discourage their use as fist-line agents. Modified with permission from reference 51*

Table 5. Antimicrobial spectrum of newer β-lactams against carbapenem-resistant Gram-negative pathogens. [Part of the data – reproduced with permission from reference 54]

Newer β-lactams	Carbapenemase-producing Enterobacterales			Nonfermenting Gram-negative bacilli	
	Ambler classification			*Pseudomonas aeruginosa* XDR	Imipenem-resistant *Acinetobacter baumanii*
	Class A (prototype: KPC)	Class B = MβL (prototype: NDM)	Class D (prototype: OXA-48)		
Ceftolozane-Tazobactam					
Ceftazidime-Avibactam					
Imipenem-cilastatine-Relebactam					
Meropenem-Vaborbactam					
Cefiderocol					
Avibactam+ Aztreonam					
Cefepime-enmetazobactam					
Sulbactam-Durlobactam					
Cefepime-taniborbactam[a]					
Ceftibuten-Ledaborbactam Etzadroxil[a]					

[a]Antibiotics not yet approved by the FDA; MβL – Metallo β-lactamase; XDR – extensively drug resistant; KPC – Klebsiella pneumoniae carbapenemase, NDM – New Delhi Metalloproteinase

detecting CTX-M, the most common ESBL gene via PCR (limited to blood culture or sputum samples) are confirmatory tests. In summary, AmpC or ESBL can be ascertained from cephalosporin susceptibility patterns (Table 2). The AmpCs are consistently resistant to first or second generation cephalosporins and uninhibited by clavulanate, whereas ESBLs remain susceptible to cephamycins (e.g. Cefoxitin), often exhibit elevated cefepime MIC (SDD or R) and are reliably inhibited by clavulanate (Table 2).[26]

Carbapenem resistance is mediated via carbapenemases (Table 3) or mutational cell wall (porin) alterations reducing drug permeability, in combination with cephalosporinases.[46] The degree of MIC variability depends on the level of expression. Several phenotypic and genotypic tests are approved by CLSI. Laboratory guidance from the CDC is based on prevalence, test performance, labor, and cost.[47] Knowing the carbapenemase type is important because certain newer β-lactam-lactamase inhibitors have limited activity against metallo-β-lactamases (Table 5).[47] Another reason to remain vigilant about carbapenemases is because they're often located on highly transmissible plasmids.[48]

Evaluation and Treatment

Effective approach requires the knowledge of risk factors for resistance and pathogens associated with the most probable clinical syndromes, e.g. pneumonia (pneumococci, staphylococci, etc.), urinary tract infection (Gram-negatives), etc. (Figure 2), and which pathogens consistently harbor resistance (e.g., SPICE/HECK-Yes pathogens)[49,50] Reliable antibiograms are updated at least annually and contain reports of only organisms with data for ≥30 isolates for optimal reliability.[51,52] Carbapenems are the recommended first line agents for serious infections caused by AmpC or ESBL pathogens. Quinolones or trimethoprim-sulfamethoxazole can be used for de-escalation if susceptible, but could be initial choices for non-severe infections, e.g., uncomplicated urinary tract infections. ESBL genes and other resistance genes are often in proximity and co-expressed, thus a higher likelihood for MDR among ESBLs.[8] The Infectious Diseases Society of America (IDSA), provides more detailed expert guidance for management of MDR Gram-negatives.[8] *E faecium, S aureus, K pneumoniae, A baumannii, P aeruginosa and Enterobacter* species (ESKAPE pathogens) were designated a "priority status" by the World Health Organization (WHO).[53] Biofilms, antibiotic tolerance and persistence are additional mechanisms underlying these pathogens. Table 4 summarizes their key clinical characteristics. Table 5 provides the antimicrobial spectrum of newer

β-lactams that are currently in use and those with promising data likely to be available soon.[54-57] Finally, consultation with infectious diseases improves outcomes and is recommended in the management of drug resistant and difficult to treat organisms, because of effectively exercising the above principles of practice.

Future Perspectives

The WHO has recently updated an expanded list of 15 priority pathogen families, grouped into critical, high, and medium categories for research development and public health measures.[58] They have also published the pipeline of antibacterial products in clinical development (phase I-III clinical trials) from 2017 to 2023, several are targeted towards these priority pathogens and most are in North America and Europe.[59] Their website provides an elaborate review of those in the pipeline. [59]

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Results of an Outpatient Antibiotic Stewardship Survey in Missouri

by Katheryn Ney, MPH, Michael J. Durkin, MD, Mary C. Politi, PhD, Viktoria Vonder Haar, BS, George Turabelidze, MD, PhD & Kevin Hsueh, MD

Missouri antibiotic prescribers who responded to our study reported regularly accessing guidelines and utilizing evidence-based educational materials about antibiotic use.



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Abstract

Objective

To understand the perceptions, knowledge, and opportunities to improve antibiotic prescribing practices among outpatient providers.

Methodology

We disseminated a survey to a convenience sample of primary care and internal medicine physicians and mid-level providers practicing in the state of Missouri.

Results

Sixty-seven providers completed the survey. Most (64%) providers reported reviewing best practice guidelines and educational materials on a regular basis. Providers were most interested in patient-facing educational materials that would help support best practices. However, substantial variability existed in responses about antibiotic prescribing; some (15%) respondents stated that they rarely review guidelines or use antibiotic stewardship resources. Providers felt that any feedback about antibiotic prescribing practices should be provided via email and should focus on reducing antibiotic use for viral conditions.

Conclusion

Missouri survey respondents generally support appropriate antibiotic use to address antibiotic resistance. However, findings also suggest that delivering resources to targeted populations of over-prescribers may be beneficial. Future interventions should include physician-endorsed education to support safe antibiotic use and explore electronic feedback for viral conditions.

Introduction

Supporting antibiotic stewardship is a public health priority to help reduce antibiotic resistance and improve patient safety. Public health officials have been working to improve antibiotic use in outpatient settings. However, outpatient antibiotic prescribing trends have remained largely unchanged.[1]

Several state health departments have started using large datasets to evaluate outpatient prescribing practices to identify areas for improvement. This process has included examining individual physician prescribing patterns, assessing variability between prescribers, identifying high and low outpatient prescribers of antibiotics, and assessing antibiotic appropriateness for common

Table 1. Demographic information of survey respondents.

Demographics					
Years in Practice Years	***N***	***%***	***Practice Location Location***	***N***	***%***
1 to 5	20	30	Rural	2	3
6 to 10	13	19	Small town	10	15
11 to 20	17	25	Large town	9	13
21 or more	13	19	Metropolitan	42	63
Did not specify	4	6	Did not specify	4	6
Provider Specialties Type	***N***	***%***	***Gender Identity Gender Type***	***N***	***%***
Internal Medicine	31	46	Male	28	42%
Family Medicine	23	34	Female	33	49%
Pediatrics	3	4	Prefer not to say	2	3%
Infectious Diseases	5	7	Did not specify	4	6%
Other*	9	10	***Race Race Type***	***N***	***%***
Did not specify	2	3			
Average number of patients seen per day Patients	***N***	***%***	Asian	7	10%
			Black or African American	2	3%
1 to 5	4	6	White	53	79%
6 to 10	13	19	Prefer not to answer	1	1%
11 to 15	14	21	Did not specify	4	6%
15 or more	39	58	***Ethnicity Ethnicity Type***	***N***	***%***
Did not specify	4	6			
Place of Practice Location	***N***	***%***	Hispanic	1	1%
			Non-Hispanic	61	91%
University hospital	16	24	Did not specify	5	7%
Non-university teaching hospital	1	1	***Has used PCR-Based Testing***		
Community hospital	17	25	Yes	59	88%
Outpatient only	23	34	No	4	6%
Federally Qualified Health Center	4	6	Did not specify	4	6%
Long-term Care	1	1			
Veterans Affairs	1	1			
Did not specify	4	6			

**other: convenient care, acute care, emergency medicine, wound care, and urgent care*

conditions to identify ways to improve antibiotic use on a state and national level.[2,3]

The purpose of this study was to determine how outpatient physicians and other healthcare providers in Missouri prescribe antibiotics, what resources they use, and how they would like to receive feedback on antibiotic prescribing if statewide antibiotic stewardship interventions are performed in the future.

Methods

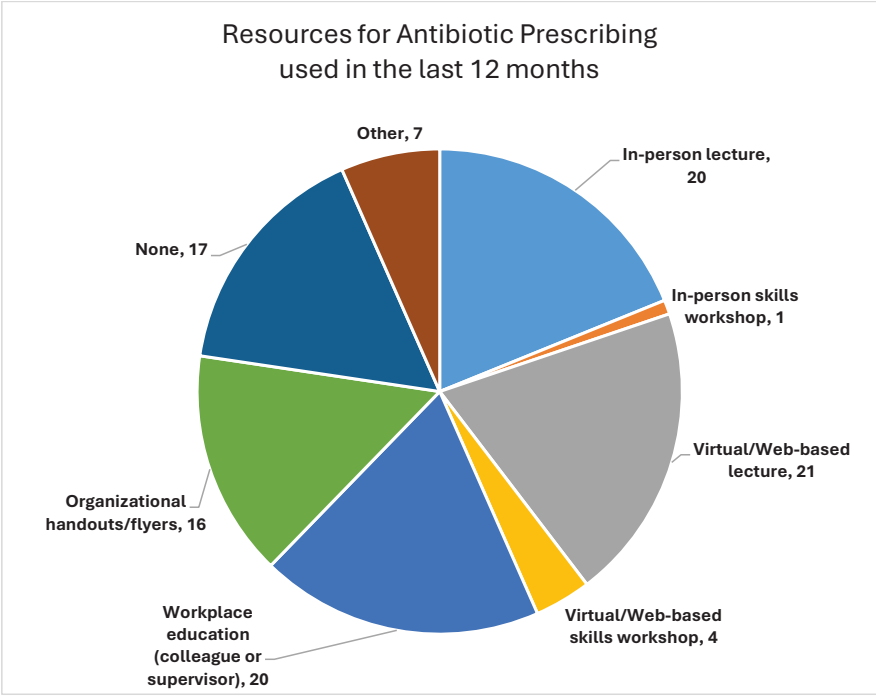
We created an online REDCap survey with items from similar studies in other settings[5] (see https://collaborativecare.wustl.edu/items/2023-2024-patient-caregiver-and-clinician-perceptions-of-guidelines-about-antibiotic-stewardship-for-asymptomatic-bacteriuria/). Providers were recruited via email, newsletters, and presentations through the following sources: American College of Physicians – Missouri Chapter, St. Louis Area Business Health Coalition, Mercy, BJC Healthcare, The University of Missouri, and the Missouri Primary Care Association Annual Conference. Providers were eligible if they practiced medicine and could prescribe antibiotics in Missouri. At the end of the survey, they could opt to receive an electronic gift card as an incentive. The protocol was reviewed and approved as exempt research by the Washington University Human Rights Protection Office (IRB# 202401039).

Results

Participant Characteristics

Sixty-seven individuals completed the survey. Most had been in practice for one to five years, saw 15 or more

Figure 1. How Missouri antibiotic prescribers obtain educational information about antibiotic use.



patients a day, and specialized in Internal Medicine. About 34% (n=23) of providers worked in outpatient-only practices, closely followed by community-based practices, and university-based practices. Regions of practice was mostly concentrated to metropolitan areas (63%; n=42) (Table 1).

Sixty-four percent (n=43) of Missouri physicians and mid-level providers who responded to the survey reported receiving training on prescribing antibiotics in the last 12 months. Virtual or web-based lectures (i.e. non-interactive, self-timed presentation) were the most common source of antibiotic prescribing education (Figure 1). Most (58%; n=39) of providers indicated that they typically review antibiotic prescribing guidelines at least two times a year.

Respondents also addressed potential antibiotic use in the setting of diagnostic uncertainty. Most (N=49, 73%) providers indicated that they would request more clinical tests to support their decision-making process, followed by patient education (N=45, 67%), and using a watch-and-wait approach (N=37, 55%) to see if symptoms resolve or worsen before prescribing an antibiotic.

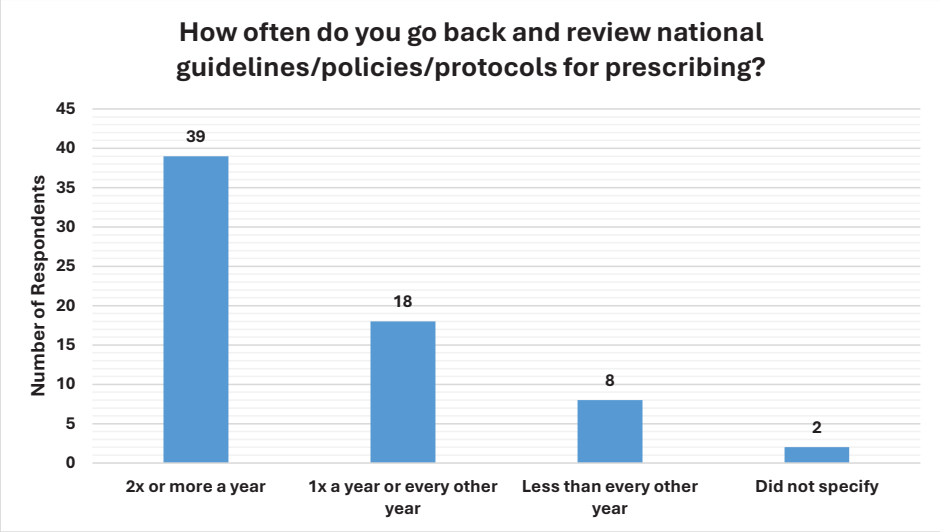
Respondents felt that interventions combatting antibiotic resistance would be most effective at the prescriber level (N=55, 82%; see https://collaborativecare.wustl.edu/files/2025/07/Ney-et.-al-MO-Med-2025-Supplemental-only.pdf), through patient and family education (N=51; 76%), and at a regional or national level (N=38, 57%). However, opinions varied regarding how this data should be shared. Fifty-eight percent (n=39) of practitioners indicated that they would want to receive the data blinded, meaning the data would not be linked to specific providers and/or locations. Another 24% (n=16) of providers indicated they would like to receive the data with practitioner names and locations, limiting access only to providers who are prescribing antibiotics. Regarding receiving data that provides feedback related to prescribing practices, providers indicated that they would most want to receive antibiotic prescribing rates for viral conditions (n=32, 48%).

Optional open-ended comments at the end of the survey found that some providers recommended utilizing hospital-based antibiotic stewardship program approaches in outpatient settings. Other providers commented on struggles and frustrations with patients wanting antibiotics without being further assessed or commented on treating patients who have received multiple antibiotics for a variety of reasons in a short amount of time.

Discussion

Missouri physicians and mid-level providers reported regularly accessing educational materials and routinely reviewing best practice guidelines about antibiotics at least annually. Similarly, most respondents also provided expert-endorsed responses on to how they handle diagnostic uncertainty with

Figure 2. Missouri prescribers self-reporting rates of reviewing antibiotic guidelines.



antibiotic prescribing in their practices. However, substantial variability existed in responses, and some respondents stated that they rarely review guidelines or use antibiotic stewardship resources. To our knowledge, this is the first survey in Missouri asking how physicians would want their antibiotic prescribing practices to be shared. Respondents felt that feedback to high antibiotic prescribers should target viral conditions, be blinded to peers, and should be shared via email.

These findings provide insights on how the Missouri Department of Health and Senior Services should utilize limited resources to address antibiotic overuse. As most physicians reported that they have adequate access to resources and regularly review guidelines, additional resources could be spent on developing materials to assist physicians who are focused on prescribing antibiotics responsibly. This may include patient handouts and educational materials that will help reinforce physician messaging about appropriate antibiotic prescribing. Several of these resources exist in government and research settings but have not yet penetrated into routine practice. Some resources helping clinicians address viral conditions without antibiotics include prescription pads for patients provide information for symptom relief,[7] a shared decision tool for diagnosing and prescribing antibiotics for UTIs,[8] and self-guided communication skills training to help clinicians maintain patient satisfaction while avoiding unnecessary antibiotic prescriptions.[9]

The high degree of variability in survey responses suggest that there are likely some outliers in antibiotic prescribing that would benefit from additional feedback. Indeed, a recent study suggests that 9.3% of prescribers are responsible for 50% of antibiotic prescribing in some regions—which suggests that targeted interventions towards individual high-volume antibiotic prescribers should be considered.[2] A recent narrative review found that outpatient antimicrobial stewardship strategies focusing on provider and patient education, support systems for clinicians, and policy changes had the most impact on reducing antimicrobial resistance rates and improved appropriate antibiotic prescribing.[6] These interventions should also be explored in Missouri.

Several state governments have started to look for antibiotic over prescribers using national data—with the goal of providing feedback about antibiotic use compared to peers. The current interventions, to our knowledge, have focused on sending letters in the mail and reviewing the total number of antibiotic prescriptions written by a single prescriber. The results of this survey suggest that Missouri physicians want more convenient information delivery (via email) and more specific feedback metrics (antibiotic prescription rates for viral conditions). Future interventions should take prescriber preferences into consideration both in Missouri and other states. Outpatient antibiotic appropriateness metrics is increasingly headed in this direction. The National Committee for Quality Assurance has developed a new Healthcare Effectiveness Data and Information Set (HEDIS) measure called the Antibiotic Utilization for Respiratory Conditions as a way to more closely assess how often people are prescribing antibiotics for viral upper respiratory tract infections.[4]

There were limitations to this study. The population of prescribers that responded skewed towards urban-practicing and younger physicians. Our survey did not ask participants to include their geographic location in Missouri, so some regions may be under represented, despite our efforts to contact and disseminate the survey statewide. Respondents may have also been more responsible antibiotic prescribers than non-respondents. We do not know how many people viewed the survey request, thus could not calculate an overall response rate. In addition, sampling was not random, making this study a convenience sampling approach. These may have limited the generalizability of our findings. The small number of participants limited our capacity to perform more robust statistical analyses.

Conclusion

Missouri antibiotic prescribers who responded to our study reported regularly accessing guidelines and utilizing evidence-based educational materials about antibiotic use. They also reported regularly using best practices to improve antibiotic use. Future interventions to improve antibiotic use should focus on patient educational materials and high-volume antibiotic prescribers for viral conditions, with outliers receiving blinded data via email.

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Disclosures

MP reported being a consultant for UCB Biopharma 2024 and Epi-Q, Inc. 2023 on topics unrelated to this paper. Artificial intelligence, language models, machine learning, or similar technologies were not used in the conceptualization, study, research, preparation, or writing of this manuscript.

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Nitazenes: An Old Drug Class Causing New Problems

by Evan S. Schwarz, MD, Frank Dicker, MD, Emilie Lothet, MD, Hannah Spungen, MD & Michael Levine, MD

These incredibly potent opioids with an increased risk of overdose indicate that increasing and improving addiction care and offering harm reduction are even more important.



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Abstract

The illicit opioid supply is increasingly adulterated with novel synthetic opioids such as nitazenes. Nitazenes are very potent opioids and are increasingly associated with opioid overdoses and deaths. Despite their potency, nitazenes are reversed by naloxone. Given the high risk of overdose associated with these agents, improvements in the delivery of addiction care and naloxone distribution are needed to prevent morbidity and mortality from nitazenes and other novel opioids.

The Evolution of the Opioid Crisis

More than 107,000 drug overdose deaths occurred in 2022 with an age-adjusted rate of 32.6 deaths per 100,000 of the standard population.[1] Since 2002, the age-adjusted rate of drug overdose deaths increased for both men and women, although from 2021 to 2022 the rate decreased by one percent for women. In 2021 and 2022, drug overdose death rates were highest for adults aged 35-44 years old; people over the age of 65 had the largest percent increase from 12.0 to 13.2%. Regarding overdoses involving synthetic opioids, including fentanyl and fentanyl analogs, rates increased from 2013 to 2022 (1.0 to 22.7%), while rates from heroin overdoses decreased from 2.8 to 1.8% from 2021 to 2022.

This is all consistent with the changing phases of the opioid crisis from mainly heroin-based to more potent synthetic opioids such as fentanyl and fentanyl analogs. The increase in morbidity and mortality was not only due to this change from heroin to fentanyl but also due to adulteration of the drug supply, including non-opioid adulterants such as designer benzodiazepines and other sedatives.[2–4] Additionally, more novel synthetic opioids were also added to the drug supply including fentanyl analogs such as carfentanil, and non-fentanyl analogs such as U-4700 and AH-7921.[5] Nitazenes are one of the latest classes of novel synthetic opioids to be found in the illicit drug supply.[6]

What Are Nitazenes?

2-Benzylbenzimidazole opioid agonists, otherwise known as nitazenes, are an older class of opioids developed by a Swiss pharmaceutical research

laboratory in the 1950s.[7] Interestingly, members of this class that lack opioid agonism are also used as fungicides to treat nematode infections.[8] Carbendazim is a well-known antifungal benzimidazole. Other members of the nitazene family were demonstrated to have opioid-like effects but were determined to be very potent with a high risk of addiction. As such, further development was halted, and they were never released for human use.[9] This class of opioids all contain a benzimidazole ring (a benzene ring attached to an imidazole ring) with substitutions creating analogs with potentially unique properties (Figure 1). Their chemical structures are distinct from morphine so will not be identified by standard drug screens.[8] Nitazenes can be consumed similar to any other opioid, including intranasally, intravenously, and by inhalation.

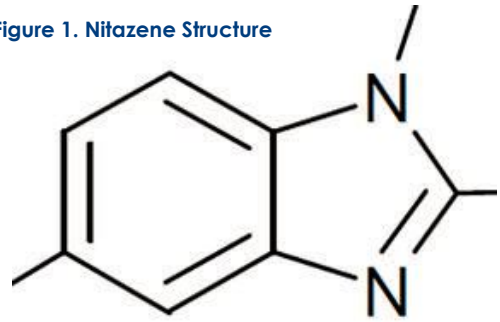
According to the Drug Enforcement Agency's (DEA) National Forensic Laboratory Information System (NFLIS) Drug database, clonitazene and etonitazene were initially identified in the drug supply between 1999-2004 before reemerging in 2019.[7] Isotonitazene was identified in street drugs in Europe in 2019, and since then, has been implicated in more than 200 deaths in Europe and North America.[10,11] Another analog, metonitazene, was first detected in the drug supply during COVID-19 in early 2020.[12] The NFLIS-Drug database has identified more than 4,300 reports of nitazenes since 2019.[7] As of January 2024, forensic and toxicology reports identified 20 unique nitazenes, although there are likely substantially more in the drug supply now. Clonitazene and etonitazene were both scheduled in the 1960s.[13] Isotonitazene was made a schedule I substance in 2020, and other nitazene opioids have since followed. However, many still fall outside the Controlled Substances Act and so may be legal, and none are approved for medical use in the United States.[14]

Are They Really That Potent?

Nitazenes are very potent opioids, demonstrating a potency up to 500 times that of morphine[13] (Table 1). Their metabolites may also have activity at the mu receptor, contributing to further respiratory depressant effects.[15] In one animal study, the respiratory depressive effect was greater and the time to recovery of baseline respiratory rate was longer for an isotonitazene metabolite compared to an equivalent amount of fentanyl. Nitazenes are also metabolized in the liver by the P450 system.[13] As such, polymorphisms including deficiencies or dysfunction of certain CYP enzymes may also impact their clinical effects, similar to other opioids.

Their potency has garnered much attention, both due to the possibility of greater adverse effects (e.g., respiratory depression) and because of misconceptions or misunderstandings regarding the term potency and what it means from a clinical perspective.[5,16,17] Potency is the ability of a substance to exert a chemical effect. Put simply, substances with high potencies need smaller amounts to obtain the same effect comparted to a less potent substance. Clinically, we see this with other opioids that we commonly administer in the hospital. Fentanyl

Figure 1. Nitazene Structure



Reproduced from : https://picryl.com/media/nitazene-structure-f88d10

Table 1. Relative Potency of Nitazenes

Drug	Relative Potency to Heroin
Fentanyl	50
Metonitazene	50
Protonitazene	100
Isotonitazene	250
Etonitazene	500

Table reproduced from Holland et al.[21]

is more potent than morphine. This is partially reflected in the fact that fentanyl is dosed in micrograms and morphine in milligrams when administered in the hospital. However, if enough morphine is administered, a similar magnitude of effect (analgesia and respiratory depression) can be obtained. This means nitazenes may have smaller therapeutic windows compared to other opioids, which is likely part of the reason that development for medicinal use was halted. In essence, very small amounts may mean the difference between therapeutic effects (e.g., analgesia) versus over sedation and respiratory depression (i.e., an overdose). Their greater potency, therefore, implies that it may be easier to overdose on nitazenes compared to other opioids, especially in consideration of the lack of control and precision when they are added in illicitly obtained drugs.

Importantly, potency is independent from a substance's ability to bind to a receptor (binding affinity), remain on a receptor (dissociation), or its duration of effect. This means that very potent substances may bind poorly (have a low affinity) to a receptor or come off the receptor (dissociate) very easily. As an example, methadone is more potent than morphine but equivalent, small doses of naloxone can knock both of them off the mu-opioid receptor and reverse their effects.[18,19]

Another example of these pharmacologic properties is with buprenorphine. Buprenorphine has a very high binding affinity at the opioid receptor, meaning that it binds more avidly to the receptor than most other opioids. In addition to its ceiling effects for (or limit on its ability to cause) respiratory depression, its high binding affinity is another reason it is used to treat patients with opioid use disorder. Once someone is on buprenorphine, even if a very potent illicit opioid is then used, the buprenorphine will remain on the opioid receptors due to its higher binding affinity, thereby competitively inhibiting the binding ability of the more potent opioid. These examples are intended to illustrate the difference between potency and other pharmacologic properties of opioids. This concept will become important in the following discussion of how to manage patients following a nitazene overdose.

Nitazenes in the Drug Supply

Nitazenes are increasingly being detected in the drug supply in the United States and Europe, both in heroin and fentanyl, but also in illicitly obtained alprazolam, oxycodone, and other drugs.[20] They can be manufactured rapidly and are inexpensive to produce making them attractive to illicit drug manufacturers.[8,21] Additionally, they do not require crops to produce, which is important because certain countries are prohibiting the cultivation of the poppy plant and production of opium from it. Etonitazene or etodesnitazene was the first nitazene detected in the illicit drug supply.[14] It was first detected in Italy in the late 1960s, Germany in the 1980s, Russia in the 1990s, and the United States in 2003.

Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) is a drug surveillance programming monitoring trends across Wales and the United Kingdom.[22] Nitazenes were first detected by WEDINOS on April 14, 2021. From April 2022 to March 2023, WEDINOS detected 36 samples containing nitazenes. None were originally thought to contain nitazenes with eight (22%) thought to only contain benzodiazepines (alprazolam and diazepam).

In another report, nitazenes were identified in what was thought to be counterfeit hydromorphone.[11] The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) received reports from multiple countries of counterfeit oxycodone tablets containing metonitazene and etonitazepyne, as well as brorphine, from 2021-2022.[23] Brorphine is a benzimidazolone, which is structurally similar to nitazenes and fentanyl.[14] It was first known to be synthesized in 2018, and like the nitazenes, is also an agonist at opioid (mu) receptors. Its identification and detection coincided with the declining production and

distribution of isotonitazene due to the latter being made a controlled substance. Similar to other novel opioids, brorphine was detected in forensic samples from fatal overdoses.[24]

The Tennessee State Unintentional Drug Overdose Reporting System (TN SUDORS) was searched for reports of nitazenes from January 2019 to December 2021.[25] SUDORS collects information associated with overdose deaths. During this interval, 52 nitazene-involved fatal drug overdoses were identified. The implicated nitazenes were isotonitazene, metonitazene, etonitazene, and protonitazene. Four times as many nitazene-involved overdoses were identified in 2021 than in 2020. Additionally, tablets packaged as health supplements were seized from an international mail facility in the United States from December 2021 to May 2022.[26] Etonitazene, etodesnitazene, and isotonitazene were all identified in the tablets.

Implications for Treatment

Nitazenes produce clinical effects similar to those of any other opioid including sedation and respiratory depression. Morbidity and mortality from nitazenes are therefore due to hypoxia following hypoventilation and apnea. Resuscitation should be directed at restoring respiration and oxygenation, which includes rescue breathing and naloxone.

Nitazenes should respond to naloxone. As of this writing, there is not an opioid that naloxone has failed to reverse. There is speculation that due to the potency of some nitazenes and other novel opioids, that larger amounts of naloxone or longer acting opioid antagonists are required.[14,16,17] It is true that some patients are receiving larger doses of naloxone following suspected or confirmed opioid overdoses.

However, there are several plausible explanations for this that do not implicate nitazenes as requiring higher doses of naloxone for reversal. First, more naloxone is being administered prior to arriving at the hospital either by the lay public or first responders due to using the standard 4 mg intranasal (IN) devices, which is the lowest amount that they can administer. As such, doses will be larger when compared to historical data from patients that only received naloxone in the hospital and thus generally received smaller amounts of naloxone, initially. Second, as many patients are hypoventilating or apneic prior to receiving naloxone, they may have very high amounts of carbon dioxide in their system causing respiratory issues or altered mental status even if all the opioid was already reversed. In this situation, someone may continue giving them naloxone as they are still altered or not breathing well. Finally, the persistent respiratory depression or altered mental status may be due to other non-opioid sedatives such as xylazine and benzodiazepines in the illicit opioid supply. Clearly, naloxone or any opioid antagonist will not reverse effects of non-opioid substances.

As previously discussed, potency is independent of other pharmacologic properties so it is not necessarily correct that highly potent opioids require large amounts of naloxone. The use of naloxone was investigated in patients presenting to the emergency department following suspected nonfatal opioid overdoses.[27] Data was abstracted from the electronic health record and waste blood samples were sent for analysis. Patients were included if their samples tested positive for nitazenes or brorphine. From September 2020 to September 2022, nine patients met inclusion criteria. Of the six with known naloxone doses and not in cardiac arrest, two patients received 2 mg or less, one received 4 mg IN followed by 0.2 mg intravenous [IV], one received multiple doses for a total of 0.36 mg followed by a naloxone infusion, and one received 2 mg IN followed by two doses of 0.04 mg IV. The remaining patient received 8 mg IN. As such, the authors believe it is reasonable to start resuscitation with standard doses of naloxone (either 0.04 or 0.4 mg of IV naloxone or the 2 or 4 mg IN naloxone devices in the prehospital

setting) and titrate up to the improvement of respiratory status.

Conclusion

These incredibly potent opioids with an increased risk of overdose indicate that increasing and improving addiction care and offering harm reduction are even more important. This includes low barrier access to medications for opioid use disorder and increasing access to buprenorphine and methadone especially in more rural areas. From a harm reduction perspective, naloxone distribution is even more important. The public should be trained to administer it and patients at risk should leave the emergency department or hospital with naloxone in hand as opposed to just with a prescription.

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Opioid Exposure and Associated Numeric Pain Scores in Adults with Chronic Musculoskeletal Pain

by Ray Segebrecht, MD, Abat Khan, MD & Xiangni Wu, MD, PhD

The results of the study align with existing evidence, reinforcing the notion that opioids offer no substantial advantage in pain management for chronic musculoskeletal pain.



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Abstract

The opioid epidemic claims tens of thousands of lives annually in the United States (US) where opioids are prescribed more per capita than in any other country. Primary care providers contribute to nearly half of these prescriptions, often for chronic non-cancer pain conditions such as back, hip, and knee pain. Despite widespread use, evidence suggests that opioids do not improve pain control for chronic non-cancer musculoskeletal pain.

This study aimed to assess whether an opioid prescription in the three months preceding internal medicine primary care appointments was associated with lower pain levels, as reported on a 1 to 10 scale during medical assistant check-ins, among patients with chronic non-cancer musculoskeletal pain. Using a cross-sectional design, we analyzed pain scores for adult patients who had been prescribed opioids versus those who had not. Our findings revealed no statistically significant difference in pain levels between the two groups, with both opioid and non-opioid users reporting similar median pain scores. These results align with existing evidence, reinforcing the notion that opioids offer no substantial advantage in pain management for chronic musculoskeletal pain.

Introduction

The prescription and consumption of opioids increased dramatically in the late 1990s, when pharmaceutical companies reassured healthcare providers that opioids were not addictive.[1,2] Then opioid-related deaths nearly doubled between 1999 and 2009,[3] at which point the US consumed 30% of the world's opioids, including 99% of the global hydrocodone supply and 80% of oxycodone worldwide.[1,3,4] Opioid prescribing peaked in 2012 with 81 prescriptions issued per 100 people.[3,4]

In response to the opioid crisis, the Centers for Disease Control and Prevention (CDC) released prescribing guidelines in 2016 and 2022. The 2022 recommendations aimed at reducing the risks associated with opioid therapy while encouraging

alternative pain management strategies.[5] Although opioid prescribing rates fell from 81 prescriptions per 100 people in 2012 to 38.5 per 100 people in recent years, overdose deaths continued to escalate, driven by a rise in synthetic opioid use and misuse of prescription opioids.[1,3,6,7] In 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency. By 2020, opioids contributed to nearly 75% of drug overdose deaths, then surpassed 75% in 2022, indicating the persistent role of opioids in overdose mortality.[8] While the overall opioid death rate eventually decreased by 12.5% in 2022 due in part to public health interventions, deaths involving prescription opioids have not seen such a decline, highlighting the ongoing need for safer opioid prescribing practices.[7]

Opioid prescribing rates in the US continue to surpass those in any other country with more frequent, higher-dose prescriptions administered at earlier stages of pain management.[4,9,10] Patient expectations and demand for opioids have contributed to the high prescribing rates, and so have less stringent regulations around opioid prescribing in the US that leave many prescribing decisions to individual providers who may have limited training in pain management.[4,11] Primary care providers, many of whom lack specialized pain management expertise, account for nearly half of all opioid prescriptions in the US, reflecting the decentralized approach to opioid prescribing.[4,12]

Current clinical evidence does not support the long-term benefit of opioid therapy for chronic non-cancer musculoskeletal pain. Studies indicate that opioid use for conditions like chronic low back pain does not result in substantial or sustained pain relief and may even worsen outcomes in osteoarthritis, where patients experience limited functional improvement and higher risk of adverse effects.[5,13,14] Additionally, prolonged opioid use can lead to opioid-induced hyperalgesia, a phenomenon where patients develop increased sensitivity to pain, effectively counteracting the intended analgesic effect.[15,16]

Opioids are associated with increased life-threatening risks, including falls, fractures, opioid use disorder, myocardial infarction, dementia, central nervous system and respiratory depression, and overdoses, and they increase overall all-cause mortality.[5] Among patients treated with opioids for non-cancer pain in primary care settings, approximately one in four develops opioid dependence.[17] As such, any treatment with this degree of disproportionately high risk should provide equally remarkable improved outcomes in pain management. To further inform decision-making, we designed this study to assess whether patients receiving opioids for chronic musculoskeletal pain experienced significant improvements in pain control that might justify the associated increased risks of opioid use.

Methods

This cross-sectional study was conducted to investigate the relationship between opioid use and pain levels in adult patients with chronic musculoskeletal pain. The study included data collected from July 1, 2019 to June 30, 2024 from University Health Primary Care Internal Medicine Clinics and the University Health Truman Medical Center – Center for Family Health, in Kansas City, Missouri. The primary objective was to determine whether pain levels, measured on an ordinal scale, differ between patients prescribed opioids and those using non-opioid analgesics. Secondary objectives included evaluating differences in pain levels across specific medication classes such as NSAIDs, acetaminophen, duloxetine, gabapentin and skeletal muscle relaxants.

The study population included adult patients aged 18 years or older who had a documented diagnosis of chronic joint pain identified by ICD-10 codes M16, M17, M25, M54, M53, and their subsets. Participants were required to have recorded pain scores at each clinic visit. Patients under 18 years of age or those with encounters lacking pain assessment data were excluded from the study. Pain scores, as recorded on a scale of 0 to 10 during each clinic encounter, served as the primary data source. Prescription records for opioids (e.g., Norco, hydrocodone, tramadol, oxycodone, Percocet), non-opioid analgesics (e.g., NSAIDs, acetaminophen), and adjunctive therapies (e.g., duloxetine, gabapentin, skeletal muscle relaxants) were used to classify patients into treatment groups.

The primary outcome was the distribution of pain scores, categorized by the type of medication

prescribed in the three months preceding the time of the encounter. Since the pain scale data was ordinal, the Kruskal-Wallis test, a non-parametric statistical method, was used to compare pain scores between the treatment groups. Secondary analyses explored differences in pain levels across specific medication categories, assessing whether any particular class of drugs was associated with significantly different pain scores. Statistical analyses were conducted using appropriate software with a significance level set at $p<0.05$.

Results

After excluding patients under 18 years of age and those with encounters lacking pain assessment data, the total number of cases before removing duplicate data was 3,211. After eliminating duplicates, the final dataset consisted of 2,885 cases. Our age range was 20-94, and our gender breakdown was n = 1,774 (61.5%) female and n = 1,111 (38.5%) male with a range of 22 musculoskeletal conditions identified by ICD-10 codes M16, M17, M25, M54, M53, and their subsets (Table 1). Patients could contribute to more than one medication, so the sample was not limited to those on monotherapy for pain.

Table 1. Case breakdown by condition, age and gender

Characteristic	n (%)
Sex	
- Female	1,774 (61.5%)
- Male	1,111 (38.5%)
Age Range (years)	20–94
Conditions	
- Osteoarthritis (OA)	278 (9.6%)
- Effusion of joint	16 (0.6%)
- Pain in unspecified joint	33 (1.1%)
- Pain in right shoulder	149 (5.2%)
- Pain in left shoulder	148 (5.1%)
- Pain in unspecified shoulder	41 (1.4%)
- Pain in elbow	27 (0.9%)
- Pain in wrist	65 (2.3%)
- Pain in joints of hand	12 (0.4%)
- Pain in hip	184 (6.4%)
- Pain in knee	428 (14.5%)
- Pain in ankle and joints of foot	69 (2.4%)
- Other joint disorder	14 (0.5%)
- Sacrococcygeal disorders, not elsewhere classified	13 (0.5%)
- Radiculopathy	67 (2.3%)
- Cervicalgia	203 (7.0%)
- Sciatica	49 (1.7%)
- Lumbago with sciatica	61 (2.1%)
- Low back pain	575 (19.9%)
- Pain in thoracic spine	25 (0.9%)
- Occipital neuralgia	3 (0.1%)
- Dorsalgia	425 (14.7%)

The details of analgesic prescriptions in the three months preceding each encounter date were as follows: Acetaminophen n=159; baclofen n=121; celecoxib n=95; cyclobenzaprine n=124; diclofenac topical n=920; duloxetine n=133; gabapentin n=395; ibuprofen n=98; lidocaine topical n=302; meloxicam n=148; methocarbamol n=17; naproxen n=67; tizanidine n=185; opioid n=103.

Our results showed no statistically significant improvement in pain control in patients who had received opioids in the three months before their encounter dates compared to patients who had received other non-opioid treatments (Figure 1). No non-opioid medication showed clear superiority over alternate non-opioid or opioid therapy (Figure 2).

Pain Levels in Opioid and Non-Opioid Groups

Figure 1 compares the reported pain levels between patients prescribed opioids and those using non-opioid analgesics. The median pain scores were similar for both groups, with opioids (n = 100) showing no significant reduction in pain compared to non-opioids (n = 2785) (p = ns). Patients in the opioid group reported consistently high pain scores, typically ranging from 7 to 9, indicating that opioid use did not provide superior pain relief over non-opioid alternatives.

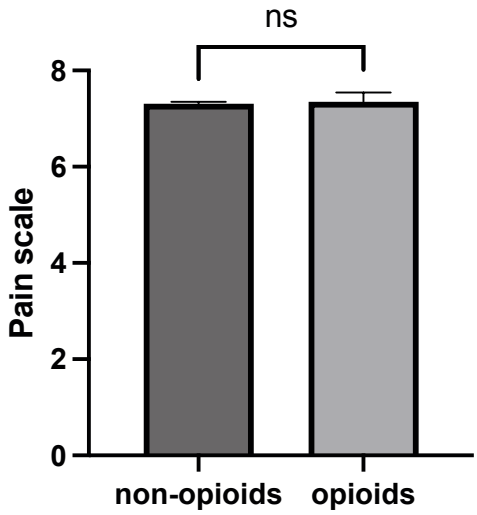


Figure 1. Comparison of Pain Scores Between Non-Opioid and Opioid Groups
Pain scale comparison between non-opioid and opioid user groups, highlighting that the median pain scores for both groups were similar, around 8, with no statistically significant difference (ns). This suggests that opioid use does not result in lower reported pain levels compared to non-opioid analgesics.

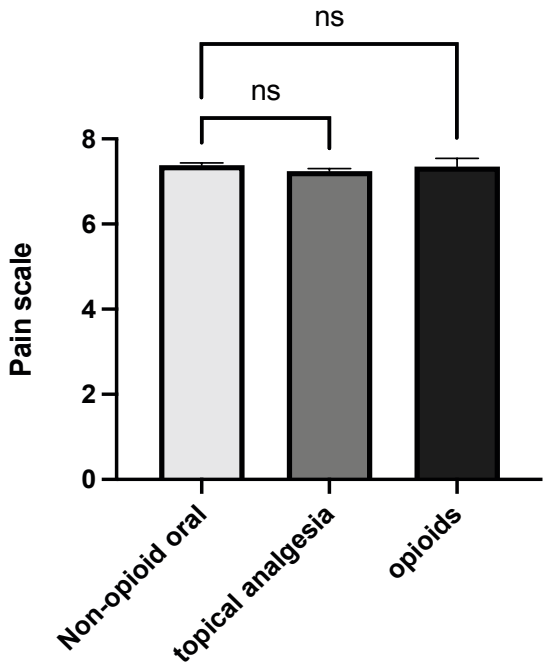
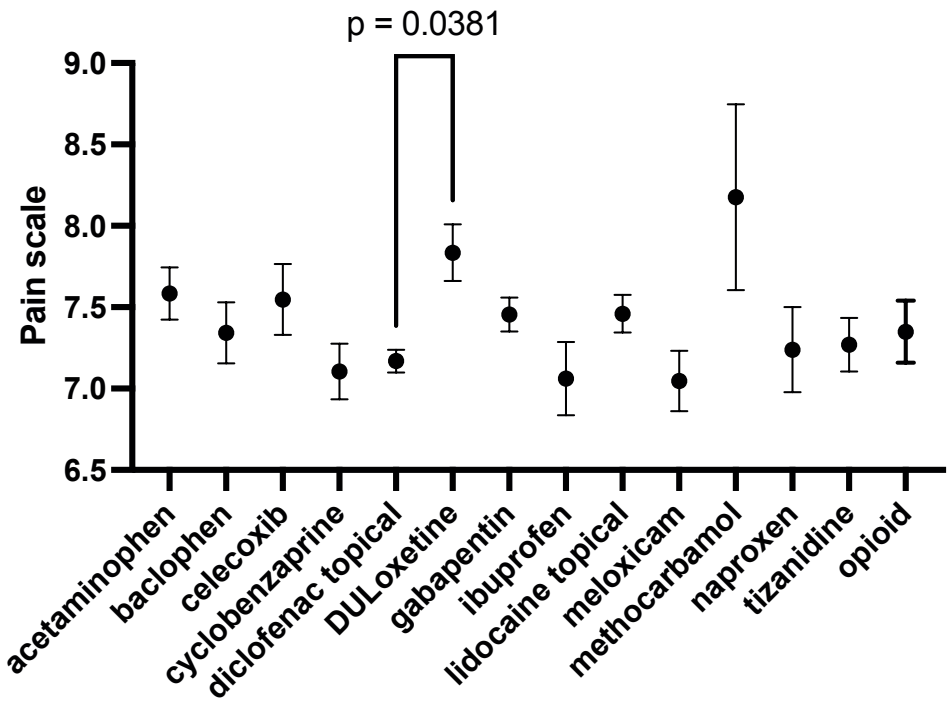


Figure 2. Pain Levels for Non-Opioid Oral, Topical Analgesia, and Opioid Groups
Comparison of pain scores among three groups: non-opioid oral medications, topical analgesics and opioids. The results indicate no statistically significant differences (ns) in pain levels among the groups, with all groups showing median pain scores ranging from 7 to 8. This finding underscores the comparable efficacy of topical and oral non-opioid analgesics to opioids in managing pain.

Figure 3. Pain Levels Across All Sub-Groups
Among non-opioid medications, notable differences in pain scores were observed across sub-groups (p = 0.0381). Pain scores of patients who had been prescribed opioids showed no superior pain relief compared to the pain scores of patients on non-opioid options.



Comparison of Pain Scores Across Oral Non-Opioid, Topical Analgesics, and Opioid Groups

As shown in Figure 2, pain levels were compared across patients using medications in three groups: oral non-opioid medications, topical analgesics and opioids. The median pain scores for all groups were comparable, falling within a range of 7 to 8, with no statistically significant differences observed (p = ns). These results suggest that topical and oral non-opioid analgesics are as effective as opioids in managing chronic joint pain.

Subgroup Analysis of Non-Opioid Medications

Figure 3 examines pain levels across specific non-opioid medication subgroups, including NSAIDs, adjunctive therapies (e.g., duloxetine, gabapentin), and muscle relaxants (e.g., baclofen, cyclobenzaprine). Significant variation was observed within the non-opioid group between certain medications, such as topical diclofenac and duloxetine (p = 0.0381), with diclofenac associated with slightly lower pain scores. This finding highlights the potential variability in pain relief among different non-opioid treatments.

Discussion

Close to one-third of the US population suffers from chronic pain.[16] As opioid prescription-involved deaths have recently hit all-time highs, physicians who vow to "do no harm" must ensure their individual prescribing practices with respect to opioids are supported by guidelines and evidence. Studies so far show opioid use for chronic non-cancer pain has minimal or uncertain benefit, especially for longer than 8 weeks.[5,9,13,14] In addition, multiple studies show that opioids do not provide effective pain relief in the long-term past six months.[18–20] Pharmacologically, this makes sense because of opioid-induced hyperalgesia, where patients on opioids actually become more sensitive to painful stimuli.[15]

Our cross-sectional study sought to add to the current evidence by assessing how pain control of patients with chronic non-cancer musculoskeletal pain who have received opioids compares with patients who received other analgesics in a novel way. Using pertinent ICD-10 codes, medical assistant intake pain level scores on a scale of 1 to 10, and the presence—or absence—of an opioid prescription in the preceding three months, we compared the level of pain control of adult patients in an academic internal medicine clinic who had received different pain control modalities in the preceding three months. In conclusion, we found no statistically significant improvement in the level of pain control in the patients who had received opioids compared to patients who had received only non-opioid pain control treatment modalities.

The lack of improved pain relief with opioids compared to other modalities, combined with the known increased risks of opioids, further strengthens the argument for cautious prescribing and highlights the need to address over-prescribing. Similarly, the equivalent level of pain control in patients on non-opioid therapy supports the role of a multimodal, patient-centered approach to pain management that includes patient-appropriate non-opioid medication in addition to evidence-based, non-pharmacologic therapies such as physical therapy, exercise, and cognitive behavioral therapy.[17, 18] The finding that none of the medication classes resulted in statistically significant lower pain scores than opioids underscores the limitation that can occur in pain reduction from any medication used as monotherapy without non-pharmacologic therapies.

Opioids continue to be prescribed for chronic non-cancer musculoskeletal pain despite a lack of strong evidence for multiple reasons; these include patient expectations, the flexibility individual prescribers have in the United States to dictate their own opioid prescribing patterns and systemic barriers such as insurance coverage and transportation for non-pharmacologic therapies like physical therapy.[4,21,22] However, we hope our results give pause to providers pondering opioid initiation or up-titration for chronic non-cancer musculoskeletal pain and prompt providers and patients to discuss and mutually consider non-inferior non-opioid classes of pain medication with safer side effect profiles.

Additional longitudinal studies can help determine how the level of control of chronic non-cancer musculoskeletal pain is affected over time by continued opioid use compared to other non-opioid analgesics. Future studies could also look at functional outcomes, measured by return to normal

activities or work, and at quality of life, assessed through patient-reported outcomes such as pain interference in daily activities. Evaluating pain management efficacy through this lens will be important with CDC guidelines advising functional status improvement as a central goal of treating chronic non-cancer pain.[5] Simultaneously, it is essential further studies continue to bring into light the incidence and impact of adverse effects from opioids in comparison to non-opioid treatments. As new scholarly work adds additional scrutiny to the questionable role of opioids in chronic non-cancer pain, we urge all prescribers to strive for evidence-based prescribing practices at the individual level, and at the policy level, we advocate for changes that reflect all available evidence to make our patients and communities safer amid this epidemic.

Limitations

The cross-sectional nature of the study limits the ability to establish causality between opioid use and pain outcomes. Additionally, there always exists the potential for incomplete data in patient records, including the limitation that over-the-counter medication use cannot be accurately measured. The current dataset represents pain levels at specific encounters and does not necessarily reflect the effectiveness of ongoing pain management strategies. The consumption of each prescription, including medication adherence and the proximity of doses to the timing of pain scores, was unknown, making it challenging to draw definitive conclusions about the long-term effectiveness of opioids versus non-opioids.

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Injections vs. Scalpels: Where Do Surgery and GLP-1's Align in Modern Obesity Treatment?

by Matthew Lindquist, DO, Esther Varghese, MD & Cooper Bassham, BS

"Bariatric surgery will go down in history as one of the biggest missed opportunities that we, as medical professionals, have seen over the past many years."

–Francisco Rubino, MD,
King's College, London



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Abstract

Recent advancements in pharmacologic treatment of obesity and metabolic disease with nutrient-stimulated hormones (NuSH), particularly Semaglutide and Tirzepatide, have been revolutionary, showing weight reduction results comparable to some surgical options. This is especially promising as, despite the proven efficacy and safety of metabolic/bariatric surgery (MBS), its utilization has remained quite limited. This review article discusses the current literature on the comparative effectiveness of these two treatments and their impact on comorbidities such as type 2 diabetes mellitus (DM2) and cardiovascular disease. While weight reduction with these NewSH's (sic) appears similar to a sleeve gastrectomy, though significantly less than gastric bypass, MBS remains the gold standard treatment for patients with more severe obesity especially those with higher cardiometabolic disease burden.

Introduction

Thanks to extensive data from the Swedish Obese Subjects (SOS) study, we have known for nearly two decades now that metabolic/bariatric surgery (MBS) saves lives when it comes to patients with obesity.[1] Unfortunately, we as a medical society, have underutilized this life-changing treatment, with roughly 1% of those who meet criteria actually receiving it.[2] (MBS Criteria: 1) BMI >/= 35 with weight-related complications/comorbidities and 2) Class 3 obesity w/ BMI >40 with or without weight-related complications/comorbidities.) Thankfully, after decades of trial and perhaps too much error, we have since developed, in the class of nutrient-stimulated hormones (NuSH's), pharmacotherapy options capable of weight loss near what we see with some surgical options. For better or worse (likely better, in my opinion), they have also become part of the national zeitgeist though I must acknowledge history is not on our side here (See: Obetrol in the 1960s and Fen-Phen via the 1990s).

Our historical short-comings aside, we now have medication options that can compete on average total body weight loss (TBWL) with surgery. To whit: Semaglutide 2.4mg injected subcutaneously once weekly and Tirzepatide 15mg injected subcutaneously once weekly have shown 15% and 21% mean TBWL respectively, at one year.[3,4] Compare this to 25% for a laparoscopic sleeve gastrectomy (LSG), 31% for roux-en-y gastric bypass (RYGB), and 13% for laparoscopic adjustable gastric banding (LAGB).[5] Given these results and even more medications in the pipeline such as Retatrutide, the first triple-agonist (GLP1, GIP, Glucagon), showing an average TBWL of 24%, the questions have arisen of where, when, and whether MBS fits in the treatment algorithm for patients with obesity.[6] Do our esteemed bariatric surgery colleagues have to go back to appendectomies or, gasp, clinic? This paper aims to guide primarily non-obesity clinicians such as PCPs and other specialties on how to approach current treatment options.

Treating A Chronic Disease With Lifestyle Changes

In 2013, the American Medical Association was the first major US medical organization to identify obesity as a chronic disease, noting "obesity as a disease state with multiple pathophysiological aspects requiring a range of interventions to advance obesity treatment and prevention."[7] This is a critical point prior to discussing advanced treatment options like pharmacotherapy and surgery. Just as we should recommend lifestyle therapy but not require it for the appropriate treatment for other chronic diseases such as cancer, hypertension, DM2 which are similarly affected by genetics/epigenetics, environment, and individual lifestyle behaviors; we should not withhold obesity treatment in the same manner.

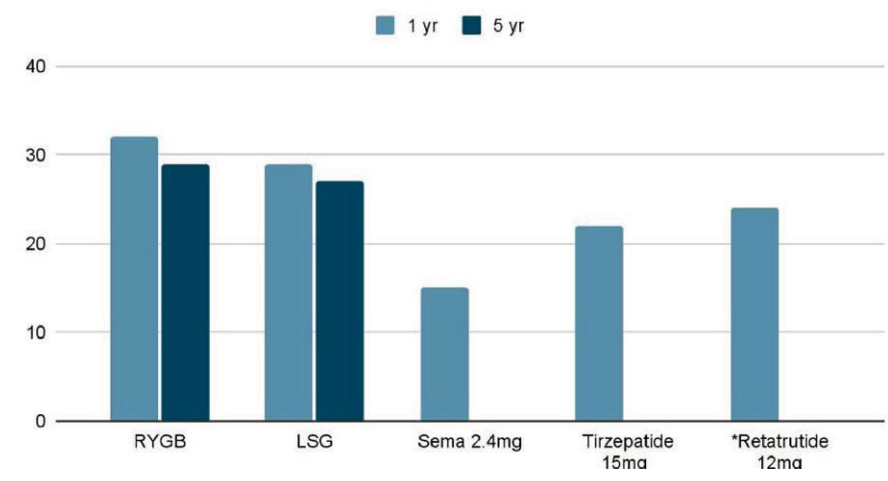
To that point, let's be clear on what results intensive lifestyle intervention (ILI) has historically offered and why most patients will "fail" this from a weight loss perspective. Decades of data from Look AHEAD, Diabetes Prevention Program (DPP), etc., have shown about one-third of patients will not achieve even 5% TBWL at one year and two-thirds will not achieve 10%.[8]

So why is it that so few people with obesity see truly meaningful weight loss (especially sustained) with lifestyle interventions? In my years of taking care of executives, physicians, and other driven, successful people, I can assure you it's not for lack of effort. You weren't going to say will power, were you? In the same vain that our bodies regulate our temperature, sodium, etc., they also regulate our weight. Before you label me a master of the obvious, I make this point as many of us somehow disregard this basic physiologic function. Now, more specifically, and frustratingly, they aggressively protect our fat mass. When people with obesity lose weight or simply fat mass as they diet and exercise, hunger hormones like ghrelin increase and satiety/neuromodulatory hormones like GLP-1 (heard of it?), peptide YY, and leptin, just to name a few, decrease. The result is an increase in perceived hunger, decrease in satiety, and a decrease in metabolic rate. Once excess weight has settled in, our bodies defend it and will do so at increasing "set points."[9]

Recent Pharmacotherapy

Historically, we could comfortably, though sadly, tell patients with severe obesity that we had nothing to offer them that could come close to surgical options. FDA-approved options like Phentermine, Bupropion/Naltrexone SR, Liraglutide 3mg offered an average of around 5-6% TBWL at one year. Phentermine/Topiramate (Qsymia) had been the leader with 8.7% TBWL at two years.[10] Good results, but 1) roughly one-third the weight loss seen with an LSG, and 2) many are not great candidates. Orlistat tolerance and efficacy issues (3% TBWL) made for a poor option for most. It should be no surprise that surgeons led the charge in treating those with severe obesity and metabolic disease for the last few decades.

Figure 1. Total Body Weight Loss



The Promising Beginning of a New Age of Obesity Treatment

The announcement of the STEP 1 trial in June 2020 came with considerable fanfare. For the first time, we had a nonsurgical option in Semaglutide 2.4mg once weekly that helped patients achieve an average of 15% TBWL at one year and one-third of patients even saw 20%. Not to mention, Semaglutide had already been approved for DM2 and further studies showed benefit in preventing diabetes and treating metabolic-associated steatohepatitis (MASH). So, not only were we seeing nearly double the weight loss compared to previous medications, we were often seeing clinical remission of their weight-related complications.[3,11,12]

Tirzepatide Has Entered The Chat

Next up in the realm of blockbuster pharmacotherapy was Tirzepatide 5, 10, and 15mg subcutaneous injections once weekly, the first dual GLP-1 and GIP via SURMOUNT-1 data showing average TBWL of 15%, 19.5%, and 21%, respectively. Categorical data now also showed 36% of patients achieving 25% weight loss.[4]

A New Horizon

After years of dormant discovery, the obesity and metabolic disease pipeline is suddenly looking robust, if not almost crowded. One of the next blockbuster/headline drugs in line, pending FDA approval, is Retatrutide, mentioned above. With a maximum dose of 12mg weekly that ups the ante again with average TBWL of 24% at maximum dosing of 12mg weekly and, again, adds an extra categorical cohort with 26% of patients now seeing 30% TBWL.[6] For my nonsurgical colleagues that are as competitive as I am, this is a reasonable time to feel, dare I say, confident?

Figure 1 shows where the treatment options stand with regard to TBWL. Clearly, when we are discussing the treatment of obesity, weight loss is an important outcome though it is, of course, not the only one nor perhaps even the most important. Let's look at how the treatment options compare in treating diabetes mellitus type 2, reducing major adverse cardiac events (MACE), and improving mortality.

DM2 Superiority

We first need a champion for this fight against the long-reigning surgeries. SURPASS-2 showed the superiority of Tirzepatide over the other titan, Semaglutide, in treating patients with DM2. Compared to 66% of patients achieving an A1c <6.5 in the Semaglutide 1mg group, 87% achieved this in the Tirzepatide 15mg group. The clear difference, however, is in 2.5 times the rate of patients achieving an A1c <5.7% in the tirzepatide 15mg vs. Semaglutide 1mg groups.[13] Following Semaglutide 2mg approval for DM2, a follow-up adjusted indirect treatment comparison (aITC) of Tirzepatide 5, 10, and 15mg vs. Semaglutide 2mg again showed superiority for both Tirzepatide 10mg and 15mg.[14]

So how does our best medical therapy in Tirzepatide compare to MBS? In lieu of head-

	Sleeve Gastrectomy	Gastric Bypass	Tirzepatide 15mg (SURPASS-4)	Tirzepatide 15mg (SURPASS-5)
Mean Age (years)	48	48	64	60
Mean BMI (%)	36	37	32.5	33
Mean Hemoglobin A1c (%)	9.5	9.3	8.5	8.3
Total Body Weight Loss (%)	25%	31%	13%	8.80%
Mean HbA1c Reduction at 1 yr	2.80%	2.90%	2.58%	2.4%

Table 1. Comparison of baseline age, mean BMI, mean HbA1c, and 1 year (40 weeks for SURPASS-5) outcomes for TBWL and mean HbA1c reduction from sleeve gastrectomy and gastric bypass arms of the STAMPEDE trial and Tirzepatide 15mg arms from SURPASS-4 and the SURPASS-5.

to-head trials of Tirzepatide, or semaglutide for that matter, we will compare the results of the STAMPEDE trial from Schauer, et al. to the Tirzepatide 15mg arms in the SURPASS-4 and SURPASS-5 trials, which were chosen as the closest comparators to the STAMPEDE cohort. SURPASS-4 enrolled those with obesity and uncontrolled DM2 with any combination of metformin, sulfonulurea, or SGLT2i and, in SURPASS-5, those uncontrolled on once daily insulin with or without metformin. These two groups compare much closer to those in STAMPEDE in which just under half of patients were on insulin and roughly 80% were taking at least two therapies across both bypass and sleeve groups. Shown in Table 1, despite demographics with higher BMIs and worse levels of HbA1c, sleeve gastrectomy and gastric bypass showed clear superiority over Tirzepatide 15mg for both weight loss (by more than two-fold) and HbA1c reduction.[15, 16, 17]

Mortality

The long-awaited SELECT trial had Semaglutide 2.4mg weekly again making headlines in November 2023 as it showed, at 40 months, a 20% relative risk reduction in death from cardiovascular causes, non-fatal MI, and non-fatal stroke in patients with obesity and established cardiovascular disease. This has since led to an FDA-approval for MACE risk reduction in this population.[18] Compare that to Doumouras et al.'s work in 2021 and data from the Scandinavian Obesity Surgery registry basically doubling the RRR with 42% at 4.6 years and 48% at 8 years, respectively.[19,20] Similar numbers are seen in mortality reduction in patients with obesity and DM2. Marso et al. showed Semaglutide led to a 19% reduction in all cause mortality vs. placebo.[21] More recent data from Tirzepatide was more encouraging with a 42% reduction.[22] However, these are still short of 47% seen in MBS. Again, the clear winner here with secondary prevention of MACE and, slightly less convincingly with mortality in DM2, is in favor of MBS.

Important Considerations

I find it important to note a disease in which the data appears to be moving in the opposite direction is in alcohol use disorder (AUD). We have known for over a decade now that AUD risk is increased after MBS, particularly with gastric bypass.[23] Many of these cases are new onset, as well. Somewhat preliminary, though, consistent data is showing reduced risk with GLP1's.[24,25] Understanding more studies are essential to identify which patients will benefit more from MBS despite previous, current, or high risk for postop-AUD, current findings would suggest GLP1's as optimal initial therapy in this group.

Conclusion

Breakthroughs in obesity pharmacotherapy with NuSH's have heralded an era in which people with obesity have access to nonsurgical treatment options that can lead

to disease and comorbidity remission, coverage and cost barriers notwithstanding. However, current data still support MBS as the reigning gold standard treatment, especially for patients with severe obesity and/or with established cardiovascular disease or DM2. As a society, we would be amiss to continue with our historical trend of MBS under-utilization. My hope with new pharmacotherapy options is it has made us clinicians feel more able to treat and with that, fewer patients have continuously progressive disease to the point of requiring MBS for a healthy life. Until then, though, know there are many of your patients that might benefit greatly from NuSH's but would be optimally treated with MBS.

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