Missouri Medicine

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Big Bold Food Labels Reduce Junk Food Consumption

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GUEST EDITORIAL
Big, Bold Warning Labels Can Steer People Away from Junk Food
by Lindsey Smith Taillie, PhD 96

PRESIDENT'S FORUM
MSMA & MAOPS: Pitching Our Advocacy Tent
by **Lancer Gates, DO** & Victoria Damba, DO 99

PERSPECTIVE
Beta Blocker Nasal Spray for Actue Migraine
by Parashar Koirala, MD 102

The Generous Reimbursement of Non-Physician Clinical Services - Part I: A Deep Dive into the Resource-Based Relative Value Scale
by **Gary Gaddis, MD** 105

Mental Health and the Graduate Medical Education Trainee: Emergent Concerns
by **Brook V. Nelson, MD** 113

INSPIRING LIVES AND CAREERS
My Story
by **Charles Van Way, III, MD** 116

AS I SEE IT
Learning to be Vulnerable
by **Joanne Loethen, MD** 119

SCIENCE OF MEDICINE | FEATURE SERIES

The New Age of
by University of Missouri - Columbia

Advances in the Endovascular Management of Cerebrovascular Disease
by Ravi Nunna, MD, Farzana Tariq, MD, Fareed Jummah, MD, Navpreet Bains, DO, Adnan I. Qureshi, MD& Farhan Siddiq, MD 127

Seven Decades of Neurosurgery at MU Columbia
by **Michael Chicoine, MD** 128

Advances in Cranial Surgery
by Farzana Tariq, MD, Fareed Jumah, MD, KaushikRavipati, MD, Michael Ortiz-Torres, MD, Steven B. Carr, MD & **Michael R. Chicoine, MD** 136

Cutting Edge Developments in Spine Surgery at the University of Missouri
by Ravi Nunna, MD, Farzana Tariq, MD, Michael Ortiz, MD, Inamullah Khan, MD, Sabrina Genovese, BS & Paul Santiago, MD 142

Role of Functional neurosurgery in Improving Patient Outcomes in Epilepsy, Movement Disorders, and Chronic Pain by Wesley Chen, MD, Farzana Tariq, MD, Komal Ashraf, MD, Thorklid Norregaard, MD, Andrew Youkilis, MD, Bornali Kundu, MD, PhD & Farhan Siddiq, MD 149

SCIENCE OF MEDICINE
Obesity and Anesthesia: Challenges in the Perioperative Period
by **Sarah Von Thaer, MD, Janette McVey, MD, James Shelton, MD** & Quinn Johnson, MD 156

Telehealth Visits have Lower Non-attendance than Traditional Orthopaedic Clinic Visits
by Bradley S. Spence, MD, Mark J. Lambrechts, MD, Zhengye Si, MA, Emily V. Leary, PhD & Sumit K. Gupta, MD, MPH 164

CRISPR Advancements for Human Health
by Daniel J. Davis, PhD & Sai Goutham Reddy Yeddula, DVM 170

FROM YOUR ASSOCIATION
Correspondence 121
New Members 124
1 Picture = 1,000 Words 163

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

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Big, Bold Warning Labels Can Steer People Away from Junk Food

by Lindsey Smith Taillie, PhD

Something as simple as changing food labels making them more understandable and easier to read can decrease the purchase of 'junk' foods.

My daughter screamed in the medicine aisle. There she was, a toddler with strep throat, dehydrated, red-faced, pulling cough drops off the bottom rack in the supermarket as I shopped for things to help her feel better. I grabbed a bottle of juice emblazoned with "100% Vitamin C" and rushed over to comfort her. When we got home, I realized the juice I'd hastily picked had more added sugar than a bar of chocolate.



As a nutrition epidemiologist, I study the health effects of consuming sugary drinks and ultra-processed foods, two of the top drivers of poor health outcomes in kids, including dental cavities, weight gain, and type 2 diabetes. Yet with no time to think, I was just like any parent who reaches for a product with the cleanest colors and boldfaced promises of healthfulness. If I can't get it right, who can?

My research has found that among fruit drinks, nutrition-related marketing tactics are nearly universal. Claims like "100% All Natural" lead consumers to incorrectly believe a product is free of added sugar. This phenomenon, known as the "health halo" effect, occurs when a single marketing promise leads consumers to believe a product is healthy when it isn't.

Lindsey Smith Taillie, PhD is an associate professor and co- director of the Global Food Research Program at the Gillings School of Global Public Health at the University of North Carolina, Chapel Hill.
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Compounding the problem, consumers often have only a few seconds to make decisions about food purchases.

Few report using the back-of-the package nutrition information (Figure 1). Even for those who do, the vast amount of information—nutrients, ingredients, and numbers—makes it difficult to distinguish between healthy foods and ultra-processed products high in sugar, sodium or saturated fat, the ones most likely to increase risk of chronic diseases.

To address this problem, the US can learn from Chile, another high-income country that grapples with nutrition and health problems. In 2016, as part of a wider law to prevent further increases in childhood obesity, Chile became the first country to implement warning labels on foods high in nutrients of concern, including most ultra-processed products. The stop-sign-shaped warnings appear on the front of packages, with text cautioning consumers that the product is high in sugar, sodium, saturated fat or calories (Figure 2).

The results are compelling. Following implementation of Chile's law, calories consumed from consumer purchases of products with warning labels dropped by 24%, with similar results for sugar and other ingredients. The law also spurred the food and beverage industry to reduce the amount of sugar and sodium in many of their products, leading to a healthier food supply. Beyond Chile, ample experimental research in the US shows that bold warning labels help consumers quickly identify unhealthy foods and make healthier, informed choices. Chile's simple black-and-white design grabs consumers' attention and has shown to be easily understood even by children. Following Chile's lead, eight other countries have since implemented similar labeling regulations—covering most of South America as well as Mexico and Canada.

Not long after our experience in the medicine

Figure 1. US Food Labels are time-consuming to read, complex and difficult to interpret.



Nutrition Facts
34 servings per container
Serving size 1 bar (31g)

Amount per serving
Calories 140

	% Daily Value*
Total Fat 5g	6%
Saturated Fat 3.5g	16%
Trans Fat 0g	
Polyunsaturated Fat 0.5g	
Monounsaturated Fat 1g	
Cholesterol 0mg	0%
Sodium 85mg	4%
Total Carbohydrate 23g	8%
Dietary Fiber 1g	4%
Total Sugars 13g	
Includes 12g Added Sugars	24%
Sugar Alcohol 0g	
Protein 1g	
Vitamin D 0mcg	0%
Calcium 10mg	0%
Iron 0.7mg	2%
Potassium 80mg	0%

* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

Source
US Food and Drug Administration

Figure 2. In 2016, Chili adopted black stop-sign-shaped warnings to appear on the front of food packages, with text cautioning consumers that the product is high in sugar, sodium, saturated fat or calories. The results are compelling. Consumer purchases of foods with the new, easy to read and understand warning labels dropped by 24%.

2016 Law by the Chile Ministry of Health

1. Requires **warning labels** on foods and drinks that contain added sugar, sodium, and saturated fat and exceed thresholds for these nutrients and/or calories.
2. Protects children under 14 years of age from marketing for food with warning labels.
3. Prohibits the sale, promotion, or free distribution of foods with warning labels at pre-school, elementary, and secondary schools.



aisle, my daughter and I got to see the labels in action when we spent a semester in Chile. In the grocery store, the warnings helped me figure out which products were unhealthy. The Chilean law also restricts the use of cartoons, characters, or other techniques that appeal to kids on any product carrying a warning label. In the US, Greta begged me for the "PAW Patrol" Popsicles or yogurts bearing colorful princesses—a phenomenon known in my field as "pester power." But in Chile, she didn't demand as much. The absence of child-directed marketing tactics combined with the warning labels created a simpler shopping experience: it was easier for me to make healthy choices. On a later visit to Peru, which has similar labels as Chile, Greta learned to use the warnings herself to pick out snacks that she liked and I approved.

In testimony recently before the Senate Committee on Health, Education, Labor, and Pensions, I presented evidence that a multi-pronged package of actions is needed for chronic disease prevention. These include fiscal policies, restrictions on child-directed marketing, and revised school food standards. But front-of-package food labels are a clear first step. They are one of the best evidence-based tools we have to help consumers make educated choices, and the US Food and Drug Administration is actively researching them. During my testimony, I also acknowledged a major barrier to progress in the US: the food industry. Food manufacturers have long attempted to circumvent new labeling regulations by arguing they already provide this information to consumers. That's true. But does it matter if no one can understand the information? "Facts Up Front," the industry's voluntary front-of-package labels, are poorly understood and typically perform worse compared with other front-of-package labeling options, according to research in my lab and elsewhere.

Another example, the industry's "Smart Choices" labeling system, awarded its own seals of nutritional approval for things like sugary cereals that added a few vitamins. Fortunately, this misguided program was short-lived: participating companies abandoned it after the FDA announced it would take steps to address misleading labels. Around the world, one of the food industry's main arguments against labeling regulations is that such laws are bad for business and expensive for consumers, particularly when the cost of reformulating products is passed along. Yet in Chile, a team of researchers found, the laws had little to no effect on wages, employment, or profits in the food and beverage industry sector. Importantly, researchers found the law also had no effect on food prices, even for products that were reformulated.

Another criticism from the industry is that labeling systems should reflect nutrients or ingredients to eat more of, like fruit or fiber, not just warnings on nutrients to limit, like sugar. For example, the food industry has promoted a label that summarizes all nutrients using a score or stars. Although such a proposal seems reasonable on its face, it is not backed by science: The presence of fruit in a fruit drink, for instance, does not offset the impact of added sugar on the body. And nearly 10 years after Australia and New Zealand implemented a health-rating system awarding stars based on a selection of ingredients, a number of studies have found no evidence that it improves the nutritional quality of what people buy. Lastly, the lack of detail on specific nutrients of concern like sugar or sodium can make it harder rather than easier for consumers to identify the products that pose the greatest risk to their health. Today, as the FDA searches for a more promising, mandatory front-of-package labeling system, it would do well to follow Chile's lead. Effective labels need to be simple, easily noticed, and quickly understood. Championing clear text on stop-sign-like labels maximizes consumers' ability to quickly and accurately identify unhealthy products, and visuals like icons or symbols further improve comprehension.

In addition to labels that indicate high levels of sugar, sodium, and saturated fat, the FDA could consider a warning on diet sweeteners like aspartame, ensuring that cuts in sugar don't lead to increases in other sweeteners, similar to what Mexico, Colombia and Argentina have done. Most important, the FDA must ensure that progress towards clear, informative labeling is led by governments and public health experts, not commercial interests.

My screaming toddler is now an opinionated six-year-old who loves to choose her own snacks at the grocery store. Now in the US, she'll reach for a sugary sports drink and argue that without a warning, it must be healthy. She asks me: "Mom, when will we get labels here too?" Hopefully soon. **MM**



MSMA & MAOPS Pitching Our Advocacy Tent

by Lancer Gates, DO & Victoria Damba, DO

Physicians and Their Missions

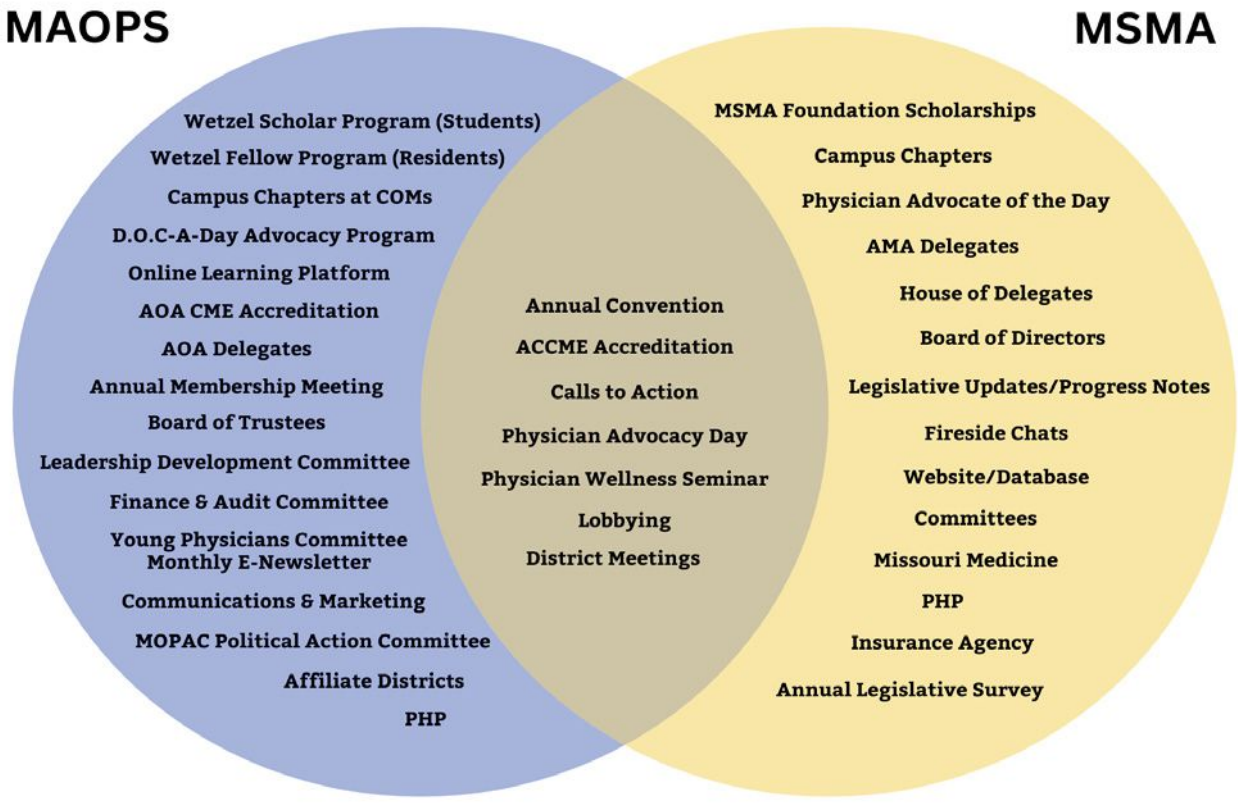
The Missouri State Medical Association (MSMA) and the Missouri Association of Osteopathic Physicians and Surgeons (MAOPS) serve all the physicians of Missouri. Founded in 1850, MSMA aims to serve its members through the promotion of the science and art of medicine, protection of the health of the public, and betterment of the medical profession in Missouri.[1] Founded in 1897, MAOPS aims to advance the distinct practice and philosophy of osteopathic medicine.[2] Many medical students and practicing physicians in Missouri are members of both MSMA and MAOPS.





Lancer G. Gates, DO, FACOI, is the President of the Missouri State Medical Association for 2023–2024. He is a Hospitalist from Kansas City, Missouri. Victoria Damba, DO, is the President of the Missouri Association of Osteopathic Physicians and Surgeons for 2023-2024. She is a Family Physician from Festus, Missouri.

Across the country, it is rare for allopathic and osteopathic state medical societies to collaborate, e.g. the Utah and New Hampshire allopathic medical societies administer their respective osteopathic state medical societies. Fortunately, our Missouri state medical organizations realize that sharing administrative resources improves member services. This year, MSMA and MAOPS collaborated on the Physician Advocacy Day, the Physician Wellness Seminar, the Virtual Osteopathic Conference CME, and the Legislative Summit.



The Juggling Act of Organized Medicine

Your organized medicine ringmasters are MSMA Executive Vice President Jeff Howell and MAOPS Executive Director Brian Bowles. After years of practice, they have mastered juggling member benefits and organizational costs. Today, ballooning inflation has raised the financial tightrope, and the juggling degree of difficulty, to dazzling new heights.

These ringmasters, addressing their elephant of expenditures, are working on the possibility of holding a combined Annual Convention. Other potential collaborations will require the flexibility of a contortionist. Lions yet to be tamed include a shared staffing model, a shared communications platform, and a shared physician wellness program.

While most collaborative efforts will bring economic savings to both organizations, the most crucial collaborative effort, physician advocacy, will give a voice to Missouri physicians that will make a carnival barker envious.

Advocacy Tent Making

On November 14, 2023, MSMA and MAOPS leaders assembled a collaborative task force to pitch our advocacy tent. Tentmaking has come a long way since the Apostle Paul handcrafted tents. Our MSMA-MAOPS collaborative task force requires many hands to pitch the advocacy tent for all physicians while preserving the distinctiveness of osteopathic and allopathic history and traditions. Your collaborative task force comprises MAOPS representatives Victoria Damba, DO, David Tannehill, DO, and Jeff Davis, DO, and MSMA representatives Lancer Gates, DO, George Hubbell, MD, and Brian Biggers, MD.

In 2024, your MSMA-MAOPS collaborative task force focused on making physician advocacy more effective. We started by coming together on December 18, 2023, to discuss our shared positions and priorities on issues affecting physicians in the 2024 legislative session. We facilitated policy discussion among the legislative committees of MSMA and MAOPS. We coordinated attendance at the MAOPS "Doc of the Day" and the MSMA "Physician of the Day" held at the Capitol on Tuesdays and Wednesdays throughout the legislative session. We held our second annual combined Physician Advocacy Day on March 5. Finally, we encourage physicians to contribute to the Missouri Medicine PAC, and the MAOPS PAC, and directly to candidates and legislators.

The Jefferson City Three-Ring Circus

At the beginning of each year, the Missouri Senate, the Missouri House, and the Missouri Governor convene under the big top in Jefferson City. Occasionally, side shows with clowns and Missouri tigers occur, but at the end of the session, we truly appreciate our elected officials' service.

Organized medicine works with legislators each year to create and modify bills affecting physicians. Some issues present themselves year after year but in different costumes, e.g. a caravan of advanced practice providers disguised as camels are trying to expand their scope of practice by getting their noses under the tent of organized medicine. On November 13, 2023, advanced practice nurses filed an initiative petition (2024-168) with the Missouri Secretary of State's office to enshrine in the Missouri Constitution their ability to forego collaborative practice agreements, allow them to prescribe controlled substances, and empower the State Board of nursing to solely regulate nurses without any oversight from the Executive Branch of the Missouri Legislature.[3] This initiative petition, provided the required signatures are obtained, will be included on the November 2024 statewide ballot. If approved by the Missouri voters, it will be enshrined in the Missouri Constitution.

An Old-Fashioned Tent Revival

Organized medicine has something for every physician, young (student section) and old (retired section). If you know of a colleague who is not a member of MSMA or MAOPS, ask them to "step right up" and get their tickets to MSMA and MAOPS…the greatest "show-me" in the nation.

Sources

1. MSMA Mission Statement
2. MAOPS Mission Statement
3. Missouri Secretary of State

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We welcome your feedback about this collaboration. Please share your thoughts with Jeff Howell at jhowell@msma.org and Brian Bowles at brianb@maops.org

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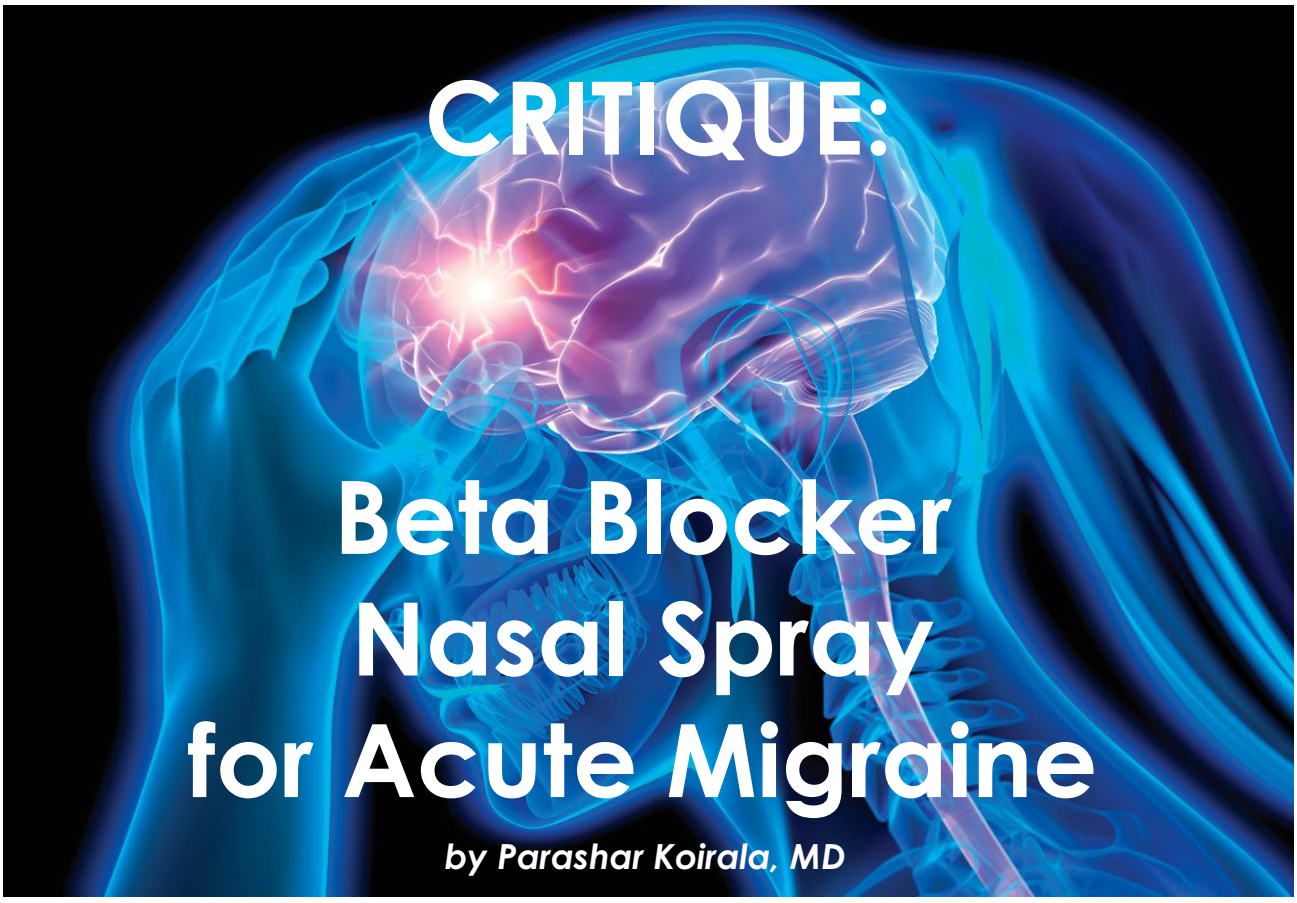
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CRITIQUE:

Beta Blocker Nasal Spray for Acute Migraine

by Parashar Koirala, MD



Parashar Koirala, MD, is Assistant Professor, Department of Neurology at the University of Missouri - Kansas City, Kansas City, Missouri.

Migraine is a leading cause of disability worldwide[1] and imposes a substantial global burden[2] with increased individual medical expenses[3] and diminished productivity.[3] The intensity and severity of migraines can be categorized as episodic (<15 headache days per month) or chronic (≥15 headache days per month). Treatment approaches include acute or abortive and prophylactic, with the objective of abortive therapy being resolution of pain within two hours with a single medication and minimal adverse events.[4] An effective preventive modality would aim to reduce the number of migraine occurrences, their intensity, and consequently, improve the quality of life.[5]

Existing acute migraine treatments demonstrate variable efficacy and undesirable side effects. Over-the-counter analgesics are less effective and require caution among those with gastrointestinal disorders. Conversely, prescription medications such as ergotamine and triptans need careful consideration, especially in patients with underlying coronary disease, stroke, or peripheral vascular disease.[6] The safety profile of calcitonin gene-related peptide (CGRP) inhibitors is noteworthy; however, their high cost makes them financially inaccessible to many. Concerns about abuse potential and rebound phenomena present distinctive challenges in migraine treatment.[7] Despite intensive efforts to address migraines, inherent resistance to treatment and lack of efficacy have made migraine

If the beta blocker nasal spray is proven effective in rigorous clinical trials, this innovative approach to acute treatment would significantly enhance the care of migraine patients, particularly underserved and vulnerable patients who are uninsured or underinsured.

treatment particularly challenging, prompting a continuous search for superior and innovative therapeutic options.

Timolol was the first β-blocker approved by the FDA for topical use in 1978 as a treatment for glaucoma. Despite promising reports as early as 1980 showing the effectiveness of Timolol drops in treating headache[8] there is a paucity of comprehensive studies and reports on this subject. While Timolol is an FDA-approved treatment for migraine prophylaxis, with various other β-blockers its role in abortive therapy remains under-explored. The precise mechanism of action of β-blockers in migraines is not fully elucidated; however, their known effects include inhibition of nitric oxide synthase, interaction with the serotonergic system, inhibition of thalamic relay neurons, and block of central sensitization.[9]

Migliazzo and Hagan revived the applicability of β-blocker ophthalmic drops for the treatment of migraine with their case series in 2014.[10] They administered β-blocker ophthalmic drops to treat acute migraines, proposing the hypothesis that these drops led to immediate instillation and rapid systemic absorption of solution by the nasal mucosa via the lacrimal duct. This process enhances bioavailability and expedites absorption by bypassing the first-pass metabolism, to achieve blood levels comparable to intravenous injection. This administration route addresses the prompt relief sought by migraine patients due to the intense and debilitating nature of the condition.

The widespread usage of β-blocking eye drops indicates their safety across diverse populations. Along with its affordability, wide availability, overall tolerance, and favorable benefit-to-risk ratio, it enhances its appeal. Importantly, it may be more applicable to the elderly or individuals with cerebrovascular or cardiovascular diseases, conditions that contraindicate the use of triptans or other sympathomimetics. Although migraines generally tend to diminish with age, a significant subset of older patients still experience migraine pain. Existing literature points to additional common side effects, such as generally mild hypotension, bradycardia, and bronchospasm. Consequently, patients with reactive airway disease and bradycardia are considered relative contraindications for topical β-blockers.

In the manuscript titled "Intranasal Administration of 0.5% Timolol Beta Blocker for the Successful Management of Acute Migraines in a Referred Headache Clinic: A Case Series" authored by Kosa and Hagan,[11] a retrospective analysis of patient records was conducted to assess the effectiveness of intranasally delivered timolol in treating acute migraines in patients previously refractory to other treatments. An intractability score was assigned based on patients' migraine histories to categorize the refractoriness of their migraine headaches to prior treatments.

Patients were instructed to administer one spray (0.1 ml) of 0.5mg of timolol in each nostril at the onset of an acute migraine, with the option of a second set 15 minutes later in cases of persistent symptoms. The total number of sprays was limited to four within 24 hours. Out of the 30 prescriptions for nasal spray, a little more than half filled the prescription. Lack of insurance coverage, lack of familiarity, or intolerance of nasal spray medications being the main reasons for not taking the spray. Among the patients who used the nasal spray, 62.5% reported a favorable response and chose to continue it as an abortive migraine treatment. Only one reported mild nasal congestion as a side effect but continued the medication. The intranasal

application of timolol was well-tolerated, overcoming hurdles associated with topical eye medication.

While the report is encouraging, certain gaps remain unaddressed. Specifically, the report lacks details about the patients' ongoing migraine medication and its most recent dose. Introducing a washout period between the current treatment and the nasal spray would have enhanced the interpretation of observations linked to the nasal spray. Although patients were instructed to use the nasal spray exclusively, adherence to this directive remains unclear, creating uncertainty about the potential concomitant use of their previous medication.

The results are reported as positive response to the nasal spray, but the definition of a 'positive response' is not provided. The report does not explore the intractability with the nasal spray, and information regarding the frequency of nasal spray usage per episode, time for pain resolution, and the extent of improvement achieved is also unavailable. The report lacks details on the number of prior episodes and whether there was a reduction in the frequency and intensity of migraine after using the nasal spray. These considerations should be considered when evaluating the efficacy of the nasal spray. It is also crucial to note the small sample size and the absence of a control group.

Although this is a retrospective chart review with inherent constraints, the paper has several strengths. This report contributes to the promising literature recommending timolol as a viable option for acute migraine treatment using a novel delivery. To my knowledge, it stands as the first world literature report of patients treated with a β-blocker nasal spray for acute migraines, with no stronger study designs available in the literature. There is a clear demonstration of efficacy in a well-established migraine population, including documentation of the refractoriness of migraine to prior abortive therapies using an intractability score that was not self-reported by the patient but assigned to by a neurologist.

The authors acknowledge the imperative need for further research to substantiate timolol's effectiveness in treating migraines through larger prospective blinded randomized placebo-controlled trials. These trials should assess the efficacy, tolerability, safety, and dosing using clearly defined subsets of patients with migraine (episodic or chronic, with or without aura). This report highlights the potential of intranasal β-blockers, especially timolol as an alternative approach to abortive migraine treatment.

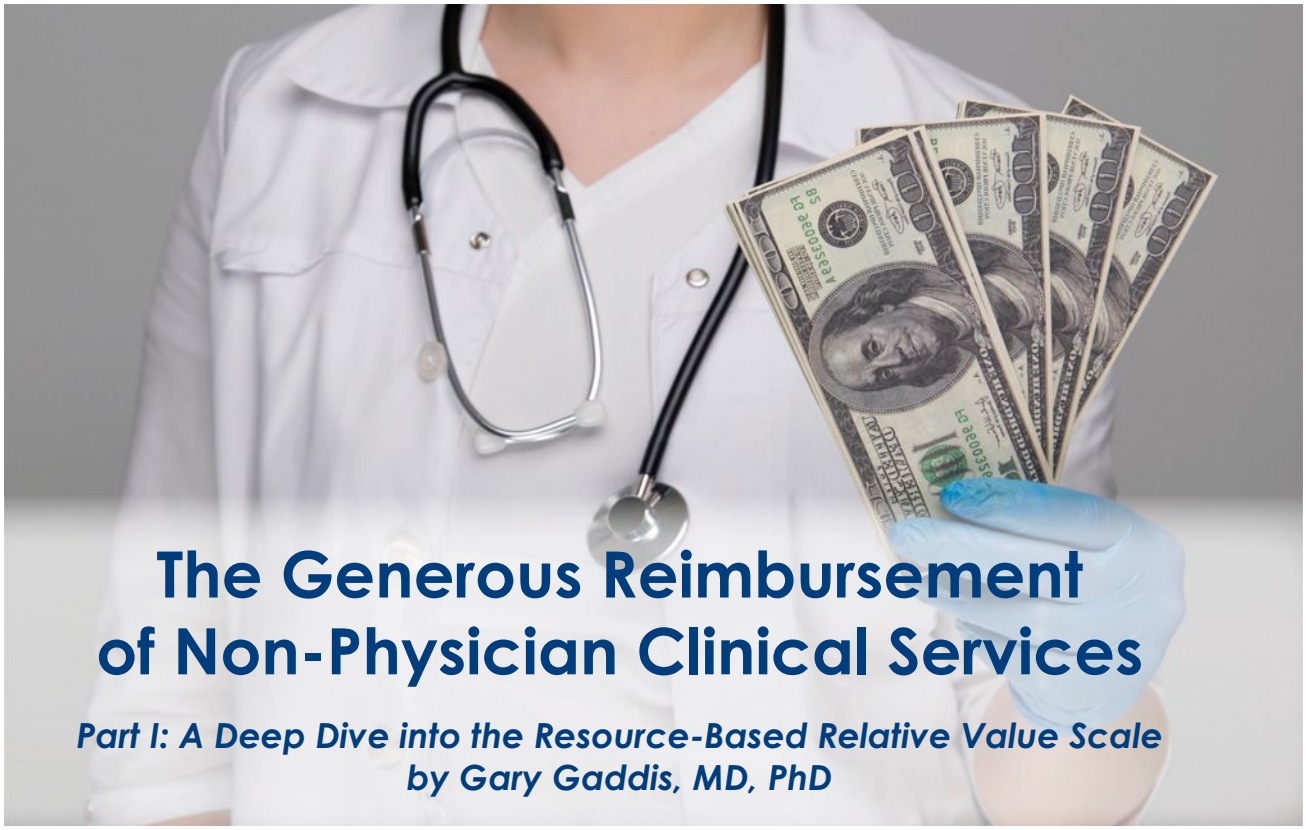
The low cost, widespread availability, favorable adverse event profile, and relatively successful tolerance of this medication support its use. The immediate systemic absorption may provide quick, safe, and inexpensive treatment for a prevalent, globally impactful condition associated with significant disability. If the β-blocker nasal spray is proven effective in rigorous clinical trials, this innovative approach to acute treatment would significantly enhance the care of migraine patients, particularly underserved and vulnerable patients who are uninsured or underinsured.

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Response Drs. Kosa and Hagan

The authors of the study in question, Drs. Steven C. Kosa and John C. Hagan, III agree with this assessment of their manuscript and thank Dr. Koirala for his comments. **MM**



The Generous Reimbursement of Non-Physician Clinical Services

Part I: A Deep Dive into the Resource-Based Relative Value Scale

by Gary Gaddis, MD, PhD

Many Missouri patients and physicians value the care that Physician Assistants (PAs) and Advanced Nurse Practitioners (ANPs) can provide. Missouri requires ANPs to work in cooperation with a collaborating physician.[1] Missouri PAs cannot practice independently.[2] However, in some states, ANPs have been granted "Full Practice Authority" (FPA) and can legally diagnose and treat patients without physician supervision, under authority of a State Board of Nursing.[3] Recently, some PAs have been seeking an equivalent status. Utah, North Dakota, and Wyoming appear to be the closest to permitting this.[4]



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Under Medicare and the Balanced Budget Act of 1997, non-physician-directed care is reimbursed at one of two rates. Those rates are lesser of the 80% of the charged amount, or 85% of the fee that Medicare would agree to pay a physician.[5,6] However, ANPs have been seeking reimbursement parity with physicians since at least 2011.[6-8] They argue that equivalent work should yield equivalent pay.

On the surface, pay parity may appear reasonable. However, the ANPs' arguments for pay parity conveniently overlook Medicare's payment methodology. Medicare rules include that an ANPs' reimbursement should be less than a physician's, because their preparation is much shorter in time and less extensive in depth.[5] Further, ANPs' advocacy for pay parity includes specious arguments that ANP and PA care is equivalent in quality and not higher in cost, compared to physician care.

These matters underpin this manuscript, as the first of a two-part series. This installment will present:

- Compelling evidence that non-physician led care is less safe and more costly than physician-led care.

- An overview of the "White Paper" from the Robert Wood Johnson Foundation that underlies and explains non-physicians' seeking of what they would call an expanded scope of practice, but which most physicians would term "scope creep."
- An overview of what "Full Practice Authority" is and where it has been granted to ANPs.
- General factors that influence payment for medical services rendered, as provided by the Resource-Based Relative Value Scale (RBRVS).
- What is necessary to enable a physician to legally bill under their name, when providing care in conjunction with an ANP or PA.
- Not only is non-physician-led care more costly and less safe, but the ANP community is not being truthful when they argue that they are the solution to rural Missouri's care access disparities.

The second installment of the series will explain:

- In detail, why pay parity with physicians for non-physician-directed care would not be consistent with Medicare law.
- Why it is proper to assert that non-physicians who bill Medicare or commercial insurers for the clinical care they have rendered are currently being systematically overpaid. (Current reimbursement practices to not appropriately discount ANP and PA reimbursement consistent with their lower "opportunity cost" to obtain their professional degree and certification.)
- A numeric justification to quantify a decreased range for Medicare reimbursement of ANPs and PAs that would be consistent with Medicare's payment methodology.
- Troubling aspects of many ANP training programs suggest the reform of ANP training programs is long overdue. Many ANP programs retain an "apprenticeship" model. Such program design in medical education was eradicated by the Flexner report of 1910.[9]

What about Non-Physicians' Quality and Cost Arguments?

The quality and cost assertions proffered by non-physicians ignore recently published and important findings:

1. Research performed at a multispecialty clinic in Hattiesburg, Mississippi, at which some patients were managed by non-physicians while others were managed by physicians, clearly indicated the superiority of physician-led care:[10]

> Data from 2017-2019, derived from more than 20,000 Medicare beneficiaries, revealed that non-physician primary care providers had an 8% higher referral rate per disease to specialists than did primary care physicians. Patients not managed by physicians were 1.8% more likely to have visited an emergency department, compared to patients managed by a primary care physician. Such outcome disparities would not have existed if ANP and PA care was equivalent to physician care, because patients managed by non-physicians were demonstrably younger and healthier. Concerning disparities were also observed outside of primary care. Non-physicians working in specialty departments were 7% more likely than physicians to refer their patients to another specialist. Overall, physicians performed better in 9 out of 10 quality metrics and received higher patient satisfaction scores.[10]
>
> Cost data were compelling. Spending for patients enrolled in the Hattiesburg Clinic's Medicare Accountable Care Organization (ACO) was nearly $43 higher per member per month for patients whose primary care was directed by a non-physician, translating to an additional $10.3 million in spending annually. After further adjusting for the increased complexity that characterized physician-managed patients, that number jumped to over $119 per member per month, or $28.5 million more annually."[10]

It is not good for Medicare's financial health to place lower wage non-physicians in charge of patient care. America has more than 65 million Medicare enrollees.[11] An added cost of $43 per Medicare enrollee per month projects to an added burden to

> America's financially-challenged Medicare program to nearly $2.8 billion per month, or $33.5 billion annually. The incremental cost of $119 per member per month that corrects for patient age and acuity projects to more than $7.73 billion per month, or more than $92.8 billion annually. Medicare's trust fund is currently projected to be depleted by 2031.[12] For 2022, the most recent year with complete data, Medicare spending grew 5.9% to $944.3 billion.[13] A sum of $92.8 billion would represent 9.83% of the Medicare spending for the entire year of 2022!
>
> Fortunately, most care of Medicare enrollees is led by physicians, so these numbers are useful for illustration only. However, these projected numbers show how America would be paying dearly if our nation transitioned to non-physician-led care.

2. Data from 44 Veterans Administration emergency departments, published by two economists with no reason to favor or disfavor physician-led care, yielded concordant conclusions, when outcomes for physician-led care versus ANP-led care were compared:[14]

> On average, ANPs "…use more resources but achieve worse patient outcomes relative to physicians." When delivering emergency care, ANPs had 11% longer lengths of stay and a 20% higher rate of preventable hospitalizations, and ordered more tests and specialty consults, when compared to emergency physicians. Further, the costs of lower productivity of non-physicians surpassed the pay differences between the professions. NPs increased the cost of ED care by about $66 per patient, or 7%.[14]
>
> The authors did note that the disparities between results obtained by physicians versus ANPs narrowed for more-experienced ANP, when compared to less-experienced ANPs.[14] This suggests that the clinical preparation of the ANPs, before they were hired and deployed in VA emergency departments, was inadequate. Inadequate educational preparation of ANPs should be concerning not only to physicians. Policy makers should be especially alarmed. These matters will be further discussed in the second manuscript of this series. That manuscript will advocate for changes to the ANP educational system analogous to the educational reforms promulgated after the Flexner Report of 1910,[9] because the current clinical training model of NPs remains mired in an apprenticeship model that is long overdue for reform.

3. With the current opioid death epidemic, it is also relevant that using 2015 Medicare claims data, a retrospective analysis by Lozada et al.[15] determined that when compared to opioid prescribing patterns of physicians, ANPs or PAs who worked in primary care and prescribed at least 50 prescriptions, prescribed many more opiates than physicians:

> Six point three percent of ANPs and 8.4 percent of PAs prescribed opioids to more than 50 percent of their patients, compared to just 1.3 percent of physicians. ANPs and PAs in states with independent prescription authority for schedule II opioids were 20 times more likely to overprescribe opioids than ANPs and PAs in states with restricted prescription authority.[15]

Why Have the Numbers of ANPs and PAs Proliferated, and What Underlies "Scope Creep?"

No examination of non-physician reimbursements for clinical care would be complete without also explaining the recent proliferation of ANPs, as well as the "Scope Creep" for which ANPs (and, to a lesser extent, PAs) have been advocating.

Advocacy for the "scope creep" sought by many ANPs is grounded heavily in the 2011 "White Paper" from the Institute of Medicine (IOM), funded by the Robert Wood Johnson Foundation (RWJF), entitled "The Future of Nursing: Leading Change, Advancing Health."[6]

The four key recommendations of that IOM "White Paper" included:

1. Nurses should practice to the full extent of their education and training.
2. Nurses should achieve higher levels of education and training through an improved education system that promotes seamless academic progression.
3. Nurses should be full partners, with physicians and other health professionals, in redesigning health care in the United States.
4. Effective workforce planning and policy making require better data collection and an improved information infrastructure.

Figure 1. Advanced Practice Nurse Practice Laws in the United States



Source: American Association of Nurse Practitioners October 2023

These recommendations underpin advocacy for nationwide development and deployment of a cadre of ANPs, with "Full Practice Authority." Much less attention has been paid to the idea of developing an "…improved education system." Indeed, the nation still awaits such educational reform, as will be further detailed in Part II in the next issue of *Missouri Medicine*.

What is "Full Practice Authority?"

"Full Practice Authority" is defined as a condition under which non-physicians can prescribe, diagnose, and treat patients without physician oversight.[3] Non-physicians who practice in "Full Practice" states are also allowed to establish and operate their own independent practices in the same manner as physicians.[3]

Where Do ANPs and PAs have Full Practice Authority?

Figure 1 shows the three different statuses enjoyed by ANPs.[17] Two states that adjoin Missouri, Nebraska and Iowa, grant ANPs "Full Practice Authority."[3] Further, every state located north and west of Missouri, plus Colorado, New Mexico, Nevada, and Arizona, and Maryland, the District of Columbia, and all of the New England states, also permit Full Practice Authority for ANPs.[3]

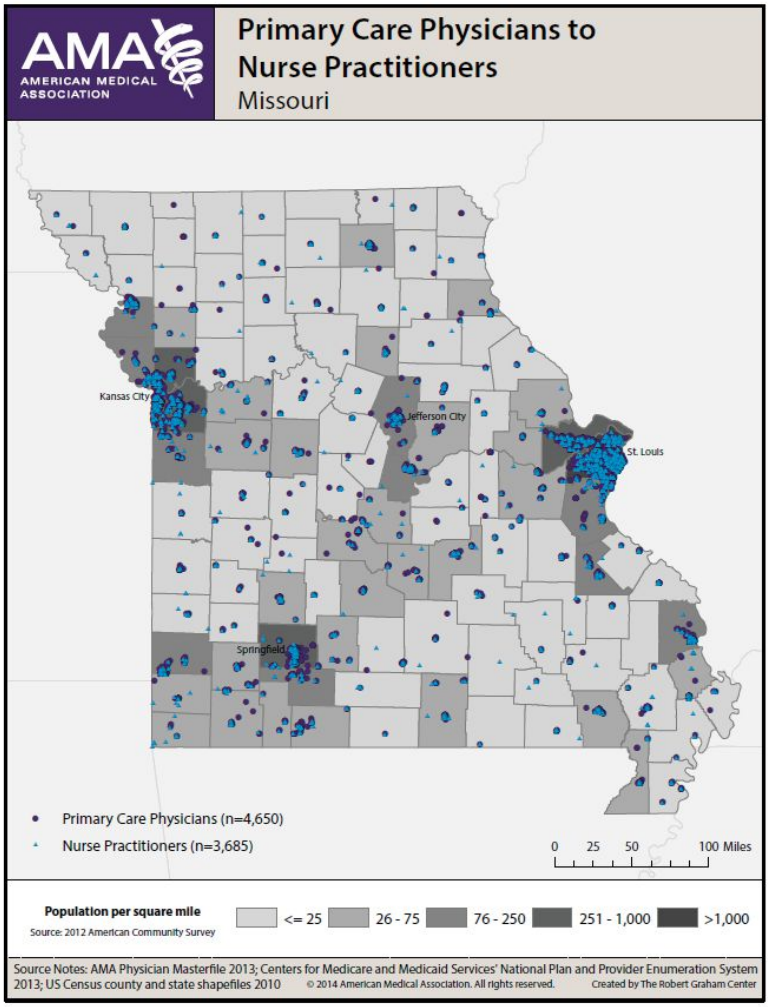
Fortunately, Missouri, as well as nine other states, restrict ANPs to "Limited Practice Authority," meaning that they must practice in close collaboration with a collaborating physician.[3,17]

Currently, no states grant FPA to PAs, but PAs have come closer to obtaining FPA in at least three states (UT, ND, and WY, as noted above).[4]

An Understanding of the Resource-Based Relative Value Scale (RBRVS) is Crucial

In directing a focus back to non-physician reimbursement for medical services rendered, a direct application of the RBRVS formula, as adopted by federal law, demonstrates that when

Figure 2. Primary Care Physicians to Nurse Practitioners. Missouri, 2013



they are not supervised by a physician, ANPs and PAs are currently being overpaid, when compared to physicians. This potentially explosive allegation is supported by the fact that current Medicare reimbursement rates are not consistent with the Resource-Based Relative Value Scale (RBRVS) formula, as first developed by W.C. Hsiao and others in the 1980s,[18,19] and subsequently utilized by the Centers for Medicare and Medicaid Services (CMS) since 1992.[20]

The mechanics of the RBRVS formula explain this assertion. The RBRVS is used to convert codes for procedural (Proc) services and "evaluation and management" (E&M) services to the number of "Relative Value Units" (RVU) that correspond to each existing code.

Key Mechanical Features of RVUs in the RBRVS

The two key factors for determining the RVU value of any medical services provided are:[18-20]

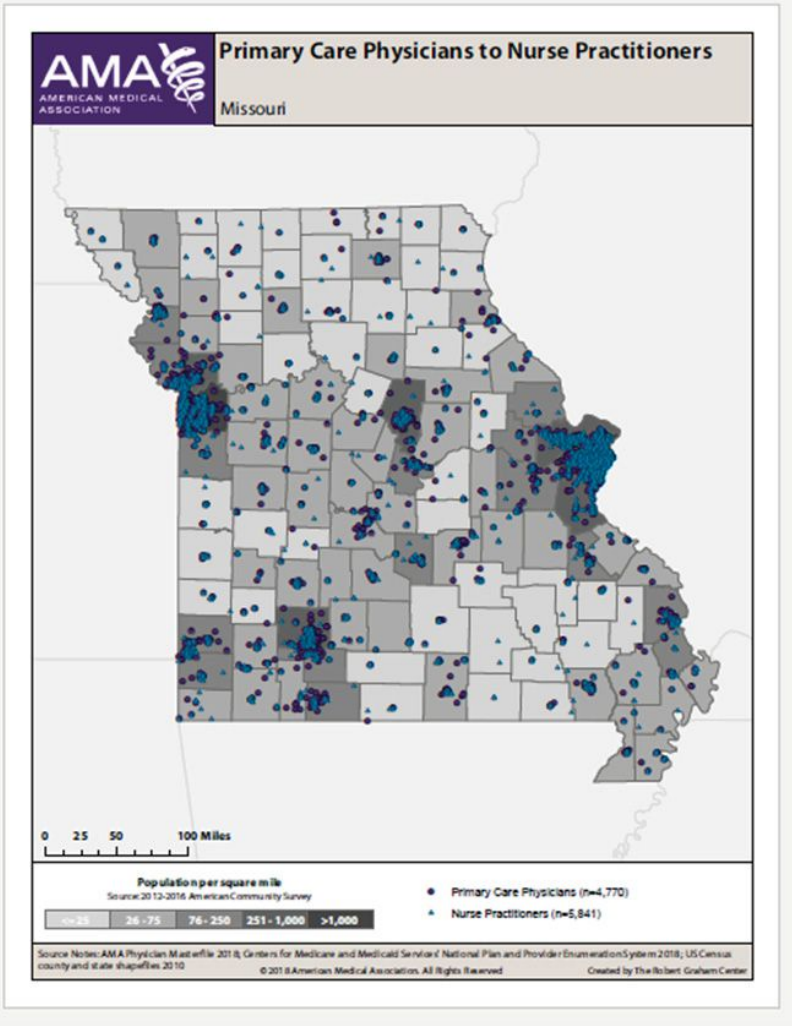
1. The complexity of the service
2. The *amount of training required* to be capable of providing that service.

Under Medicare, the RVU assigned to each Proc or E&M service, as coded under the guidance of the American Medical Association's "Current Procedural Terminology" (CPT) resource,[21] is multiplied by a Conversion Factor (CF), to yield the reimbursement provided for that service or procedure.[18-20] Along with applying the CF, various other adjustments are made, related to one's geographic location and to the variable and fixed costs that accrue to the different medical specialties, to determine the exact payment for any medical service. This is further detailed below.

Because the duration of training of all non-physicians is markedly less than that of physicians, one would logically expect that the RVUs that correspond to the clinical services they provide would be directly proportionately less than the RVUs credited for physician-provided care. Such is currently not the case, and advocacy for pay parity on the part of ANPs conveniently overlooks this difference.

Most commercial insurers reimburse at a multiple of the Medicare rate for all Proc and E&M codes. Thus, not just Medicare reimbursements, but also reimbursements paid to non-physicians by commercial insurers also represent overpayments. The key "take-away" is that ANP clinicians practicing independently are being excessively compensated for virtually all clinical care not remunerated by the Medicaid program or by the TriCare program for military members.

Figure 3. Primary Care Physicians to Nurse Practitioners. Missouri, 2018.



How Does Physician Supervision Impact Medicare Reimbursement?

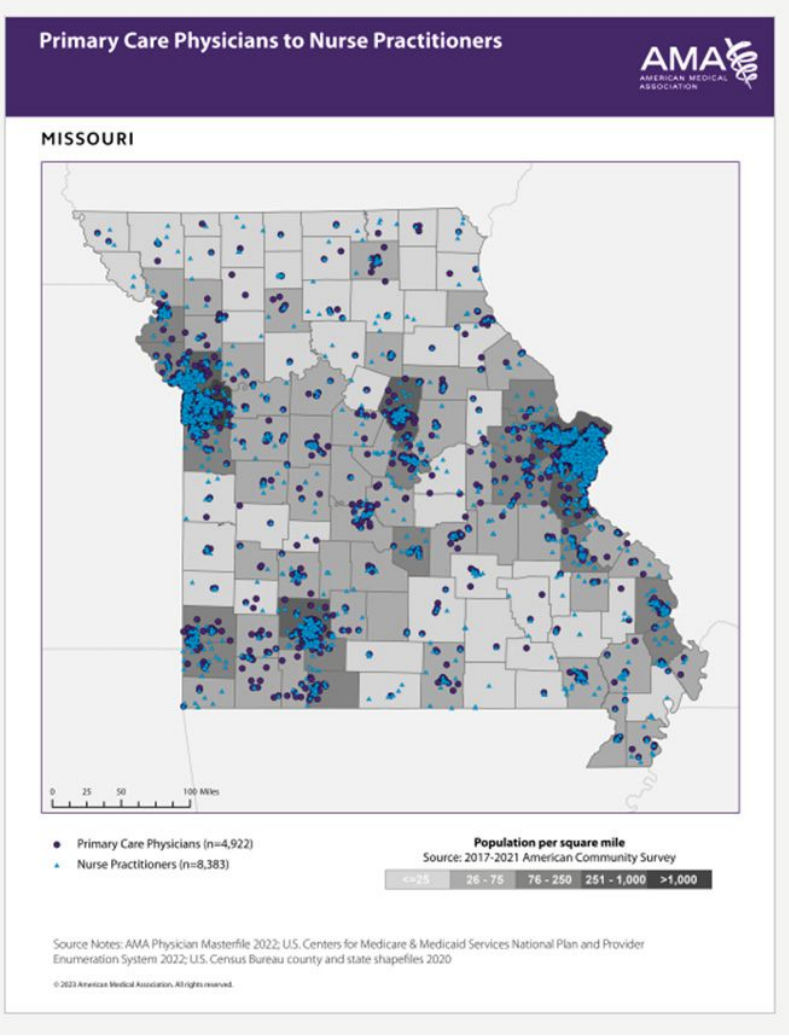
As briefly noted above, Medicare's reimbursement for care provided by a non-physician depends upon whether direct on-site physician supervision and participation in that care has occurred. Medicare payment is made at 100 percent of the Medicare rate when care is supervised by the physician and billed under the physician's name. Reimbursement occurs at 85 percent of the Medicare physician rate when that care is billed under a non-physician's name,[5] such as occurs when a collaborating physician is not involved in real time with the patient's care, or when an ANP is practicing with "Full Practice Authority."[4] This is true whether that care is billed utilizing an E&M code or a Proc code.

For independently practicing physicians and for organizations that employ physicians who work alongside PAs and ANPs, this differential in reimbursement (85% vs. 100%) provides a strong motivation for physicians to closely supervise their non-physician ANP and PA colleagues in real time, to legally enable maximization of revenues. For clinical services to be legally billable under the physician's name, the physician must have performed a "substantive portion" of the service during the face-to-face clinician-patient encounter. A "substantive portion" of the service having been provided by a physician is defined to have occurred when 1) the physician personally performs either the history, exam, or medical decision making (in its entirety), or 2) the physician provides *more than half of the total time* by expended by both the physician and the ANP (or PA), when considering both the "face-to-face" and the "non-face-to-face" components of patient care activities, or 3) the physician supplies the medical decision-making.[22]

Thus, it is incontrovertible that under current law, payment for non-physician care at 100% of the physician's RVU value can only occur when the non-physician health care provider works jointly and closely with a physician. By extension, it is also incontrovertible that current reimbursement law inherently rewards physician-led care in a manner that recognizes and rewards their extra training and preparation.

The "take-away" is this: clearly, for physicians to bill for ANP-provided or PA-provided care at 100% of the physician rate, they must have been heavily, directly and concurrently involved

Figure 4. Primary Care Physicians to Nurse Practitioners. Missouri, 2022



in providing that care in collaboration with the ANP or PA. And, it is clear under current law that ANPs operating under "Full Practice Authority," and ANPs not working alongside a collaborating physician are to be reimbursed at 85% of the physician rate.

What is the National Total of Clinical Care Currently Provided by ANPs and PAs?

Due to the fact that much ANP- and PA-provided care is provided in conjunction with a physician and billed at 100% of the physician rate, and because physicians are meeting the "substantive portion" requirement and directly supervising the care provided by their non-physician colleagues, it becomes difficult if not impossible to utilize data bases tracking medical payments to fully quantify the amount of clinical care currently provided by non-physicians.

Do ANPs Locate to Areas that Are Medically Underserved?

Examination of the American Medical Association's "Primary Care Physicians to Nurse Practitioners" maps for Missouri for 2013[23] (Figure 2), 2018[24] (Figure 3) and 2022[25] (Figure 4) clearly demonstrate that the ANP community's assertion that ANPs will fill medical care access disparities that plague rural areas of our state are a form of systematic prevarication. This information adds to the body of data regarding the lesser quality and financial efficiency of non-physician care, and supports the premise that the ANP community is systematically misleading Missouri legislators and Missouri's citizens regarding the quality of their care, and where they provide such care.

Missouri's legislators would be wise to adopt a "buyer beware" (*caveat emptor*) approach to the claims of ANPs who seek Full Practice Authority.

Part II - An Indication for Non-Physician Education Reforms

Having begun to introduce the RBRVS in this manuscript, Part II will lead the reader through a "deep dive" into RBRVS methodology, toward a quantitative explanation why it is correct to assert that non-physicians are currently reimbursed more generously than an even-handed application of the RBRVS methodology would allow. Further, in focusing attention upon ANPs' educational processes, the reasons why ANPs underperform physicians will be

delineated. The manuscript will close by advocating that an overhaul of ANPs' educational processes, in a manner analogous to the changes in medical education occurring after the Flexner Report, is clearly indicated and long overdue, to remediate the numerous deficiencies in current training of ANPs.

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MM

Mental Health and the Graduate Medical Education Trainee: Emergent Concerns

by Brook V. Nelson, MD

When we honestly look at our profession, identifying some of our challenges does not take long.



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Seated in a cold lecture hall at a national meeting of surgeons, a chill ran up my spine as I heard for the first time that 20% of surgical trainees experience suicidal ideation at some point during their training. As a new program director, I was horrified, shocked, and deeply saddened. Over the subsequent years, I have learned that burnout, depression, and thoughts of suicide are much more common in graduate medical education trainees than most of us have ever imagined, and the problem seems to be worsening. It is incumbent upon those who work in graduate medical education, especially programmatic leadership, to address these concerns early in training and keep an open line of communication with trainees to allow early intervention.

Between 2000 and 2014, 324 residents died in ACGME-accredited residency programs. Suicide was the leading cause of death for male residents and the second leading cause for female residents.[1] Approximately 300 – 400 physicians die each year due to suicide, averaging over one physician dying every day, a rate twice as high as the general population, even higher than the military and law enforcement officers, and four times as high for women physicians as for the average woman.[2] The increased risk of suicidality can begin even earlier in training, with some studies showing medical students to be three times as likely as age-matched peers in the general population to die from suicide, with nearly 10% of graduating medical students and residents in all specialties reporting suicidal thoughts within the prior two weeks.[3]

As physicians, we naturally ask why this is occurring and what puts us at such elevated risk. When we honestly look at our profession, identifying some of our challenges does not take long. From entry into medical school, trainees are vying against a greater number of candidates annually for a limited number of residency training positions, with 48,156 applicants for residency positions last year alone and an 81% overall match rate for active applicants.[4,5] Trainees face incredibly high debt

Table 1. The Five Vital Signs of Physician Mental Health[11]

Health	Increasing use of medications and/or alcohol or illicit drugs Talking about wanting to hurt themselves or die
Emotions	Experiencing extreme mood swings Feeling hopeless or having no purpose
Attitude	Being negative about professional and personal life Having inappropriate outbursts of anger or sadness
Relationships	Withdrawing or isolating themselves from family, friends, and coworkers Talking about being a burden to others
Temperament	Acting anxious or agitated; behaving recklessly Being uncomfortable, tired, or in unbearable pain

burdens, personal and family expectations, sleep deprivation, and secondary trauma from their experiences providing care to the most ill.[3] It is also no secret that, as physicians, we are often some of the worst patients, and over 40% of physicians report reluctance to seek treatment for mental health concerns.[6] Concerns over being able to maintain unrestricted licensure, what has been described as the "physician personality," with an exaggerated sense of personal responsibility, isolation, a survival mentality, and pervasive imposter syndrome are all reasons that have been cited for physicians being less likely to reach out for help.[6]

The ACGME has been working to address the concerns of resident well-being by expanding the Common Program Requirements (CPR), explicitly addressing the increased risk of burnout and depression in faculty and trainees. Within the CPR, multiple mandates are in place for programs, including having 24/7 access to mental health assessment and services and self-screening tools. The ACGME also stipulates that trainees must have time off to attend appointments for medical care, including mental health care.[7]

In addition to implementing the ACGME CPR for well-being, what can a training program do to reduce the risk of suicidality in their trainees? One of the most effective ways program directors reach their trainees is to normalize and increase awareness of the problem. Help the trainees understand that depression during training and their careers is common and not unexpected. Talk openly about imposter syndrome, burnout, and how common it can be to have thoughts of self-harm, and that the most important thing they can do is to reach out to a peer, their program administration, or other services. Program Directors must ensure that all trainees have ready access to their ACGME-mandated mental health services, usually in the form of an Employee Assistance Program (EAP), and that other resources, such as the National Suicide Prevention Lifeline (which is accessible by calling or texting 988, or chatting at 988lifeline.org), and that these resources are readily available and posted in resident work areas, lounges, and available online on resident management software such as New Innovations. At minimum, resident well-being must be addressed at every semi-annual evaluation, and residents should be encouraged to reach out about peers concerned may be at risk.[8] Additionally, consider using natural light lamps in workspaces for residents on night shifts or during the winter months; this can be tremendously helpful for trainees who may have struggled with seasonal affective disorder in the past.[9]

Addressing specific concerns that lead to increased risk of depression in physicians and, subsequently, increased risk of suicidality is undoubtedly beneficial. Regarding seeking treatment, the American Medical Association continues to work with licensing bodies to not penalize physicians for seeking treatment for mental health concerns, advocating for a

change of wording on licensure applications to read, "Are you currently suffering from any condition for which you are not being appropriately treated that impairs your judgment or that would otherwise adversely affect your ability to practice medicine in a competent, ethical and professional manner? (Yes/No)."[10] Implementing this policy by all licensing bodies would increase the likelihood of physicians seeking treatment for mental health concerns.

Vital Signs: The Campaign to Prevent Physician Suicide has become a new and outstanding resource for combating this pervasive problem.[11] Offering resources and toolkits, and much like other algorithms physicians use to evaluate patients, it encourages us to look for the suicide prevention vital signs in our trainees and peers. On NPSAday.org, training institutions can denote their support, find toolkits with many resources for physicians and training programs, and access personalized support resources for physicians and trainees.

Since sitting in that lecture hall and first hearing the chilling statistics of physician suicide and the risk trainees experienced, my world as a program director has changed. I speak openly of suicide and depression risk to my trainees multiple times per year. I encourage a culture of safety where anyone can reach out about a peer who may be having challenges at any time in a confidential manner, and I have implemented all the techniques I have listed above. I have seen the direct positive results of residents feeling comfortable reaching out and sharing if they struggle. Physicians, especially those responsible for training future generations, must address depression and suicide risk in trainees aggressively from orientation onward. We must lead the way to positive change in our profession and address barriers to physicians seeking mental health treatment. We must confront the aspects within ourselves and our profession that have resulted in being a physician becoming the occupation with the highest risk of suicide.

September 17 has been designated National Physician Suicide Awareness Day. I encourage you to share the risk of physician suicide with your colleagues, to reach out to that colleague or trainee you are concerned about and let them know they are not alone. I encourage all of us to let go of shame or fear of reprisal associated with seeking treatment for mental health concerns and challenge us to create a better future for our trainees.

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MM

My Story

by Charles Van Way, III, MD

Growing up, I tried out several careers. To begin with, I was destined to become an Army officer. Raised in an Army family, I wanted to follow in my father's and grandfather's footsteps. But by high school, I became a serious tech nerd. I was going to be an engineer! I worked summers in one of the early computer development labs at the National Bureau of Standards. Engineering lasted through my freshman year at Cornell. I transferred to Yale as a Physics major. That lasted one year, too. Then I decided to go to medical school. I majored in History, but I got into Johns Hopkins anyway. In those days, a liberal arts major was a plus.

While surviving medical school, I vacillated between cardiology and surgery. I chose surgery, and trained at Vanderbilt in General, Vascular, and Cardiothoracic surgery at Vanderbilt. Training was a little broader in the 1960s than it is today. By the time I finished, I was committed to an academic career. I've never had any regrets. Combining operative surgery with training of residents and medical students, and then being able to carry out research as well, has been deeply satisfying. I've had a wonderful professional life.



Dr. Van Way presenting at the Meuse-Argonne National Cemetery, France, 2022.

Medical research has been a major part of my career. During medical school, at the National Institutes of Health, I worked in a laboratory studying hemoglobin. Then I did a research fellowship in Clinical Pharmacology, at Vanderbilt. Later, in Colorado, I was the director of the surgical research laboratory. And in Kansas City, I carried on at University of Missouri-Columbia, eventually setting up the Shock Trauma Research Center with Drs. David Morrison and Nilo Qurishi. Through all this, I continued clinical research in nutrition support.

So… what about the Army? Back in the 1960s, you signed up with the Barry Plan or you were drafted. I signed up under the Barry Plan, completed my residencies and fellowship, and served two years at Ireland Army Hospital, Ft. Knox, KY, as chief of thoracic surgery. I liked the Army. Several years later, I rejoined the Army Reserve, and served another 25 years. I've been all over the US, to Japan and Okinawa, commanded units of all sizes, attended the Army War College, and have had a rewarding military career. In my way, I kept up the family legacy.



Charles Van Way, III, MD, Thoracic Surgeon, Colonel, US Army, Missouri Medicine Contributing Editor, and MSMA Past President.



Dr. Van Way at the battlefield, Second Battle of the Marne, 2023.



Dr. Van Way with wife Gail at his inauguration as MSMA President in 2007.

After Fort Knox, I took a job at the University of Colorado, under Tom Starzl, MD. It was an exciting place to work. I operated, did research, published books and papers, spent a tour as chief of surgery at Denver General Hospital, learned to ski, and generally had a fine time for 14 years. But Dr. Starzl left, and what with one thing and another, I felt it was time to move. I accepted a position as the Program Director of Surgery at St. Luke's in Kansas City. The St. Luke's program was academically tied to UMKC, and we merged the surgical residencies in the 1990s. I became Chair of Surgery at UMKC in 2000, moving my practice to Truman Medical Center. After another few years, I moved to the Sosland Endowed Chair of Trauma Research at UMKC. After another few years I decided to retire. Instead, the hospital offered me a part-time job supervising nutrition support. I'm still working at University Health, but I must admit that it's nice to be just part-time. My academic appointment is Emeritus Professor.

I should comment on my interest in nutrition. Going back to my Vanderbilt years, I worked with some of the pioneers in parenteral and enteral nutrition. I've published papers, and several books on nutrition. I've been President of the American Society for Parenteral and Enteral Nutrition (ASPEN), held several other offices with the organization. My activities in ASPEN have been a constant anchor for my often-changing professional life. While my primary clinical interest has always been general and thoracic surgery, my work in nutrition has been a major part of my professional life. I was honored with a "Lifetime Achievement Award"at the ASPEN meeting in March 2024.

Somehow, I've always been involved in leadership activities. I was chair of surgery at Denver General Hospital early in my career. I had leadership positions in Kansas City, first at St. Luke's Hospital, and then at the UMKC. As noted above, I had several leadership positions in the Army. And after I came to Kansas City, I became active in organized medicine. I joined the Kansas City Medical Society (then the Metropolitan Medical Society of Greater Kansas City) in the early 1990s. I was editor of their journal for about 20 years, was on the Board,and served as President. I became active in the Missouri State Medical Association,

serving on the Council, and then as Chair of Council and President. After that, I joined the MSMA Delegation to the American Medical Association. I'm still doing that. I've been a Contributing Editor to *Missouri Medicine* for 20 years.

I've done a lot of things in my career—published papers, conducted research, authored books, served on national committees, and edited journals. But the greatest satisfaction has come from three things. First, caring for patients has been a constant source of satisfaction. Second, relating to colleagues, including doctors, nurses, and all the others in the health care team. And third, training younger colleagues as surgeons. They have gone out into practice, or academics, and have done amazing things. For example, Jonathan Patterson, MD, when he became a Missouri State Representative, introduced me on the floor of the House. Scott Kujath, MD, was president of the Kansas City Medical Society, and Brian Biggers, MD, is Chair of Council of MSMA.

From a personal perspective, I was married to Margery in medical school. In Nashville, we had two boys, Craig and Brian. Things began to fall apart in Denver, and we divorced after 25 years. It was painful, but probably the best for both of us. The boys still live in Colorado. One is a software engineer for Oracle and the other works for a law firm in Colorado Springs. Then, I married Gail in 1987. We have a daughter, Whitney, who lives in Kansas City and works at CBIZ Corporation, on the Plaza.

Retirement has been its own reward. (Okay, semi-retirement.) I have always been interested in military history. I've been a volunteer at the National World War 1 Museum and Memorial for the last nine years. We even have our own lecture series among the volunteers. And, our own YouTube channel.

Long ago, I became an amateur radio operator in high school. I dropped out when I became too busy as a surgeon. I've taken it back up and have been active in amateur radio for 10 years as N0CVW. We have a station affiliated with the World War 1 Museum, WW1USA.



Above, Dr. Van Way, his wife, Gail, at daughter Whitney's graduation from Southern Missouri University in 2011.
Below, Dr. Van Way with sons Brian and Craig, in 2007.



I'm still getting up in the morning, eager to see what the day brings. The last couple of summers, I've gone to France to visit the World War 1 battlefields. Volunteer work at the World War 1 Museum and Memorial in Kansas City is fun. I still dabble with computers and software, six decades after my summer experiences with early computer development. Part time medical work is rewarding. It's been a great life, and there are still new things to do and to learn. Finally, I'm very thankful for my family, all my friends, and all my professional colleagues at University Health, and especially at the Missouri State Medical Association. **MM**

Learning to be Vulnerable

by Joanne Loethen, MD

"I think I'm having a stroke."

The words struggled to leave my mouth as I spoke to the 911 operator. Emotionally in disbelief, the words seemed so unusual to say out loud. Moments before, overwhelming nausea and drenching sweats had abruptly awakened me from sleep. Immediately regretting my meal the night before, I proceeded to the bathroom only to realize the room was relentlessly spinning—vertigo. Though the nausea could be blamed on my last meal, the vertigo could not.

The cool tile on the bathroom floor was a welcome sensation. The moisture on my skin succumbed to the coolness of the floor and the air around me. Between heaves, another sign suggested something was amiss.

"My swallow is off."

I said these words out loud on the off chance the emptiness of the room might respond. But even the escape of those words didn't seem right. Dysphagia and dysarthria. We use these two terms frequently in medicine to describe difficulty with swallowing and speech, respectively. The terms are not necessarily diagnoses themselves but are typically signs of an underlying cause. I still couldn't make sense of it all. The last sign became the final clue.



Joanne Loethen, MD, practices primary care in Internal Medicine and Pediatrics at University Health in Kansas City. She is an Assistant Professor of Medicine at the University of Missouri Kansas City. She is the MSMA Council Vice Chair and on the Missouri Delegation of the American Medical Association.

Had I slept in a way to make my left arm fall asleep? If so, why would my leg feel this way too? Numbness and tingling—the final pieces. Confusion was replaced by the realization: I was having a stroke.

Making my way dizzily back to bed, I noted the time—2:23 a.m. If this was indeed a stroke, I knew time would be important. Over the next two minutes, I had more questions than answers. But as I slowly came to terms with reality, I knew one question had to be answered: "Do I call 911?"

In retrospect, the question seems absurd, but given the improbability of the previous 10 minutes. My confusion at the time made it seem like a reasonable ask. I thought: "I'm only 37! Things like this don't happen to people like me,"

The arrival of emergency personnel was comforting. The initial evaluation revealed no obvious emergency—I was alert and answering questions, my vital signs were normal, and I didn't appear to be in any distress. "Would you like us to take you to the hospital?" they asked. I hesitated. I knew I needed to go. If a stroke was on the differential, certain tests and immediate treatment were needed.

"How much will it cost?" I asked. Such a strange question. Looking back now, I don't know why I even asked. It was probably a reflexive response. Having worked in a safety net hospital with countless uninsured or underinsured, I was well aware of the high cost of medical care. The cost of tests, procedures, and services was always top of mind.

The ambulance ride brought a sense of comfort. I still couldn't confirm what was happening, but the company of healthcare professionals was a welcome comfort in a time of unease. I was taken to the nearest stroke center—a place that happened to be where I trained as a physician. Memories of this hospital as a physician giving care would now be shared with memories as a patient getting care.

The nurses in the emergency room went through their pattern of lines, monitors, and initial questioning. I felt like a character in a well-rehearsed, choreographed performance. The physician soon followed. Imaging confirmed the diagnosis—a vertebral artery dissection was the culprit. The stroke was a consequence.

As the physician explained the findings, initial confusion was replaced by a sense of clarity. It felt like the "ah-ha!" moment at the end of a suspense movie—when the prior scenes that seemingly made no sense, suddenly clicked to explain the entire plot. In the preceding weeks, neck pain, paresthesias, and headaches pervaded my daily activities. Recurrent sleepless nights ensued as I tried to find relief from the discomfort. I attempted home remedies and inquired with colleagues about the presumed pinched nerve or muscle strain I continued to blame for my symptoms. Now, lying in the emergency department, the pieces fit. The small flap of an arterial wall deciding to divorce from its native position explained all of it.

Unease. Disability. Debt. Loneliness. Vulnerability. The flood of thoughts and emotions over the next 48 hours was incessant. I had cared for many patients with acute or prior stroke. Never did I think I would be on their side of the experience—at least not at my age. The affected part of my brain was small, and I was assured a full recovery. Still, the persistence of vertigo and dysarthria in the initial hours left me with uncertainty on the off chance a full recovery would not eventuate. With that unease came fears of disability. The career I'd poured exorbitant amounts of time, energy, and heart into—could it all be gone in an instant?

Being admitted to the intensive care unit once again brought anxiety about the financial implications. I knew the average daily cost of this level of care was in the tens of thousands of dollars. You might assume I would be grateful to be getting the care I needed, no matter the cost. You might think: "This is what insurance is for, right?" But I was not oblivious to the realities of our medical system. Even with insurance, thousands of dollars would be my responsibility—thousands of dollars I didn't have.

The most difficult emotions, however, were the loneliness and vulnerability of being hospitalized. One day I was vibrant and living a normal life and the next day I was alone and afraid lying in a hospital bed surrounded by alarms and well-intentioned strangers. Add to this the feeling of vulnerability from realizing I'm no longer invincible. The emotions I held steadfast throughout my life were now being painfully reshaped for all to see.

I wondered about the times I may have under-appreciated these same emotions in my patients. By not acknowledging the patient's vulnerabilities, does this shield us from having to face our own?

My experience is not unique but contains perspectives often overlooked in the care we provide. I wondered about the times I may have under-appreciated these same emotions in my patients. By not acknowledging the patient's vulnerabilities, does this shield us from having to face our own?

In the end, my story has a happy ending. I knew the signs of a stroke and understood they couldn't be ignored. My knowledge of strokes made seeking emergency care a non-negotiable. Family, friends, and my employer lent support that many could only imagine. My initial deficits diminished with time. Though the financial impact was great, I eventually overcame it. And be it fate or chance, a week later I met the love of my life—a man who would go on to become my husband. I know others under similar medical circumstances do not have a similar story.

Will this experience change the way I practice medicine? Probably not. Will it help me better appreciate the fear and uncertainty patients often face? I sure hope so.

Correspondence

Gaize Technology: Catch Cannibas-Impaired Drivers?

Last summer, at our Greene County Medical Society (GCMS) Breckenridge Conference, we learned that Colorado legalized recreational marijuana over ten years ago, and that the motor vehicle accident fatality rate related to marijuana had increased by 138% during that time.

We felt that the GCMS DWI Task Force should look into possible ways to deter similar problems in Missouri before we suffer a similar fate. A few weeks ago, I spoke with Gaize founder and CEO Ken Fichtler about the headset his company had developed to assist in the establishment of impairment secondary to drugs. We were specifically interested in evaluation of the impairment of drivers who had been using cannabis (THC is the psycho-active component). We knew that breath, serum, and urine THC levels do not correlate with impairment as a result of THC use. We also knew that certain eye changes seem to correlate with THC impairment. Mr. Fichtler indicated an interest in having the GCMS facilitate a study that would evaluate the correlation, and sent us a Gaize headset to evaluate.

The Gaize headset reportedly is able to detect ocular findings consistent with use of the most common drugs that can cause driving impairment: CNS depressants, CNS stimulants, hallucinogens, dissociative anesthetics, narcotic analgesics, inhalants, and cannabis. The ocular findings tested include Horizontal Gaze Nystagmus, Vertical Gaze Nystagmus, Lack of Convergence (LOC), and Pupillary Rebound (PR). The ocular findings are the same ones that would be typically tested by a DRE police officer in investigation of impaired driving by drugs.

Two Springfield Police DRE trained officers, a Greene County Prosecutor, and I received training on the Gaize headset, and found the device training credible and user friendly. It is also apparently able to provide objective written evidence of ocular findings. Since LOC also occurs in a small percentage of the general population, any positive LOC findings would also require a simple saliva test to confirm THC exposure.

In January 2024, a group of us met to discuss the Gaize headset technology, along with the author of the *JAMA* Article: "Evaluation of Field Sobriety Tests for Identifying Drivers Under the Influence of Cannabis A Randomized Clinical Trial." (doi:10.1001/jamapsychiatry.2023.2345)

We felt that the most important component of our evaluation would be to first establish a direct correlation between the LOC (inability to cross eyes) or PR and impairment of driving skills. We have not yet identified any studies that definitively prove correlation of LOC or PR with THC-related impairment, but we will continue to research the literature. Additional basic research may be necessary to establish that correlation, and we plan to pursue that goal if necessary. Anyone having information concerning proof of correlation of THC impairment and LOC and/or PR, please contact me: Jim Blaine, MD at 417-861-9286 or email jimblaine@aol.com.

GCMS will continue to pursue basic research on LOC-THC impairment correlation followed by studies to determine if Gaize technology may enable our state to avoid the alarming increase of traffic fatalities that are occurring in Colorado and other states legalizing cannabis.

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Family Physician
Springfield, Missouri
Missouri Medicine, Contributing Editor

Correspondence

Why I Carry Naloxone

Dr. Benjamin Grin's article, "Opioid Use Disorder in Missouri,"1 provides a welcome update on this subject. It provides a caring perspective that views chronic opioid use within the spectrum of other chronic diseases. His approach is prescriptive and evidence-based, emphasizing harm reduction and effective treatment. He argues convincingly that opioid use disorder is within the scope of primary care. He also reports the benefits of methadone and buprenorphine and urges increased utilization of these first-line drugs for opioid use disorder.

Missouri has experienced a relentless rise in opioid deaths. These fatalities are primarily from illicit synthetic opioids such as fentanyl and not from prescription narcotics. The epidemic, until recently, has mainly involved urban areas and their periphery.[2] The opioid overdose landscape has evolved, increasingly hitting rural counties, including Phelps County, where I live.[3] However, several vital efforts may help stem Missouri's opioid epidemic.

The University of Missouri, St. Louis' Addiction Science Team has distributed overdose prevention kits.[4] These kits include doses of naloxone, fentanyl test strips, and instructions. An estimated 200,000 kits were delivered to Missourians in 2023. St. Louis City and County opioid fatality rates appear to be stabilizing.[3,4]

Another effort to combat overdoses in rural Missouri is aimed at training healthcare providers and social workers in preventing childhood trauma, a key risk factor for future substance abuse and overdoses.[5] Julie Kapp, an associate professor at the University of Missouri - Columbia, heads a three-year grant from the US Department of Agriculture to combat opioid deaths in five rural counties with high opioid fatality rates: Dent, Washington, Crawford, St. Francois, and Phelps.

In addition to overdoses from illicit street opioids, we have an increasing number of fatalities from counterfeit pills available online, often containing fentanyl. People who consume these counterfeit pills are often opioid naïve and may succumb to a single pill or even half a pill, as did sixteen-year-old Cooper Davis of Shawnee, Kansas in 2021.

New legislation addresses the source of many of these counterfeit pills. Kansas Senator Roger Marshall, MD proposed the Cooper Davis Act, Senate Bill 1080,[6] which has passed in the Senate and awaits a House vote. This bill will require social media companies and other computing service providers to report controlled substance violations.

We support Dr. Grin's plea for every doctor and nurse to do what they can to help reduce the tragic number of lives lost due to opioids. Our contribution is to carry two doses of naloxone (Narcan®) to save a life when the occasion arises. These lifesaving sprays, weighing less than one-half ounce, can reverse opioid toxicity and restore breathing. Access to naloxone in a pharmacy is not fast enough. We carry naloxone in our backpacks.

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Medical Illustrations Spark Joy & Memory

I would like to thank Missouri Medicine, and in particular, Mark M. Miller, for the two-part articles Medical Illustration: State of the Art & Future Considerations in Missouri Medicine's Nov/Dec 2023 and Jan/Feb 2024 issues.[1,2] Both articles give a wonderful background on this rather esoteric skill in medicine; one not formally taught in our training, but interacted with at every level of the physician's career.

I fully realize my bias towards the art of visual medicine; as the son of an artist, I grew up appreciating the painstaking attention to detail and layered meanings that characterize good art. In the field of radiology, it is a joy to use these complementary skills in the service of our patients.

Picking up my textbooks in that first year of medical school, I was struck by the artistic ability of Frank Netter's anatomy atlas[3], only later appreciating the equally detailed scientific dimensions. Part of my medical book collection includes the first (1981) and many later editions of Despopoulos and Silbernagl's Color Atlas of Physiology[4].

Why own multiple, and outdated, versions of the same textbook? Quite simply, there is joy in following the evolution of the many wonderful illustrations over the past 40 years. Simple but effective cartoons and schemata may be hand drawn or computer generated, but still have the same ability to break down sophisticated concepts into memorable images.

As Mr. Miller points out, generative AI holds great promise. However, as of March 2024, it certainly needs quite a bit of human oversight to ensure scientific accuracy.[5] An interesting alternative approach to maximum realism inverts the paradigm of 'art modeling reality'; there are exciting developments fusing technology and methods pioneered by the Pixar corporation with volume rendering techniques from radiology. This unique confluence of entertainment and medicine has given rise to "cinematic rendering," enabling the creation of near-photo realistic 3D images from CT and MR studies.[6] Although computationally expensive and not widely available, the resulting images are visually stunning.

Regardless of what other innovations lie ahead, medical illustration is a unique and aesthetic form of communication within and outside our profession that frequently goes unappreciated. Many thanks to Missouri Medicine and Mr. Miller for these timely and thoughtful articles.

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Errata

In the article "Human Platelet Derived Mitochondrial OPA-1 Isoforms and Interaction With TDP-43 in Neurodegenerative Diseases" by Lee SH et al (Missouri Medicine 2024;121(1):74-79) the following formatting changes should be made: OPA-1 for OPA1; at -800C for at80oC; 2x109 for 2X 109; 40C for 4oC; and -20 C for -2oC.



NEW MSMA MEMBERS!

* = Medical Student ** = Resident/Fellow

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Advances in the Endovascular Management of Cerebrovascular Disease

by Ravi Nunna, MD, Farzana Tariq, MD, Fareed Jummah, MD, Navpreet Bains, DO, Adnan I. Qureshi, MD & Farhan Siddiq, MD

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Technological advances in the endovascular management of cerebrovascular disease has revolutionized the medical care of this clinically challenging patient population.



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Abstract

The field of endovascular neurosurgery has experienced remarkable progress over the last few decades. Endovascular treatments have continued to gain traction as the advancement of technology, technique, and procedural safety has allowed for the expansion of treatment indications of various cerebrovascular pathologies. Interventions such as the coiling of intracranial aneurysms, carotid artery stenting, mechanical thrombectomy in the setting of ischemic stroke, and endovascular embolization of arteriovenous malformations have all seen transformations in their safety and efficacy, expanding the scope of endovascularly treatable conditions and offering new hope to patients who may have otherwise not been candidates for surgical intervention. Despite this notable progress, challenges persist, including complications associated with device deployment and questions regarding long-term outcomes. This article explores the advancements in endovascular neurosurgical techniques, highlighting the impact on patient care, outcomes, and the evolution of traditional surgical methods.

Introduction

Advancements in endovascular neurosurgery (i.e. catheter-based procedures) have created a profound paradigm shift in the treatment of cerebrovascular pathologies over past decades. Breakthroughs in the development of devices and operative techniques have created a wealth of treatment options for vascular pathologies such as aneurysms, arteriovenous malformations, carotid artery stenosis, and ischemic stroke. These treatments can be highly individualized to deliver safe and effective patient care. These procedures are performed by a team of expert cerebrovascular neurosurgeons and neuroendovascular interventionalists at the University Hospital in Columbia, Missouri, who frequently collaborate to provide comprehensive patient care. This review will present some of the recent advancements within the field in the endovascular management of cerebrovascular diseases.

Transradial Access

Access of the radial artery is becoming increasingly popular in neurointerventional procedures due to its superior access-related safety profile compared to conventional femoral access, improved patient satisfaction, and shorter hospital

School of Medicine
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Seven Decades of Neurosurgery at MU Columbia



Michael Chicoine, MD
Chair, MU Department of Neurosurgery

The University of Missouri (MU) in Columbia was established over 175 years ago and is the oldest public university in the United States west of the Mississippi River. The MU School of Medicine (SOM) celebrated its 150th anniversary this past year, 2022.

Over the years Neurosurgery at MU SOM has been lead by Samuel P. W. Black (Chief 1955-1976), Clark C. Watts (Chief 1976-1990), John J. Oro (Chief 1990-2005), Scott Litofsky (Chief 2005-2021), and Thorakild, Norregaard (Interim Chief, 2021-22) .

The specialty of Neurosurgery has thrived at the University of Missouri for nearly 70 years, and as of June 2022, the former Division of Neurosurgery within the Department of Surgery has been transformed into its own independent Department of Neurosurgery under the leadership of inaugural Department Chair Michael R. Chicoine, MD.

This establishment, as an independent department, is facilitating expansion of MU Neurosurgery across multiple pediatric and adult subspecialties. Current MU Neurosurgery faculty members include Drs. Steven Carr, Michael Chicoine, Bornali Kundu, Thorakild Norregaard, Balint Otvos, Paul Santiago, Farhan Siddiq, Carolyn Quinsey, and Andrew Youkilis.

In this issue of Missouri Medicine, we highlight some of the advances in the field of Neurosurgery in the areas of 1) endovascular management of cerebrovascular disease; 2) cranial surgery for hemorrhage, tumors, and other conditions; 3) treatment of spinal disorders; and 4) surgical intervention for functional disorders, including epilepsy, Parkinson's, disease, trigeminal, neuralgia, and other conditions. The particular expertise offered at the University Missouri in regard to these areas of specialty are highlighted.

In addition to neurosurgical care offered at the MU campus in Columbia, Neurosurgical care is becoming available in Jefferson City at Capital Regional Medical Center which has recently merged with the MU Health System. We hope that the readership enjoys this overview of the state of the art in Neurosurgery at MU, and we would be honored to participate in the care of your patients from the mid-Missouri region and beyond.

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stays. The approach has been increasingly used for diagnostic and therapeutic purposes with a notable decrease in access-related complications such as the formation of pseudoaneurysms, retroperitoneal hematoma, arteriovenous fistulas, and arterial occlusion..[1,2,2,2,2–15,15–31,31–361-4]

Invasive pre-procedure testing is not required and a simple clinical test like the Allen test is deemed sufficient.[2] Real-time ultrasonography is frequently used for establishing vessel access. The aforementioned advantages of transradial access must be balanced with the significant learning curve of the technique. It has been estimated that a minimum of 50 cases are recommended for operators to be able to perform this technique safely and independently.

Stroke Thrombectomy

Stroke is a leading cause of mortality and morbidity worldwide. The most recent American Hospital Association statistics show that every year, more than 795,000 people in the U.S. develop a stroke, and in 2020 alone, 3.48 million deaths were attributed to ischemic strokes. The financial burden attributed to stroke between 2018 and 2019 has been estimated to be around $58.6 billion. Timely diagnosis and treatment not only reduces mortality but improves the quality of life in the long term. The stroke treatment paradigm has shifted in recent years from medical treatment alone to both medical and endovascular interventions.

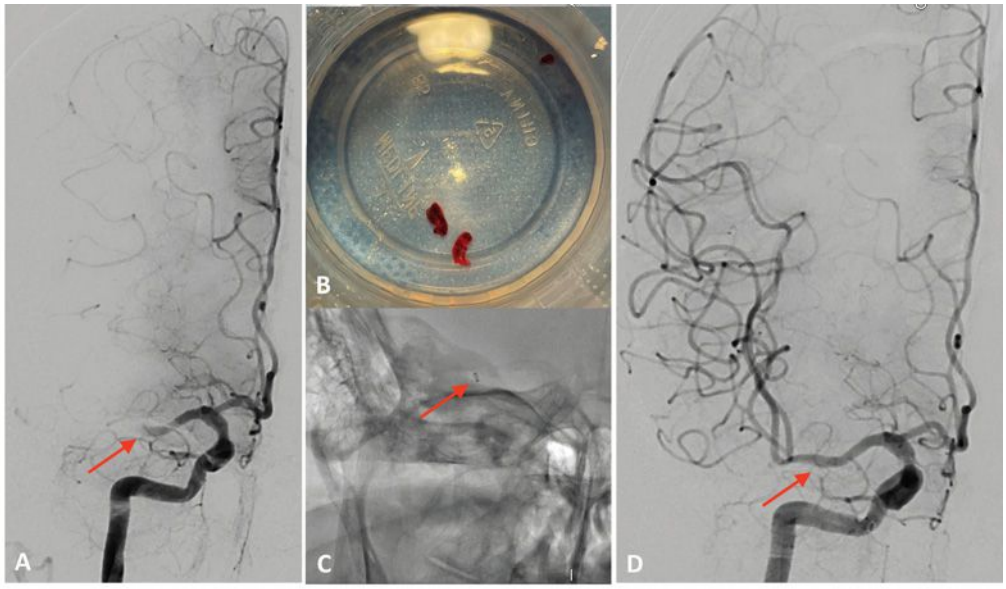


Figure 1. 84-year-old woman with acute onset left sided weakness secondary to right middle cerebral artery (MCA) occlusion who underwent thrombectomy with direct aspiration. A) Occlusion of the R-MCA (red arrow), AP view of catheter angiography, B) Thrombus removed from the R-MCA, C) Thrombus engagement of the intracranial catheter (red arrow), AP view of catheter angiography, D) Recanalization of the R-MCA (red arrow), AP view of catheter angiography.

Table 1. Landmark Trials of Mechanical Thrombectomy for Acute Stroke

Study	Specific inclusion criteria	Outcome
MR CLEAN 2015	VO: ICA, M1, M2, A1, A2 LKW<6HRS	EVT alone is equal to I/V alteplase
EXTEND-IA 2015	VO: ICA, MCA IV Alteplase by 4.5 hour Ischemic core<70cc	EVT+ Alteplase improved reperfusion, neurological recovery, and functional outcome than Alteplase alone
ESCAPE 2015	VO: Intracranial ICA, Proximal MCA LKW<12HRS Moderate-good collateral circulation Small infarct core	Early EVT after alteplase improved 90-day functional outcome and mortality
REVASACT 2015	VO: Intracranial ICA or M1 LKW <8HRS Absence of large infarct	EVT+SMT better than SMT alone Improved 90-day functional outcome
SWIFT-PRIME 2015	VO: Intracranial ICA, M1 or both LKW<6HRS	EVT+ SMT better than SMT alone improved 90-day functional outcome
DAWN 2018	VO: Intracranial ICA, MCA-M1 LKW: 6 to 24hrs Deficit infarct mismatch	EVT+SMT better than SMT alone Improved 90-day functional outcome
DEFUSE 3 2018	VO: ICA, MCA LKW: 6 to 16hrs Ischemic penumbra present	EVT+SMT better than SMT alone Improved 90-day functional outcome Reduced 90-day mortality
ATTENTION 2 2022	VO: BA LKW: <12 HRS	EVT+SMT better than SMT alone Improved 90-day functional outcome Reduced 90-day mortality
SELECT II 2023	VO: ICA, MCA proximal segment LKW: <24HRS Large infarction core 50cc	EVT+SMT better than SMT in large ischemic stroke

VO: Vessel occlusion, MT: Mechanical thrombectomy, SMT: Standard medical therapy, BA: Basilar artery, LKW: Last known well, EVT: Endovascular thrombectomy

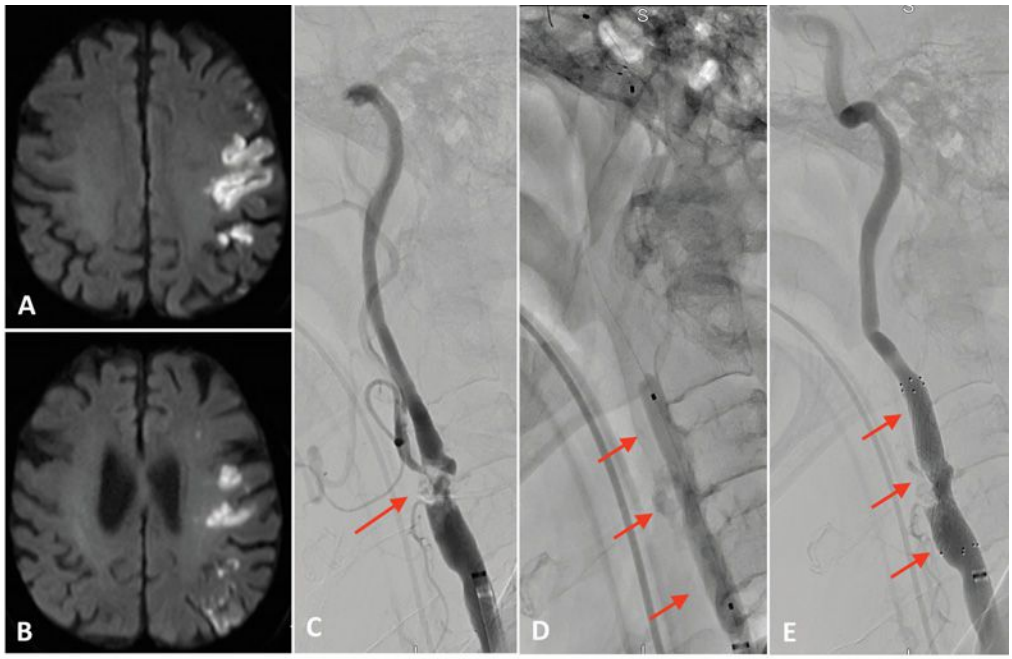


Figure 2. 79-year-old woman with aphasia secondary to embolus in the left hemisphere from an ulcerated left internal carotid artery (LICA) plaque who underwent balloon angioplasty and stenting. A,B) MRI brain with diffusion weighted restricted lesions in the left hemisphere, axial views C) Ulcerated plaque of the LICA origin (red arrow), lateral view of catheter angiography D) LICA balloon angioplasty (red arrow), lateral view of catheter angiography, E) LICA stent (red arrow), lateral view of catheter angiography

Device Evolution

Mechanical thrombectomy (MT) is the cornerstone treatment of ischemic strokes secondary to large vessel occlusion. The field of endovascular revascularization has witnessed a meteoric rise in developments in the last two decades. In 2004, the FDA approved the first-generation Merci retriever system (Concentric Medical, Mountain View, California, USA). This retriever device consisted of a corkscrew-shaped wire composed of five helical loops which gradually decrease in diameter. This wire would be unsheathed from the catheter in order to ensnare and remove the target via retrieval through a guide catheter. This device was originally used for retrieving foreign bodies misplaced during cerebral, peripheral, and coronary vascular interventional procedures. However, Concentric Medical (Mountain View, Calif.) would later acquire the license for using the device for a new indication: the restoration of vascular blood flow by removal of thrombus in patients with ischemic stroke. One of the most significant advances in the thrombectomy world was the introduction of the Penumbra System (PS) (Penumbra Inc., Alameda, Calif.) which was FDA-approved in 2007. As opposed to Merci which relied on a single stent retriever, the Penumbra system consists of a constellation of devices which use aspiration as the primary mechanism of clot retrieval. With this system, the aspiration microcatheter is passed proximal to the occlusion, followed by the passage of a separator (mounted on a guidewire) which breaks the clot, with constant suction being applied to aspirate any free clot fragments.

Due to suboptimal revascularization outcomes with the aforementioned techniques, further innovation and research spawned the era of stent retrievers. These devices utilized a stent which unsheathes within the clot, examples including the Solitaire FR (eV3 Endovascular, Irvine, Calif.) and Trevo Pro (Stryker Neurovascular, Kalamazoo, Mich.). Both were approved by the FDA in 2012. These devices have improved the recanalization rate to as high as 85%. The use of stent retrievers with suction devices has become the standard of care. Figures 1 and 2 depict case examples of endovascular interventions offered for stroke patients at the University Hospital in Columbia, Missouri (Figure 1).

Treatment Evolution

The efficacy of mechanical thrombectomy with a stent retriever was first studied in "The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial. The trial showed better recanalization rates and clinical outcome when compared with medical treatment alone. This trial was followed by a series of trials (MR CLEAN,[5]

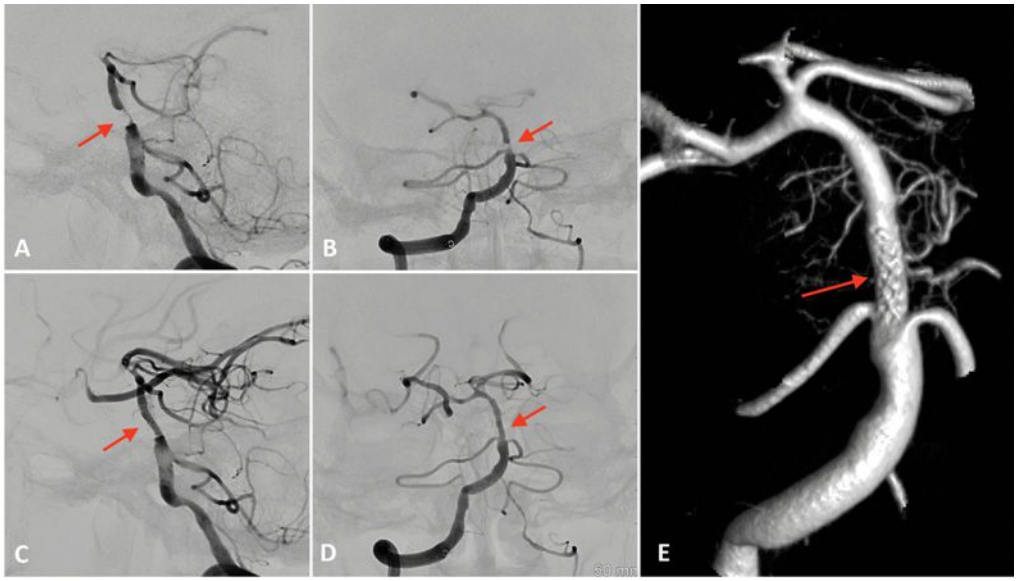


Figure 3. 67-year-old man with increased frequency of vertebrobasilar insufficiency who underwent basilar artery stenting with Resolute Onyx. A,B) Basilar artery stenosis, pre-stenting (red arrows), lateral and AP-views of catheter angiography, C) Post-stenting (red arrows), lateral-view and AP-views of catheter angiography, E) Post-stenting (red arrow), 3D reconstruction of catheter angiography.

EXTEND 1A,[6] ESCAPE,[7] REVASACT,[8] SWIFT PRIME,[9]) all of which have shown significantly improved outcomes when mechanical thrombectomy was performed with or without medical therapy. Furthermore, advanced cerebrovascular imaging with detailed perfusion analysis has made it possible to differentiate between infarcted and at-risk ischemic core, which has expanded the window for intervention (DAWN,[10] ATTENTION,[11] DEFUSE 3[12]). The 2018 American Heart Association guidelines recommend mechanical thrombectomy with a stent retriever as a standard of care and extended the limit of clot removal from six hours to up to 24 hours in selected groups of patients. More recent technical advancements in the field have further refined the treatment in patients with large infarcted cores (SELECT 2 Trial 2023)[13] (Table 1).

Carotid Artery Stenting

Carotid artery stenosis (CAS) is estimated to contribute to as much as 15 to 20% of strokes in the U.S.[14] Symptomatic patients with >50% stenosis and asymptomatic patients with >70% stenosis are generally considered candidates for intervention. Treatment is provided based on the severity of the disease, presence or absence of clinical symptoms, and medical comorbidity status. Options include medical management alone, carotid endarterectomy (CEA), and carotid artery stenting (CAS). The SPACE 2 trial[15] has shown that carotid endarterectomy, carotid artery stenting, and best medical therapy have no superiority over one another when comparing 30-day stroke rate and death and incidence of new ipsilateral stroke at five years in patients with asymptomatic moderate to severe carotid artery stenosis. In symptomatic patients, CEA is associated with a reduced risk of periprocedural stroke and CAS is associated with reduced risk of cardiac morbidity within 30 days.[15,16] Carotid artery stenting is a safe and effective alternative to CEA in high-risk patients (patients with cardiac issues, recurrent carotid stenosis, occlusive disease on the contralateral side, and in patients with excessive neck scarring secondary to irradiation. We have extensive experience at the University of Missouri with CAS done via transradial access (Figure 2). It is a safe, efficient, and effective method of treatment with a higher patient satisfaction and lower complication rates.[17,18]

Stenting for Symptomatic Intracranial Atherosclerotic Disease

Around 10% of strokes are attributed to intracranial atherosclerosis disease (ICAS).[19] Patients with moderate to severe ICAS, defined as 70-90% stenosis, have a 23% stroke risk at one year. Once a patient has a stroke, the risk of recurrent stroke ranges from 12-19%.[20] The SAMMPRIS trial[21] in 2011 aimed to establish an effective treatment strategy to prevent

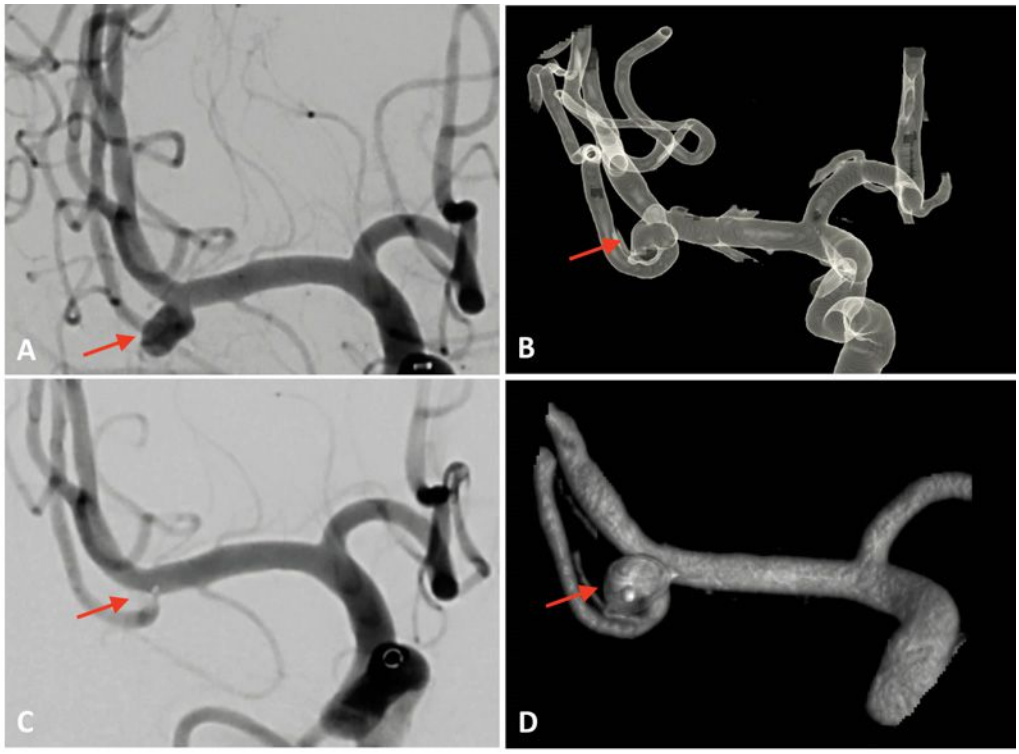


Figure 4. 73-year-old woman with aneurysmal subarachnoid hemorrhage secondary to a ruptured right middle cerebral artery bifurcation aneurysm. The aneurysm was secured with WEB-embolization. A) Right MCA aneurysm pre-embolization (red arrow), AP view of catheter angiography, B) Right MCA aneurysm pre-embolization (red arrow), 3D reconstruction of catheter angiography, C) Right MCA aneurysm post-embolization (red arrow), AP view of catheter angiography, B) Right MCA aneurysm post-embolization (red arrow), 3D reconstruction of catheter angiography.

recurrent strokes in patients with ICAD. It showed that patients who were treated with percutaneous transluminal angioplasty and stenting showed an increased 30-day risk of stroke and death. This discouraged the use of stenting for ICAD. However, recent technological advancements in devices have led to the development of drug-eluting stents (DES) and have shown encouraging results with the use of the Resolute Onyx DES (Medtronic, Minneapolis, Minn.) in terms of reduction in periprocedural stroke and rates of in-stent stenosis at 6 months.[22] A recent multi-center trial led by physicians at the University of Missouri demonstrated a significantly improved perioperative and 30-day outcomes in comparison to the interventional arm of SAMMPRIS.[37] Interventionalists at the University of Missouri are part of a select handful of comprehensive stroke centers offering endovascular treatment of symptomatic intracranial atherosclerotic disease (Figure 3).

Endovascular Treatment of Complex Intracranial Aneurysms

There has been a major shift of intracranial aneurysm treatment from craniotomies for surgical clipping to less invasive endovascular interventions. In 2002, the seminal International Subarachnoid Aneurysm Trial (ISAT)[23] established the superiority of endovascular therapy over microsurgical clipping of ruptured intracranial aneurysms, showing that the one-year disability-free survival is significantly better with endovascular coiling, and that the long-term risk of re-bleeding from the treated aneurysm are low with both therapies, although somewhat more frequent with endovascular coiling. These findings were later corroborated by the Barrow Ruptured Aneurysm Trial (BRAT) in 2012[24] which found better overall outcomes with endovascular coiling compared to surgical clipping. However, due to inherent limitations, both trials emphasized the importance of tailoring the decision making based on individual characteristics, in particular the aneurysm size, location, and shape, and the overall health of each patient. Although overall long-term outcomes and complications were better with endovascular coiling, lower complete aneurysm obliteration rates with higher recurrences led to the birth and development of newer endovascular treatments such the pipeline embolization device (PED) and the woven endothelial bridge (WEB) device.

Flow Diversion Devices

Flow diverters are tubular mesh-like stents that are deployed across the neck of the aneurysm, thereby

diverting flow away from the aneurysm into normal nearby blood vessels, which reduces the pressure within the aneurysm sac and encourages blood clot formation, ultimately sealing off the aneurysm from the circulation. Various flow diversion devices are available including the Pipeline embolization device (PED) (Medtronic, Irvine, California), Surpass streamline (Stryker Neurovascular, Kalamazoo, Michigan) and Flow-Reduction Endoluminal Device (FRED), (MicroVention, Tustin, California). They are ideal for standalone as well as adjunct treatments. They typically require dual antiplatelet therapy for at least 6 months which makes it challenging in patients with subarachnoid hemorrhage as the need for further interventions like ventriculoperitoneal shunting can be complicated by hemorrhages. Flow diverters are frequently used for complex aneurysms with wide necks, fusiform shapes involving 360 degrees of the vessel wall, dissecting aneurysms, and aneurysms in the cavernous and ophthalmic segments of the internal carotid artery. Studies have shown high occlusion rates for both small/medium (PREMIERE trial)[25] and large/giant aneurysms (PUFF trial)[26] with low neurological complications. At 2 years, the aneurysm recurrence rate is reported to be 8.1% after treatment with flow diverters like the PED.

Intra-Aneurysmal Flow Disruption Devices

The Woven EndoBridge (WEB) device is a self-expanding, mesh-like device shaped like a basket which is deployed within the aneurysm sac where it expands and bridges the neck of the aneurysm, hence diverting flow away from the aneurysm and eventually excluding it from the circulation. These devices are commercially available in the US and have been used successfully at the University of Missouri (Figure 4). They are ideal for wide-based, bifurcation aneurysms. Traditionally anterior circulation aneurysms like anterior communicating artery and middle cerebral artery aneurysms have been treated by microsurgical clipping; however, the advent of WEB device has made it possible to treat wide-necked bifurcation aneurysms successfully at these locations with a higher occlusion rates and lower recurrence rates (10% at 19 months).[27]

Endovascular Embolization of Arteriovenous Malformations

Arteriovenous malformations (AVM) are abnormal tangles of arteries and veins which lack an intervening capillary bed, therefore allowing arterial pressure to be directly transmitted to veins which leads to excessive wall shear and stress and ultimate rupture. The annual incidence of rupture in AVMs is 2.4%, and there is a significant increase in the risk of subsequent hemorrhages.[28,29] Treatment options include surgical resection, endovascular embolization, stereotactic radiosurgery, or a combination of any or all of these treatments. The traditional endovascular approach has been trans-arterial embolization. Transvenous embolization has been more recently introduced as a potentially curative intervention for carefully selected AVMs achieving 93% obliteration rate with a 4.3% rate of complications. Relative indications for this technique include small AVMs (<3 cm), deep AVM location, tortuous arterial feeders, single draining vein, and compact a nidus. The true risk-to-benefit profile of transvenous AVM embolization remains unclear due to the limited number of cases in the literature and limited post-treatment follow-up. Future studies of larger sample sizes are needed to better define the indications and long-term outcomes of this technique.

Cerebral Venous Sinus Stenting for Pseudotumor Cerebri

Pseudotumor cerebri is a syndrome characterized by raised intracranial pressure (>25cmH2O) in the absence of an intracranial mass lesion. Patient present with headaches (90%), visual disturbances (70%), and pulsatile tinnitus (10%).[31] Horizontal diplopia, papilledema, and severe optic nerve atrophy leading to blindness occurs in 10% of cases. The incidence varies between 1-2 %/100,000 to 14.9-19.3% in obese women. Weight loss[32] has been linked with significant reduction in symptoms including headaches and papilledema. However, in patients with deteriorating vision, urgent intervention is required to prevent progression. Diet modification with carbonic anhydrase treatment leads to rapid symptom improvement but undesired side effects (paraesthesia, drowsiness, alterations in appetite and taste)[33 and] have led to high rates of non-compliance.

Surgical interventions are reserved for patients who continue to have symptoms despite medical therapy. Optic nerve fenestration (ONF) and CSF shunting are the classic treatment modalities. ONF

is performed in patients with severe papilledema with high risk for visual loss but mild systemic symptoms. The treatment failure rate is around 32%.[34] Meanwhile, shunting is selected for patients with visual and systemic complaints (headaches, nausea, and vomiting, etc.). Shunt failure and revision are reported up to 40-60% depending on the type of procedure.[35]

Cerebral venous sinus stenting (CVSS) is a minimally invasive procedure performed in patients with pseudotumor cerebri secondary to venous sinus stenosis. Patients who can benefit from CVSS are those with disabling headaches and visual deterioration who have failed repeated lumbar punctures, >50% venous sinus stenosis on MRV or CTV, and failed surgical interventions like CSF shunting/optic nerve fenestration. Cerebral venography with manometry before the procedure provides evidence of venous stenosis and significant pressure gradients across the site of stenosis. There may be evidence of bilateral disease on venography, however, unilateral stenting is effective in the reduction of symptomatology.[31] Meta analysis of clinical outcomes of CVSS has shown 87% overall improvement in symptoms with a re-treatment rate of 10-12%.[36] Dual antiplatelet therapy for 3 to 6 months (allowing time for epithelialization of stent) is required after the procedure, followed by a year of aspirin.

Surgical Management of Moyamoya Disease

Moyamoya disease is a progressive steno-occlusive disease characterized by occlusion of bilateral terminal ICA and formation of abnormal collateral vascular channels as a compensatory mechanism.[37] The term "moya-moya" originated from Japanese, meaning a "puff of smoke", which describes the appearance of the newly formed vascular networks seen on imaging. There is increased prevalence of disease in Japanese and Eastern Asian populations, with a bimodal distribution affecting pediatric patients and those in their 40-50. There is no medical treatment up to date, however use of cilostazol has been linked to improved survival.[38]

Surgical treatment involves direct or indirect revascularization through a craniotomy to connect a branch of the external carotid artery to the ischemic hemisphere, and is reserved for symptomatic patients (e.g. TIA/strokes, intracranial hemorrhage, focal dystonia/dyskinesia). We work in close collaboration with neurologists to select the subgroup of patients who can benefit from revascularization procedures.

The first technique, direct bypass, is achieved by directly connecting a branch of the ECA (commonly the superficial temporal artery) to a cortical branch (commonly of the middle cerebral artery) within the ischemic hemisphere. In indirect revascularization, a branch of the ECA is laid on top of the ischemic hemisphere to encourage formation of new vasculature over time. This technique is typically preferred in children due to the small size of the blood vessels which makes direct anastomosis particularly difficult.

Summary

Technological advances in the endovascular management of cerebrovascular disease has revolutionized the medical care of this clinically challenging patient population. Pathologies that previously required craniotomies and complex microsurgery can now be managed in a minimally-invasive manner via either a radial or femoral artery puncture with current endovascular techniques. The University of Missouri Hospital Columbia, Missouri, is one of a select group of comprehensive stroke centers nationwide that offers cutting-edge endovascular treatments for a large catchment area spanning most of central Missouri. These endovascular therapies include radial access interventions, stroke thrombectomy, carotid artery stenting, stenting for intracranial atherosclerotic disease, flow-diverting stent and intra-saccular devices for the treatment of aneurysms, embolization of AVMs, and stenting for intracranial hypertension.

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Advances in Cranial Surgery

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Neurosurgery is constantly evolving with a trend towards less invasive procedures when feasible.



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Abstract

The landscape of the cranial neurosurgery has changed tremendously in past couple of decades. The main frontiers including introduction of neuro-endoscopy, minimally invasive skull base approaches, SRS, laser interstitial thermal therapy and use of tubular retractors have revolutionized the management of intracerebral hemorrhages, deep seated tumors other intracranial pathologies. Introduction of these novel techniques is based on smaller incisions with maximal operative corridors, decreased blood loss, shorter hospital stays, decreased post-operative pain and cosmetically appealing scars that improves patient satisfaction and clinical outcomes. The sophisticated tools like neuroendoscopy have improved light source, and better visualization around the corners. Advanced navigated tools and channel-based retractors help us to target deeply seated lesions with increased precision and minimal disruption of the surrounding neurovascular tissues. Advent of stereotactic radiosurgery has provided us alternative feasible, safe and effective options for treatment of patients who are otherwise not medically stable to undergo complex cranial surgical interventions. This paper review advances in treatment of intracranial pathologies, and how the neurosurgeons and other medical providers at the University of Missouri-Columbia (UMC) are optimizing these treatments for their patients.

Introduction

Modern advancements in neurosurgery such as computerized surgical navigation, enhanced microsurgical approaches, neuroendoscopy, and other modalities have enabled neurosurgeons to perform cranial surgery with more targeted techniques.[1-6] This review will focus on how the neurosurgeons at the UMC are applying these strategies for the treatment of patients with brain tumors, intracerebral hemorrhages (ICH) and other intracranial pathologies.

Intracerebral Hemorrhage

Stroke is the fifth leading cause of death and disability in the US. Annually, there are approximately 800,000 new cases of stroke in the US, of which ten percent (80,000) are hemorrhagic. Hemorrhagic stroke is associated with very high morbidity and mortality.[7] Every effort is made to improve functional outcomes. Conventional ICH treatments have

included medical management with or without surgery for removal of hematoma to decrease mass effect and prevent the resultant edema and inflammatory cascade, among other mechanisms of secondary injury.[8-10] Multiple studies have assessed the potential benefit of surgical hematoma evacuation, including the large multicenter randomized prospective controlled trials (RCT) STICH (Surgical Trial in Lobar Intracerebral Hemorrhage) I[11] & STICH II[12] which compared medical management to craniotomy or craniectomy for hematoma evacuation. The STICH trials showed a possible modest survival benefit for patients with superficial ICH without intraventricular hemorrhage but overall did not provide strong support in general for traditional surgery for ICH. In fact, the 2015[13] and 2022[8] American Heart Association/American Stroke Association (AHA/AHA) Guidelines on ICH support definitive improved outcomes for evacuation of ICH only for cerebellar hemorrhages greater than 15 mL, but not for supratentorial ICH.[8,13]

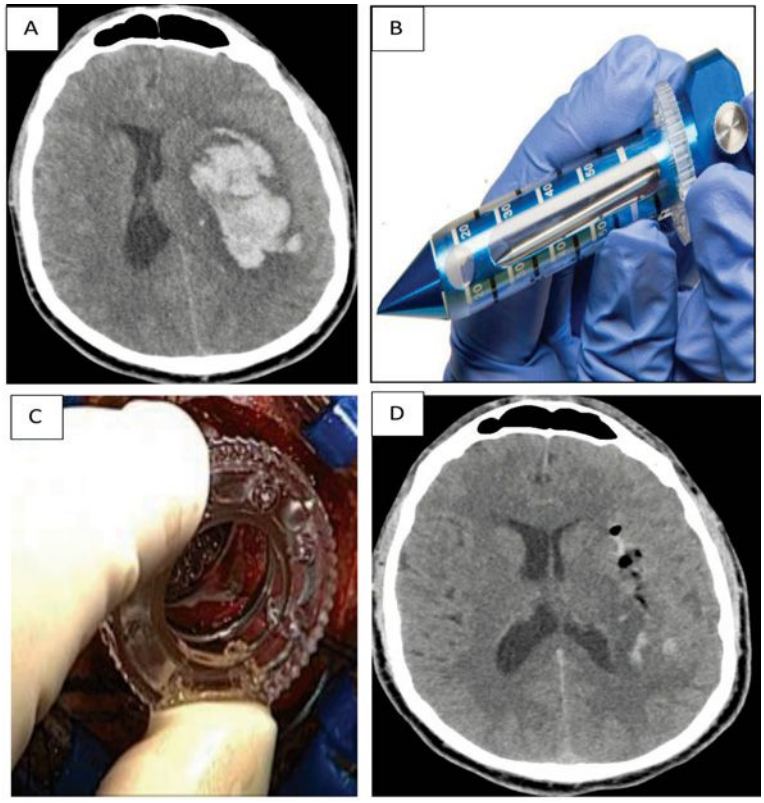


Figure 1. Pre-op CT; tubular retractor; Post-op CT.
33-year-old male with history of hypertension presented with acute neurological decline with decreased level of consciousness and dense right hemiparesis.
A. Non-contrast axial computed tomography (CT) of head large left hemisphere and basal ganglia increased density consistent with acute intracerebral hemorrhage (ICH).
B. Tubular brain retractor (Nico BrainPath device, Indianapolis, IN).
C. Tubular brain retractor inserted into brain for ICH evacuation using a small 4-centimeter craniotomy.
D. Immediate postoperative CT of head demonstrating evacuation of hematoma. Patient had persistent hemiparesis, but had rapid improvement of level of consciousness and make expeditious progress to rehabilitation.

Minimally Invasive Surgery for Intracerebral Hemorrhage Evacuation

The lack of strong evidence to support traditional craniotomy to treat supratentorial ICH has led to the exploration of a number of less invasive surgical strategies. Minimally invasive surgical procedures for ICH evacuation have included burr hole or small craniotomy techniques for evacuation of hematoma using various catheters, cannulas, or tubular/cylindrical/speculum brain retractors. These methods may variably utilize modern operative tools such as stereotactic navigation to plan the safest trajectory, instillation of thrombolytic to liquify the hematoma, specialized evacuation devices, and sophisticated visualization equipment such as exoscopes, endoscopes, and microscopes.[14-22]

Stereotactic Hemorrhage Evacuation with Thrombolytics

Stereotactic aspiration of ICH with concomitant direct thrombolytic therapy was assessed in multiple studies including SICHPA (Stereotactic Treatment of Intracerebral Hematoma by means of a Plasminogen Activator),[15] and the MISTIE (Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation) I[16], II[17] & III[18] trials. The MISTIE III trial, the largest multicenter RCT using this technique, showed significant improvement in mortality at one year in the surgical arm, but did not reach its primary targeted outcome of improved

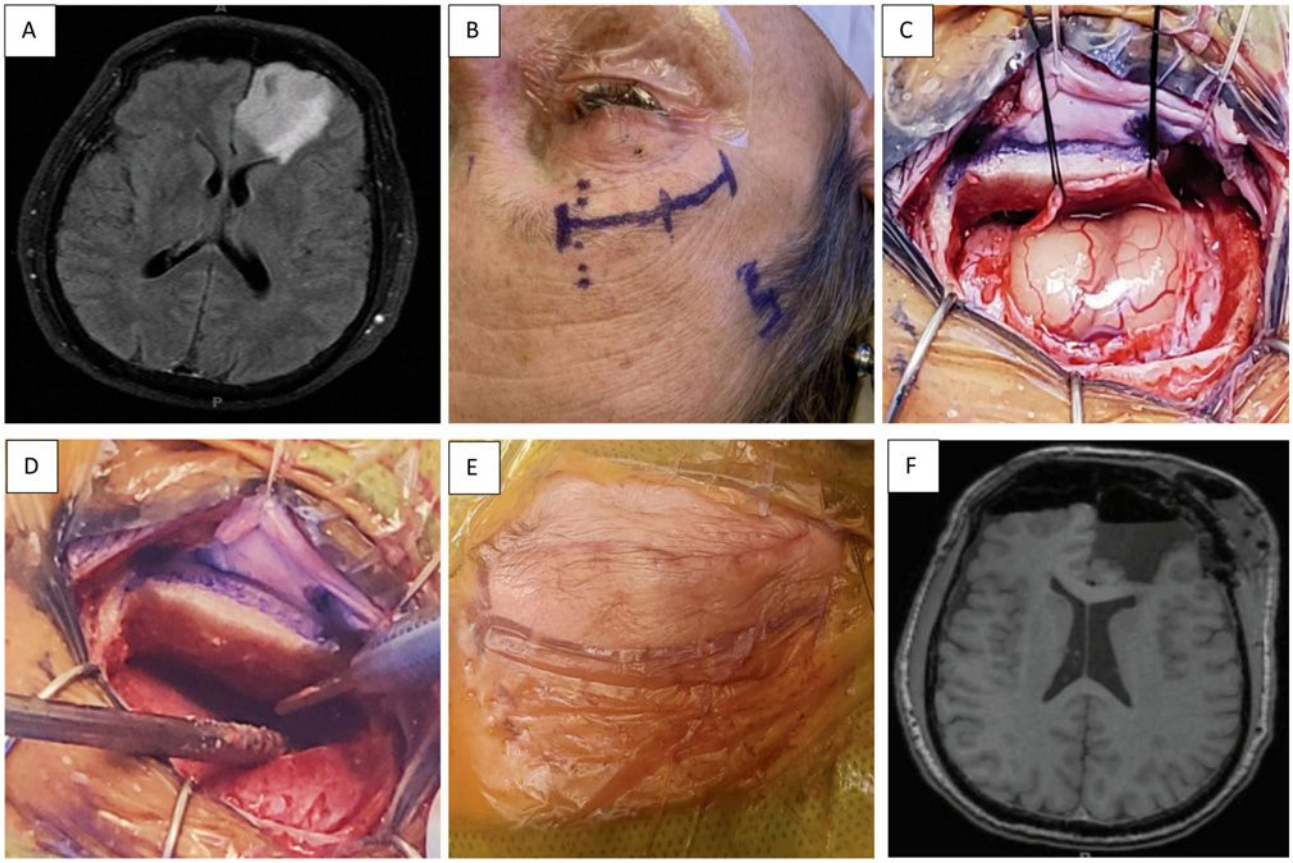


Figure 2. Pre-op and Post-op MRI
A. Pre-op MRI of left frontal glioma operated via left eyebrow approach.
B. Pre-operative marking of eyebrow skin incision.
C. Keyhole right frontal craniotomy and dural opening for exposure and resection of tumor.
D. Tumor resection using eyebrow keyhole exposure.
E. Surgical closure of eyebrow incision to achieve favorable cosmetic healing.
F. Post-operative scan of left frontal lesion operated via left eye-brow approach.

functional outcome at one year. A subsequent subgroup analysis of the MISTIE III patients demonstrated that patients with residual hematoma volume less then 15 mL after combined evacuation and thrombolytic therapy achieved measurably improved outcomes at one year. A meta-analysis by Scaggiante J. et al.[19] showed that MIS techniques have significant survival benefits over conventional medical treatment and/or traditional craniotomy approaches for select subsets of patients with ICH.

Stereotactic Hemorrhage Aspiration Without Thrombolytics

ENRICH Trial

Multiple studies have been initiated to assess outcomes of various MIS techniques for evacuation of spontaneous ICH. The recently completed Early Minimally Invasive Removal of Intracerebral Hemorrhage (ENRICH) trial[20] compared outcomes of early MIS hemorrhage evacuation versus medical management alone. This multi-center RCT evaluated the efficacy of a tubular brain retractor technique for evacuation of supratentorial basal ganglia and lobar ICH within the first 24 hours of a patients hemorrhage (Figure 1).

MIND Trial

The MIND trial (Multicenter Study of Artemis - a Minimally Invasive Neuro Evacuation Device in the Removal of Intracerebral Hemorrhage; Penumbra, Artemis, Alameda, California) is an ongoing multicenter prospective RCT comparing

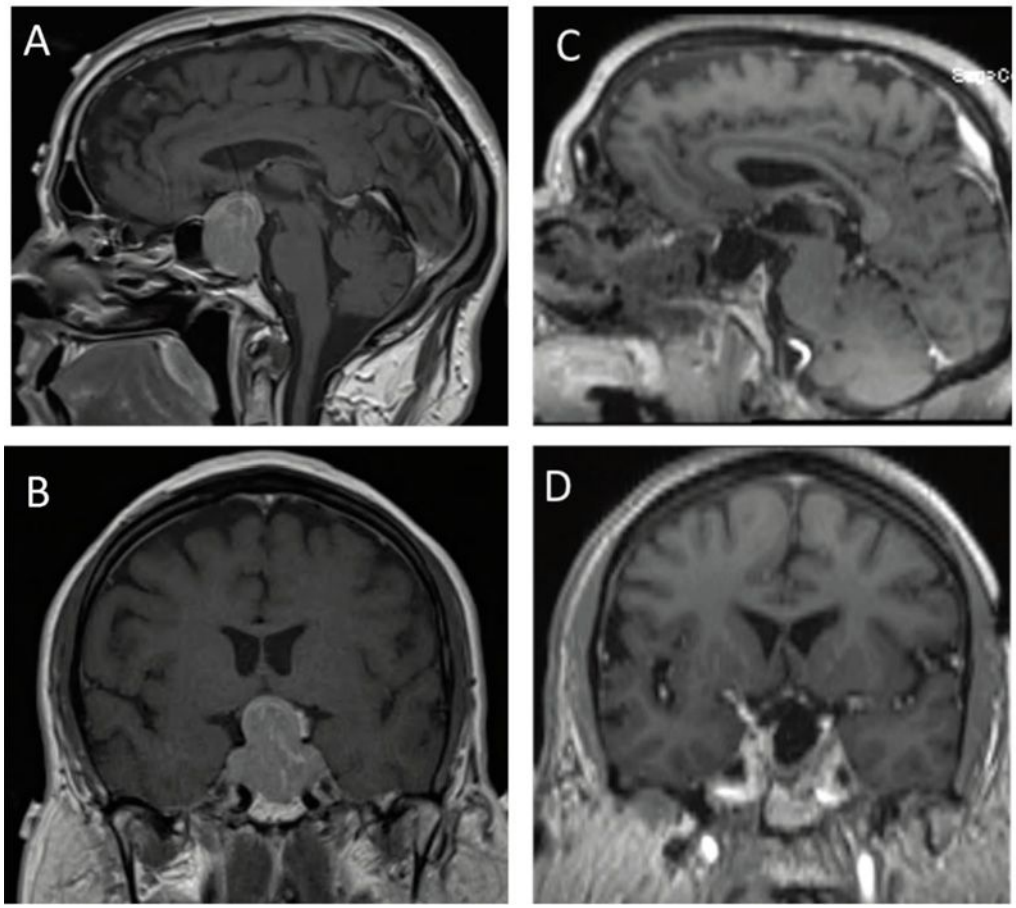


Figure 3.
Patient presents with bi-temporal hemianopsia, and laboratory testing reveals normal pituitary function. T-1 weighted MRI studies.

A and B. Pre-operative sagittal (A) and coronal (B) images demonstrating large sellar, suprasellar mass.

C and D. Post-operative sagittal (C) and coronal (D) demonstrating resection of mass and decompression of optic chiasm. Pathology confirms pituitary adnenoma.

outcomes using an MIS technique with an endoscope and a suction cannula device in patients with ICH compared to medical management alone.[21]

MIRROR Registry

The MIRROR (Minimally Invasive Intracerebral Hemorrhage Evacuation) registry is an ongoing multicenter database tracking patient outcomes using the Aurora® Surgiscope (Integra, Princeton, NJ), a tubular brain retractor device with an integrated exoscope to visualize down the tube for evacuation of supratentorial ICH >20cc within the first 24 hours of a qualifying hemorrhage.[22] UMC neurosurgery faculty utilize these techniques and in the past and present have contributed to these clinical trials in an effort to improve the outcomes of patients with ICH.

Brain Tumors

Techniques have been developed to enable safe treatment of brain and skull base tumors in some instances using less invasive modalities, including "keyhole" craniotomies, endoscopic approaches, tubular/speculum retractors, laser interstitial thermal therapy (LITT), and stereotactic radiosurgery (SRS).

Keyhole Craniotomy

A keyhole craniotomy refers to the concept of the possibility of seeing an entire room through a keyhole in the door without opening the door, and in some cases intracranial pathology can be accessed through a smaller opening instead of a larger craniotomy. Keyhole craniotomies rely on careful preoperative planning, strategic craniotomy placement, and utilizing key tenets such as following the long axis of the tumor, drainage of cerebrospinal fluid for brain relaxation, and careful consideration of the underlying anatomy. The application of keyhole techniques in select cases may enable the use of smaller and more efficient incisions, craniotomies, and dural openings, less exposed normal tissue, better cosmetic outcomes, and faster post-operative recoveries.[5,6,23-27] The prototypical keyhole craniotomy is the eyebrow

transciliary supraorbital craniotomy which can be used to treat tumors of the brain and skull base, aneurysms, and other pathologies. It is a small craniotomy that provides access to the frontal lobe, anterior temporal lobe, anterolateral skull base, optic nerves and chiasm, the vessels of the circle of Willis, and other anatomical regions (Figure 2). [5,23,24]

Endoscopic Endonasal Surgery

Transsphenoidal surgery has traditionally been used to resect pituitary adenomas and other pathologies in the sellar region and is commonly performed by neurosurgeons and otolaryngologists working together. The introduction of advanced endoscopes, neuronavigation enhanced instrumentation, neuromonitoring, micro-doppler probes, and fluorescence imaging such as indocyanine green have enabled neurosurgeons to expand access not only to the sellar and parasellar regions, but also to broader areas of the skull base including the anterior fossa, the clivus, the cavernous sinus, Meckel's cave, the foramen magnum, the petrous apex, and the jugular foramen to address a variety of pathologies including pituitary tumors, meningiomas, chordomas, chondrosarcomas, and other benign and malignant lesions (Figure 3).[28,29]

Channel-Based Retraction via Tubular Retractors

Channel-based surgery is a concept of less invasive surgery using peel-away catheters and tubular retractors to reach the lesion and maintain a working operative corridor. Peel-away sheaths are used in conjunction with a endoscopes with working channels enable access lesions in the ventricular system allowing for endoscopic treatment of hydrocephalus, intraventricular tumors, cysts and other lesions. Tubular retractors are available in different lengths and widths and can be used for both parenchymal and ventricular lesions.[3]

Laser Interstitial Thermal Therapy

Laser interstitial thermal therapy is a minimally invasive technique used to treat intracranial tumors, radiation necrosis, epileptic foci, and other brain pathologies. Using stereotactic neuronavigation, a laser probe is passed into the lesion through an opening in the skull 3 to 4 mm in diameter. During the procedure, continuous magnetic resonance imaging (MRI) including MR thermography is used to precisely assess the volume and intensity of the thermal tissue damage to the lesion. LITT is a good option for certain treatment-resistant and deep-seated tumors, intractable epilepsy, and other conditions. While it represents an effective option for some lesions, the limitations include some brain locations, large tumor volume, excessive perilesional edema, and high vascularity.[30,31]

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS)[32-34] and stereotactic radiotherapy (SRT)[35] are nonsurgical treatments for brain and spine lesions using focused radiation. Depending upon the size and location of the lesion, SRS or SRT can be performed in a single session or in multiple sessions (for example, fractionated SRS over three to five days). SRS/SRT is used as a stand-alone treatment or adjunct to microsurgical treatment of brain and spinal tumors. SRS for conditions of the brain such as metastases, meningiomas, vestibular schwannomas, arteriovenous malformations, and trigeminal neuralgia can be performed by either using a stereotactic frame secured to the head using local/regional anesthetic or with a stereotactic mask precisely contoured to the shape of the head and face. The MRI and CT images are integrated into the treatment plan which is collaboratively devised by a team of neurosurgeons, radiation oncologists, and radiation physicists. Commonly used SRS systems include linear accelerator (LINAC) photon based platforms such as the Varian TrueBeam™ (Varion, Palo Alto, Ca), CyberKnife™ (Accuray, Inc. Madison, WI), and the radioactive Cobalt 60 based technique of Gamma Knife™ (Elekta, Stockholm, Sweden).

Conclusion

Neurosurgery is constantly evolving with a trend towards less invasive procedures when feasible. The implementation and integration of modern tools and strategies such as stereotactic neuronavigation, targeted exposures, enhanced microsurgical equipment, and ablation through means other than conventional open surgery have enabled us to improve the treatment of difficult diseases. The University of Missouri Department of Neurosurgery provides exceptional care for patients with cranial pathology from central Missouri and beyond utilizing advanced contemporary techniques and a thoughtful approach to patient care.

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Disclosure

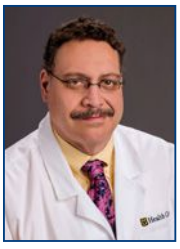
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Cutting Edge Developments in Spine Surgery at the University of Missouri

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Technological advancements include intra-operative image guidance, robotic spine surgery, minimally invasive techniques, motion preservation surgery, and interdisciplinary care of metastatic disease to the spine.



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Abstract

The treatment of spinal pathologies has evolved significantly from the times of Hippocrates and Galen to the current era. This evolution has led to the development of cutting-edge technologies to improve surgical techniques and patient outcomes. The University of Missouri Health System is a high-volume, tertiary care academic medical center that serves a large catchment area in central Missouri and beyond. The Department of Neurosurgery has sought to integrate the best available technologies to serve their spine patients. These technological advancements include intra-operative image guidance, robotic spine surgery, minimally invasive techniques, motion preservation surgery, and interdisciplinary care of metastatic disease to the spine. These advances have resulted in safer surgeries with enhanced outcomes at the University of Missouri. This integration of innovation demonstrates our tireless commitment to ensuring excellence in the comprehensive care of a diverse range of patients with complex spinal pathologies.

Introduction

The study of spinal anatomy, pathology, and even management, dates back to the time of Hippocrates (460-370 BC). Correction of spinal deformity using the Hippocrates ladder and board marks the earliest interventions used to treat spine pathologies.[1] Centuries later, the Greek physician Galen made groundbreaking contributions to the knowledge of spine anatomy, including the introduction of medical terms like kyphosis and scoliosis in addition to their treatment using devices such as chest binders and jackets. In the 19th and 20th centuries, further refinement in these non-surgical techniques and the development of surgical interventions birthed the field of spinal surgery.[2] The 21st century marks the era of technological advancements in image guidance, robotics, and the introduction of minimally invasive techniques (MIS approaches). At the University of Missouri, we treat a wide spectrum of spinal pathologies from the occiput through the sacrum. We commonly treat pediatric and adult patients with degenerative diseases of the spine,



Figure 1. A. Intraoperative CT navigation system. B. Placement of pedicle screws with image guidance.

inflammatory disorders, spinal trauma, infections, congenital disorders of the spine, spinal deformity, and malignancy.

Technological Advancements

Technological advancements in the past five decades have enabled spine surgeons to shift paradigms from open surgeries to minimally invasive spine surgery. Image guidance, new surgical techniques, and evolving instrumentation have laid the foundation for the current era of spine surgery. The following are a few of the fundamentally important innovations of the recent era.[3,4]

Intra-Operative Image Guidance

Image guidance in spine surgery has revolutionized both the safety and precision of instrumentation in spine surgery. Initially, the placement of screws and other hardware relied on anatomic landmarks that allowed for intraoperative assessment of known safe windows and trajectories. The advent of intraoperative fluoroscopy in 1955 all owed for real-time two-dimensional imaging to guide screw placement.[5] While this marked a crucial step in the evolution of surgical technique, fluoroscopy guided pedicle screw placement still reported suboptimal screw positioning rates due to the inherent limitations of using two-dimensional imaging for guidance of three-dimensional techniques. The subsequent introduction of computed tomography (CT) in 1971 followed by the magnetic resonance imaging (MRI) in the early 1980s profoundly altered the pre-operative evaluation of surgical spine patients, but challenges persisted regarding intraoperative image guidance.[6,7]

The foundation of contemporary image guidance in spine surgery consists of a navigation system that integrates patient-specific imaging data with real-time three-dimensional positioning of instruments and spinal implants. Patient-specific imaging is obtained via several mechanisms at the University of Missouri. The most basic technique comprises a pre-operative high-resolution CT image of the levels of interest which is then intraoperatively registered to the patient by selecting points on the patient's spine for surface registration. An alternative workflow consists of obtaining a patient-specific intraoperative 2D/3D image with an intraoperative CT scanner (Figure 1). This workflow allows for immediate registration of the patient's spine to the navigation system. Instruments and attached implants are outfitted with optical sensors which are tracked by a mobile optical sensing unit. Confirmation of expected implant placement is obtained with an intraoperative CT scanner. This significantly decreases the need for "take back" surgeries to revise implant placement.

Intraoperative spinal navigation was first developed to assist in the placement of C1-C2 screws (minimizing risk to the adjacent vertebral arteries) and thoracolumbar pedicle screws. However, intra-operative navigation has uses beyond the placement of pedicle screws. Intraoperative image guidance can assist in exact localization of spinal level in cases of

abnormal anatomy, osteotomy planning, interbody placement, and decompression planning.[8,9] In a study by Wang YC, the author describes navigated accuracy of cervical pedicle screw placement up to 94.1%.[10] In the thoracolumbar region optimal hardware placement via intra-operative CT has accuracy reported up to 98%.[11,12] Gelalis et al. assessed the accuracy of pedicle screw placement using freehand, fluoroscopy, and CT navigation.[13] The results revealed free-hand technique accuracy to range from 69 to 94%, fluoroscopy-based navigation from 81 to 92%, and CT navigation from 89 to 100% accurate. Intraoperative CT navigation exhibits a higher accuracy in pedicle screw placement than free-hand technique and use of fluoroscopy.[13]

Robot-Assisted Spine Surgery

The University of Missouri is one of a select group of medical centers in the state of Missouri that also performs robot-assisted spine surgery. The advent of robotics in spine surgery represents a significant leap forward in the evolution of technology. This leap combines diverse advancements into a single platform to enhance both the precision of surgery and the subsequent patient outcomes.

Robot-assisted spine surgery necessitates a complex workflow that requires extensive training for both spine surgeons and operating room nurses and technicians. The University of Missouri currently employs an advanced platform for robot-assisted spine surgery (Figure 2). This platform is integrated with both image acquisition and intraoperative image guidance to allow for seamless transitions between points in the workflow. After obtaining an intraoperative, three-dimensional image of the patient's bony anatomy, the system automatically performs segmental registration (each vertebral body individually) to each spinal level. Segmental registration is a critical step as the spine is mobile and the bony anatomy may be altered significantly by patient positioning. Pedicle screws are then planned on the navigation station and saved into the robotic system. The robotic system then automatically positions itself for placement of each pedicle screw at the appropriate depth and trajectory. Surgeons are then able to perform both drilling, tapping to create threads in the bone, and placement of the pedicle screw through the robotically-positioned guide.

The use of robotics in spine surgery has revealed promising clinical results with minimally invasive techniques. Multiple studies have shown robotic assisted pedicle screw placement to be more accurate than free-hand surgeries.[14–16] Additionally, the use of robotic guidance was shown to reduce radiation exposure and length of hospital stay.[14] However, there are still many limitations to the use of robotics in spine surgery including longer surgery times compared to free-hand techniques.[16] Additionally, the number of patients robotic surgery in general can serve is limited based on the small number of centers that can afford such technology. The current pricing on a single da Vinci robot (non-spinal robot) is approximately $1.5 to 2 million, resulting in higher initial capital investments for the hospitals and higher surgical costs for the patients.[17,18] Yet, an overall cost-analysis of the use of robotics in spine surgery revealed an overall savings estimate of $608,546 during a one-year period because of reduced infections and shorter length of hospital stay with the use of robotics.[17]



Figure 2. Robot-assisted placement of pedicle screws.

Motion Preservation Surgery in the Cervical Spine

Degenerative disc disease affects 80-90% of the population by age 50.[19] Anterior cervical discectomy and fusion (ACDF) is a well-established, clinically

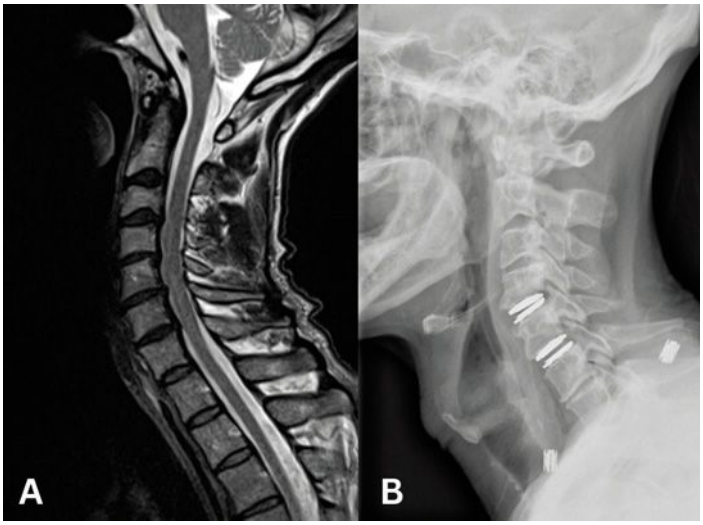


Figure 3.
A. 56-year old male presenting with neck pain and bilateral arm pain.
B. Post-operative lateral XR C4/5 and C5/6 artificial disc replacement.

effective treatment option for advanced degenerative disc disease of the cervical spine. However, there are certain drawbacks including restricted mobility at the treated level, adjacent level disease, and hardware failure.[20–22] Artificial disc replacement (ADR) is an established procedure used to treat cervical disc disease that has particular benefits such as preservation of motion and reduction in adjacent level degeneration in comparison to traditional ACDF.

Results from a number of randomized-controlled trials have demonstrated that ADR may prove to be an excellent surgical option when careful patient selection and well-trained, meticulous technique are employed.[23–26] Complications of ADR include heterotopic ossification (bony overgrowth) and implant migration or subsidence.[27,28] Careful patient selection in each treatment is key to a successful outcome. Recent series have also demonstrated that ADR may be associated with shorter length of stay and enhanced recovery times.[29–31] Spine surgeons at the University of Missouri are highly experienced in motion preservation surgery in the cervical spine via ADR (Figure 3). Our surgeons use a diverse number of available ADR devices to perform successful motion preservation surgery.

Minimally-Invasive Spine (MIS) Surgery

Degenerative disease of the lumbar spine diseases is estimated to impact around 2.06 million people annually in the U.S.[32] Historically, the approach for the treatment of most pathologies in the lumbar has been with a posterior midline incision. Such interventions can include decompression surgeries with laminectomy, discectomy, and fusion with a wide array of instrumentation. In the last several decades, several minimally invasive surgical techniques have been developed. These techniques are associated with decreased blood loss, decreased tissue injury, and in many cases, decreased risk of complications such as infection.

Percutaneous Pedicle Screw Placement

Magerl first described fixation of the lumbar spine using external fixators.[33] Later Mathews and Long used percutaneous pedicle fixation using plates.[34] This subsequently evolved into the use of rods to connect the percutaneously placed pedicle screws. In such techniques, real time neuronavigational guidance is used to identify the trajectory of pedicle screw placement. The incisions are planned based on the trajectory of each pedicle screw with minimal need for muscle retraction or dissection. Percutaneous pedicle screw placement can be utilized as a standalone treatment of vertebral fractures acting as an internal brace or supplement to anterior spinal procedures.[31, 32]

Minimally Invasive Transforaminal Lumbar Interbody Fusion (MIS-TLIF)

Interbody fusion remains an effective treatment option for patients with degenerative disc and facet joint disease. Such patients often present with mechanical back pain, radiculopathy, and claudication. In 1982, Harms and Rominger described the transforaminal approach to lumbar interbody fusion (TLIF).[35] In 2002, with the availability of more sophisticated instrumentation, minimally invasive interbody fusion was introduced by Foley and Lefkowitz.[36]

A paramedian incision is usually planned on the side of symptoms to allow for ipsilateral facetectomy and laminectomy as a mean of direct nerve root decompression. The muscle dissection is performed using tubular retractors with increasing diameters centered at the disc level of interest. The tubular

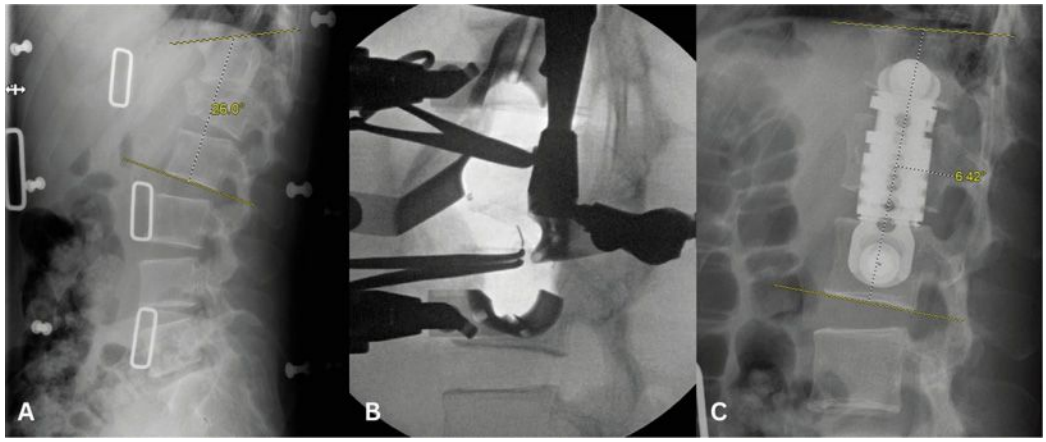


Figure 4.
A. 38 year-old male presenting with disabling pain after MVC found to have L1 burst fracture with retropulsion and kyphosis.
B. Intra-operative lateral XR with retractors in place for lateral corpectomy.
C. L1 lateral corpectomy with restoration of the anterior column and resolution of kyphosis.

retractor is placed under image guidance. Once the disc space is identified and confirmed, a microscope is brought to the field to perform a discectomy and end plate preparation for interbody cage placement. The interbody cage can be packed with graft material to facilitate fusion. Stab incisions are used to place pedicle screws at the vertebral levels above and below the disc space utilizing neuronavigational guidance. Rods are then passed through break-way guides connected to the screw heads. Once the rods are secured to the screws, the guides are broken off. The MIS-TLIF technique is associated with less blood loss, less muscle retraction, reduced postoperative pain, and shorter length of hospital stay when compared with open TLIF. However, patient reported pain scores and fusion rates are comparable for the two surgical techniques.[36,37]

Lateral Lumbar Interbody Fusion

In recent years, anterolateral approaches to the spine have gained popularity and have been refined to the point of becoming commonly used approaches for spine surgery, particularly the lumbar spine.[38] Through a small (~6cm) abdominal incision, the surgeon is able to access most of the lumbar spine. Once the skin is cut and the external fascia of the abdominal wall muscles is open, the rest of the dissection is performed bluntly and there is no additional injury to the tissues. This can obviate the need for the large midline lumbar incisions and extensive paraspinal muscle dissections that may be necessary in certain posterior approaches to the spine. This allows for more rigorous disc removal and the ability to place larger interbody grafts than are possible through a posterior approach.[39] This, in turn, results in increased ability to restore disc height, indirectly decompress the neural elements, correct spinal deformities and reduce certain fractures, making it a useful tool in cases of degenerative spinal disease, trauma, infections and even spinal tumors (Figure 4). However, these approaches are not suitable for all patients, particularly those with prior retroperitoneal surgeries.[40,41] Some of the possible complications of these approaches include hip flexion weakness related to manipulation of the psoas muscle during dissection of the lateral aspect of the spine, abdominal pseudohernias related to disruption of the abdominal wall innervation, or injury to the greater vessels, among others.[40,41] Consequently, these approaches require the spine surgeon have additional training on the retroperitoneal exposure or the help of a general surgeon for access to the spine. The use of stereotactic navigation and/or neuromonitoring can also enhance the safety of these procedures.[42]

Treatment of Metastatic Spinal Disease

Spinal metastasis is the most common bony spine tumor and the thoracic spine is the most frequently involved segment of the spine.[43] Breast (21%), lung (19%), prostate (7.5%), renal (5%), gastrointestinal (5.5%), and thyroid (2.5%) are the most common tumors that metastasize to the spine. The treatment algorithm for patients with metastatic spine disease is based on neurological dysfunction, histopathology, mechanical instability, and systemic burden of the disease. Patients who have cord compression, acute onset paralysis/paresis, and mechanical instability are often candidates for decompression and fusion. Patients with oligometastatic disease and favorable

survival are also candidates for surgery. In patients with advanced disease, subtotal tumor resection with internal fixation can be used as part of a palliative approach to cancer treatment. Surgical intervention has been shown to improve morbidity and mortality in patients with acute paralysis secondary to metastatic disease to the spind.[44,45] The recent treatment algorithm is based on Patchel R. et al,[44] landmark randomized control trial where he compared the clinical outcomes between patients with metastatic spinal cord compression treated with surgery followed by radiation and radiation alone. Patients who underwent surgical intervention followed by radiation demonstrated improved outcomes with respect to: ambulation, continence, Frankel score, and survival.

Advances in image guidance, intraoperative navigation, and percutaneous instrumentation allow spinal surgeons to deliver care to an even larger number of patients with spinal tumors of all types. By minimizing injury to adjacent tissues and shortening incisions, these tools allow patients undergoing surgery for their cancers to progress to radiation and systemic therapy sooner than when undergoing traditional surgery. "Separation surgery" involves decreasing the tumor burden around radiosensitive tissues. Stereotactic Body Radiation Therapy (SBRT) allows a team of radiation oncologists and spinal surgeons to deliver high doses of radiation to very small volumes of tissue with less injury to surrounding tissues than conventional radiotherapy. The combination of "separation surgery" and SBRT vs conventional radiotherapy allows for more effective treatment of spinal tumor burden, particularly in cases of recurrent disease.

Patients with spinal malignancies are treated by a large interdisciplinary team. This interdisciplinary team involves spine surgeons, medical oncologists, radiation oncologists, neuropathologists, and neuroradiologists. These cases are typically discussed in tumor board meetings where recommendations from all services are considered, and a unified care plan is formulated to care for these complex patients. This combined effort represents a significant advancement in the care of patients with spinal cancer.

Conclusion

The Division of Spinal Neurosurgery at the University of Missouri has sought to integrate currently developing technological advancements such as intra-operative image guidance, robotic spine surgery, minimally invasive techniques, motion preservation surgery, and the interdisciplinary care of spinal malignancy. This integration allows us to serve the needs of patients with straightforward and challenging spinal pathologies both now and in the future.

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Role of Functional neurosurgery in Improving Patient Outcomes in Epilepsy, Movement Disorders, and Chronic Pain

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This review outlines the role functional neurosurgery plays in treatment of epilepsy, movement disorders, and pain.



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Abstract

Functional neurosurgery encompasses surgical procedures geared towards treating movement disorders (such as Parkinson's disease and essential tremor), drug-resistant epilepsy, and various types of pain disorders. It is one of the most rapidly expanding fields within neurosurgery and utilizes both traditional open surgical methods such as open temporal lobectomy for epilepsy as well as neuromodulation-based treatments such as implanting brain or nerve stimulation devices. This review outlines the role functional neurosurgery plays in treatment of epilepsy, movement disorders, and pain, and how it is being implemented at the University of Missouri by the Department of Neurosurgery.

Role of Functional Neurosurgery in the Treatment of Epilepsy

Epilepsy is one of the most common neurological disorders, that affects up to 50 million people around the world, or about 1% of the population.[1] Though the number of medications for epilepsy have increased over the years, the efficacy by which they work have remained stable. One-third of patients with newly diagnosed epilepsy become drug-resistant, and an estimated one-tenth of all epilepsy patients are candidates for surgical treatment.[2] In these selected patients, surgery can improve quality of life, provide durable control of seizures, reduce medication requirements, and reduce costs of medical care.[3] Workup for surgery starts with appropriate patient and procedure selection which may include surgical resection of the seizure focus or neuromodulation in patients with multifocal epilepsy.

Defining Medically Intractable Epilepsy

Medically refractory epilepsy is diagnosed in the case in which a patient does not have seizure freedom after being treated with trials of two tolerated, appropriately chosen antiepileptic drug (AED) schedules. Studies show that ~47% of patients with new-onset epilepsy will achieve seizure freedom on one drug regimen. Importantly, the addition of a second or third AED only achieved a small additional benefit (~10% for second AED, ~1% for third AED) in rates of freedom from seizures.[2,4,5] Thus additional medications have

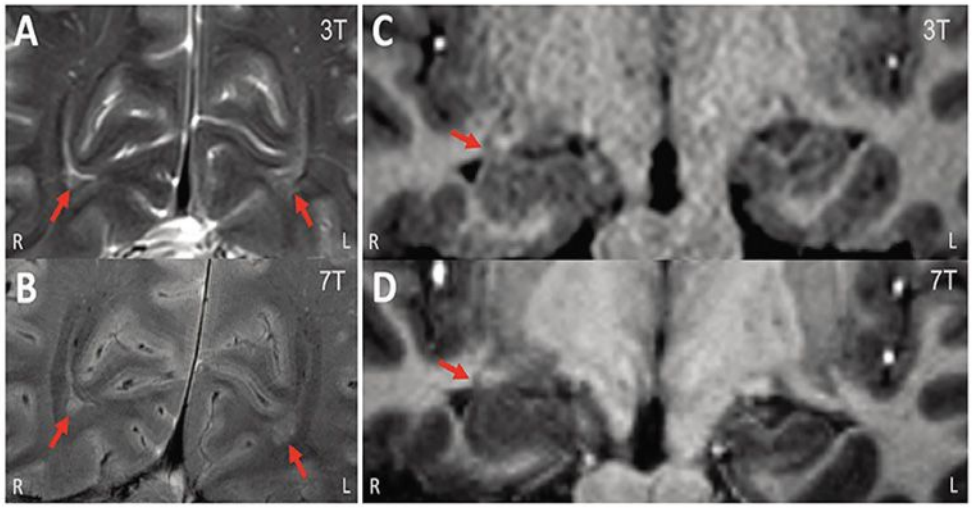


Figure 1. Comparison of 3T and 7T MRI. In this case of periventricular nodular heterotopia, the area of the right hippocampus was interpreted on 3T MRI as low-grade neoplasm (panel A, C). With better definition of 7T MRI, it was interpreted that the affected area was likely nodular infiltration (panel B, D). Eventual pathology confirmed nodular heterotopia.

diminishing benefits, even though often starting new medications can have a transient 'honeymoon' period of benefit. Patients with drug-resistant epilepsy may be candidates for surgery. Surprisingly, the average time for a surgical referral is 20 years. Pathological lesions such as hippocampal sclerosis, brain malformations, and areas of brain trauma may be addressed by surgery. Additionally, the longer a patient has epilepsy, the more likely it is to become medically refractory.[4] Thus an ongoing dialogue between neurologists and neurosurgeons is important to provide the best care for these patients.

Surgical Candidate Selection

Surgical treatment hinges upon finding the seizure focus, or nodes of the seizure network. Once a patient is referred for surgical evaluation to an epilepsy center, a multidisciplinary team of epileptologists, surgeons, neuropsychologists, and therapists come together to collate the data. The University of Missouri-Columbia is a Level 4 Epilepsy Center that is fully equipped to perform this workup. Various diagnostic techniques are employed to determine where the epileptic focus is or if it is part of a greater network in the brain.[6]

Clinical/Presurgical Evaluation

A thorough neurological history and examination of seizure semiology is imperative and can provide key localizing clues that may contribute significantly to identifying an epileptogenic focus, especially if the presentation is stereotypical (e.g. olfactory aura, feelings of déjà vu, etc. are characteristic of limbic seizures) and lateralized.[7] Thorough skin evaluation can also indicate neurocutaneous pathology.[8] Additionally, the clinical examination can exclude patients with non-epileptogenic seizures that would not be candidates for epilepsy surgery.

Scalp EEG is the mainstay for seizure localization. Usually, patients are brought in for an inpatient stay, taken off AEDs, and monitored with high-density scalp EEG in the Epilepsy Monitoring Unit, with telemonitoring beds. Ideally, at least two seizures can be captured during this time. Imaging data can support EEG data if lesions are identified on MRI. For example, hippocampal sclerosis can be identified on MRI and gives confidence in having a good surgical outcome with resection of that area.[9] Hippocampal sclerosis, which is often the culprit for temporal lobe epilepsy, can be identified on MRI with ~95% sensitivity. Other epileptogenic lesions, such as vascular malformations, cortical developmental malformations, and tumors are also detected on MRI. As technology advances, higher field magnets which can take more detailed images have improved our ability to detect structural abnormalities on MRI.[10] The University of Missouri is one of the few universities in the country with a 7T magnet, located in the NexGen Precision Health Center, that is routinely used for clinical epilepsy workups (Figure 1). Nuclear medicine imaging FDG-PET can further show decreases in brain metabolism in the seizure focus. This can help if the MRI does not detect structural abnormalities, which is often the case.[11] Ictal SPECT can highlight the seizure focus during a seizure but does have logistical challenges since radioisotope has be injected directly

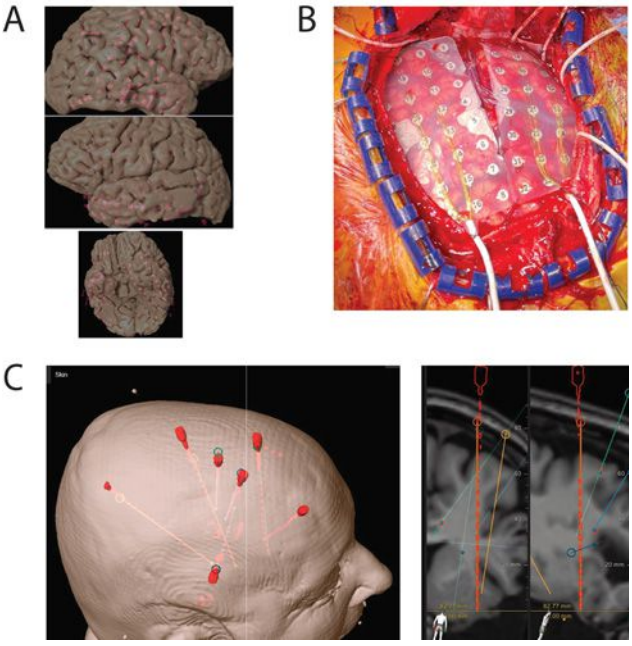


Figure 2. Phase 2 monitoring with subdural grid placement on A) 3D reconstructive software then B) *in vivo* in operating room. Phase 2 monitoring with depth electrodes to isolate deeper epileptic structures in the brain. C) 3D reconstruction of electrode trajectories and right panel shows single trajectory in the brain to the anterior insula, which was this patient's seizure onset zone.

after a seizure.[12] Patients may proceed to surgical intervention without further diagnostic workup.

However, if these data are not clearly localizing the seizure focus, the patient may require further diagnostic testing that is invasive to better localize the seizure focus, referred to as 'Phase 2' monitoring. This is done using intracranial EEG recordings using either subdural grids or depth electrodes which have better spatial resolution to anatomically localize the seizure focus. Subdural grid electrodes can sample wide areas of the neocortex, but do not pick up signal from deep areas such as the hippocampus. Depth electrodes can record from deep structures. Depending on the desired coverage and specific information required in each case, a combination of electrodes can be tailored to each individual patient to gather the information needed[13-15] (Figure 2). Stimulation can be delivered through the electrodes to both induce seizures and to map functional areas such as language and motor areas. Intra-operative functional mapping using direct cortical stimulation can also be used to map the function of the cortex, define eloquent areas, prior to surgical resection.

Open Surgery for Epilepsy

Ideally, epilepsy surgery removes the epileptogenic focus while not damaging functional or eloquent cortex. Epilepsy surgery is highly effective, and in fact, anterior temporal lobectomy for mesial temporal epilepsy is one of the most efficacious surgeries in all of neurosurgery with a number needed to treat of two.[16] In general, surgery for lesional epilepsy cases has higher rates of seizure freedom than non-lesional cases since the anatomic boundaries of surgical resection are not well defined in the latter.

Hippocampal Sclerosis-Related Mesial Temporal Lobe Epilepsy

Patients with mesial temporal lobe epilepsy often present with a history of febrile seizures that develop into focal seizures that present with automatisms and auras. MRI may show atrophy of the hippocampus. EEG will show anterior temporal interictal sharp waves. Surgical approaches include standard temporal lobe resection or selective amygdalohippocampectomy. The amygdala and hippocampus are resected along with the lateral temporal lobe and anterior temporal pole. Long-term freedom from seizures is achieved in 60-80% of these patients.[16,17]

Lesional Epilepsy

In patients with a structural lesion, which may include tumor, vascular malformation, or cortical malformation, treatment of the structural lesion itself is key. In stereotypical epileptogenic lesions such as cavernomas or dysembryplastic neuroepithelial tumor, the surgical approach hinges on resection of the lesion without damaging vital areas of the brain. If the lesion itself can be completely resected, post-operative seizure free rates reach up to 90%. However, cortical dysplasia microscopic pathology can extend past what is seen on MRI, and there can be multiple epileptogenic foci. Multifocal pathology or involvement of eloquent cortex can complicate resection, and it may not be possible to fully resect the epileptogenic foci in these cases.[18]

'Non-lesional'/MRI Negative Epilepsy

It is difficult to tailor surgical therapy to patients with 'normal' MRI scans. However, in cases in which seizures are localized to the temporal lobe, sometimes requiring Phase 2 invasive monitoring, anterior temporal lobectomy with lateral cortical resection has good results. Up to 80% of patients are seizure-free

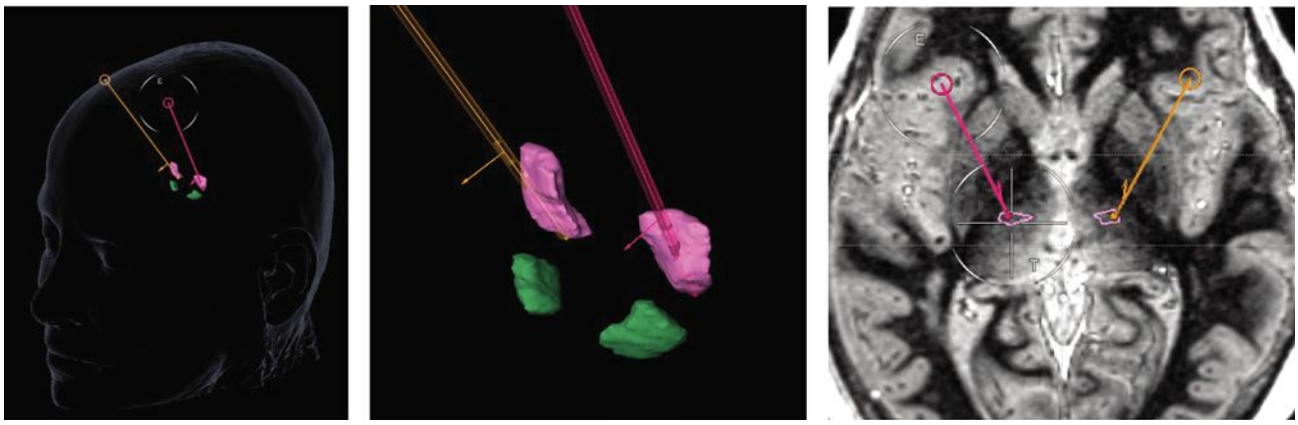


Figure 3. Deep brain stimulation for essential tremor. Electrodes are placed in the ventral intermediate nucleus of the thalamus (pink) above the subthalamic nucleus (green). Middle panel shows zoomed in view of structures with electrodes in place. Right panel shows MRI of the thalamus outlining the above-mentioned structures.

after surgery. [19] Seizure freedom in this group after surgery is only up to 50%. [19]

Corpus Callosotomy for Drop Attacks

Corpus callosotomy can reduce the frequency of drop attacks in patients with generalized epilepsy. Drop attacks are when a patient loses consciousness without any warning signs. Drop attacks are severely disabling as the patient is not able to ambulate without a helmet and often sustains significant orthopedic injuries because of unsupported falls. About 50% of patients have meaningful improvement, and up to 5% are free of seizures after callosotomy. [20]

Neuromodulation-Based Treatment

Patients with multifocal or generalized epilepsy may be a candidate for neuromodulation-based treatments (i.e. those based on brain stimulation with electrical current using an implanted device). These include vagal nerve stimulation (VNS), responsive neurostimulation (RNS, Neuropace®), and deep brain stimulation (DBS). VNS was created as an adjunct for drug-resistant epilepsy. It acquired FDA approval in 1997 and since then, more than 125,000 devices have been implanted. The device consists of a pulse generator and a lead that is placed around the vagal nerve in the neck. The anti-convulsive effects of the device are thought to be through diffuse inhibitory effects of neuromodulators in the parasympathetic system delivered via the vagus nerve to the brainstem and brain. Modulation of this network is thought to reduce ictal spread.[21] Surgery is low-risk (risk of infection and vessel injury) and can be accomplished on an outpatient basis. VNS achieves up to 50% reduction in seizure frequency in up to 40% of patients. Most patients do not become seizure-free after VNS.

Further improvements in neuromodulation have led to direct electrical stimulation of the cortex, deep nuclei, and areas of the cortex as an option for epilepsy treatment. The responsive neurostimulation, or RNS, is a device with subdural or depth electrodes that can detect seizure activity and respond by stimulating a small area of the cortex to abort the seizure.[22] The internal pulse generator and onboard computer system are housed in a case implanted into the skull. RNS is currently approved for multifocal epilepsy and used for thalamic stimulation and bilateral hippocampal stimulation most commonly.[22] Randomized controlled trials are ongoing to expand the indication to generalized epilepsies.

DBS has been used for thalamic stimulation in generalized epilepsy. Targets include the centromedian[23] nucleus of the thalamus and the anterior nucleus of the thalamus.[24] DBS involves continuous stimulation of these thalamic targets and the internal pulse generator battery is usually placed in the chest.[25] Interestingly, both RNS and DBS improve seizure control over time and reach 70% seizure control over the course of nine years. The mechanism is postulated to be related to long term plasticity of neural circuits. [26]

Role of Functional Neurosurgery in Movement Disorders

The goal of surgery for movement disorders such as Parkinson's disease, essential tremor, and dystonia

is to improve patients' quality of life by restoring motor function. The University of Missouri has a comprehensive movement disorders group consisting of movement disorders neurologists, functional neurosurgeons, psychologists, therapists, and nursing staff who specialize in the evaluation and care of these patients. Similar to epilepsy surgery, a presurgical evaluation is completed by the team. The diagnosis of the patient is confirmed and follow-up imaging and testing on and off medications is performed. Finally, if a patient is deemed a surgical candidate, the particular device and targets are chosen.

Deep Brain Stimulation Surgery

The foundational surgical method for treating this family of movement disorders is deep brain stimulation (DBS). This involves implanting electrodes into the brain, within different subcortical targets based on the particular disorder, and then implanting a subcutaneous battery to deliver current. This stereotactic surgery accurately places electrodes with millimetric precision within the brain using a frame system. A frame is mounted onto the skull and an intraoperative CT with the frame in place is obtained and merged with the patient's prior MRI imaging to create a planned trajectory for target structure. The electrodes are implanted under stereotactic guidance and functional mapping usng microelectrode recording of cellular activity through burr holes in the skull. Once the position has been confirmed, the electrodes are passed subcutaneously to attach to a pulse generator implanted in the chest. Electrodes are placed unilaterally or bilateral depending on the patient's needs (Figure 3). The mean length of stay in the hospital is between one to three days. The internal pulse generator is generally placed a week after the cranial electrodes. The DBS system is programmed two to four weeks post-op followed by fine-tuning over successive visits to optimize symptom control.[25]

DBS in Parkinson's Disease Treatment

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the onset of resting tremors, bradykinesia, and rigidity. Other features might include stooped posture, masked facies, shuffling gait, hypophonia, and micrographia. PD is caused by loss of dopamine-producing neurons in the substantia nigra and medical treatment options include replacing the dopamine orally or augmenting the existing dopamine function. Medication may provide good symptom control for three to six years but as patients requiring increased medication dosages, they may feel the effects of medication wearing off between dosing, may need frequent dosing (i.e. every two to four hours) and experience unwelcome motor symptoms (dyskinesias) with taking medication.[27] DBS of the subthalamic nucleus (STN) or globus pallidus interna (GPi) are mainly used to treat motor symptoms of PD, and may decrease the medication required so that patients experience greater relief of symptoms with less medication on board.[28,29] Efficacy of DBS for PD has been established for 30 years. Further data from the EARLYSTIM trial[30] shows that DBS helps younger patients with PD who are less than 60 years old and who have had disease for 4-plus years with maintaining better quality of life for longer periods of time. Note that DBS does not generally help with non-motor symptoms of PD including sleep disturbance, hallucinations, constipation, autonomic dysfunction, or dementia. Some of these symptoms become more prevalent later in the disease course, which is why the multidisciplinary team can help determine if the patient is in a good time window to benefit significantly from surgery.

Deep Brain Stimulation in Essential Tremor Treatment

Essential tremor is the most common movement disorder, affecting 1% in the general population. It is characterized by upper extremity tremor during voluntary movements and in severe cases it can progress to involve the head, vocal cords, and legs. Medication based treatments such as propranolol and primidone fail in about 25 to 55% of patients.[31] Other treatment options include lesional surgery like radiofrequency thalamotomy with an effectiveness of 74-90%.[32] DBS is an alternative treatment option that involves the placement of electrodes in the region of the thalamic ventral intermediate nucleus (ViM). Stable tremor control can be achieved in most patients with improvement in daily activities of life, such as being able to drink water from a glass, eat food without social embarrassment, write, perform computer-based tasks, etc. [33]

Deep Brain Stimulation in Dystonia Treatment

Dystonia is a movement disorder characterized by sustained muscle contraction, abnormal muscle twitching, and body posturing. It can be classified based on location into focal, segmental, multifocal, generalized, and hemidystonias. It can also be classified based on pathology (genetics, stroke, infections, metabolic, etc) and location (generalized versus focal segmental).[34] Patients who have become resistant to medical treatment are ideal candidates for DBS. Patients may undergo work up for the cause of dystonia such as genetic screening in pediatric patients (DYT-1 mutation is a common mutation resulting in dystonia for which DBS has favorable effects). GPi or STN DBS has been shown to improve certain types of dystonia. Efficacy can take months, implying mechanisms of neural plasticity at play.[35]

Functional Neurosurgery in Treatment of Chronic Pain

The rate of chronic pain in adults in the U.S. is 21% with 10% of patients recovering from chronic pain at one-year follow-up, with an estimated cost of 50 billion dollars per year. About 30 to 40 million patients have pain that does not respond to non-steroidal anti-inflammatory drugs like aspirin and ibuprofen. Surgical treatment of pain can be beneficial to a specific set of patients.[36]

Spinal Cord Stimulators for the Failed Back Syndrome

Spinal cord stimulation (SCS) is used to treat a wide variety of chronic pain conditions like failed back syndrome, diabetic neuropathy pain, ischemic pain from peripheral vascular disease, and complex regional pain syndromes. The procedure involves a trans-cutaneous trial for three to seven days followed by a permanent implant. For chronic low back pain, leads are placed epidurally between T8 to L2, and for chronic neck pain leads are placed above the C3 level in the epidural space. These leads are tunneled through the muscles and brought out to connect to a pulse generator usually placed in a subcutaneous pocket in the buttocks area or in the abdomen. The proposed mechanism of effect is neuromodulation of the spinothalamic tract in the spinal cord.[37] In randomized control trials SCS is shown to be superior to both repeat surgery and conservative medical management in patients with chronic failed back syndrome. There is a more than 50% reduction in pain when SCS is implanted.[37] In two randomized controlled trials, SCS has shown to be superior to best medical management in controlling diabetic neuropathic pain.[38,39]

Intrathecal Pain Pumps

The intrathecal pain pump is used to treat chronic pain associated with injury or cancer. It consists of a small catheter inserted into the thecal sac in the spine and connected subcutaneously to a small electronic pump placed in the abdomen. Medication is transferred from the pump via catheter into the thecal space and interrupts the pain signals carried via spinal nerves to the brain. Morphine, fentanyl, and ziconotide are three FDA-approved drugs to be used for IT pump delivery. The main idea is to deliver low doses of opioids to avoid undesirable side effects due to the systemic administration of these drugs. [40]

Cordotomy for Cancer Patients

Cordotomy is the targeted iatrogenic destruction of the lateral spinothalamic tract in patients with unilateral pathology that are suffering from intractable opioid-resistant pain. The procedure destroys the fibers carrying pain and temperature sensation. The procedure is a palliative option for relieving pain in patients with end-stage malignancies. Percutaneous cordotomy is performed under fluoroscopic guidance or CT guidance using local anesthesia. CT-guided C1-2 cordotomy is performed via C1-2 puncture followed by the insertion of a small electrode for radio-ablation of the target area.[41] Patient response is continuously monitored in the awake patient. The University of Missouri is one of the few centers which offers this operation.

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Disclosure

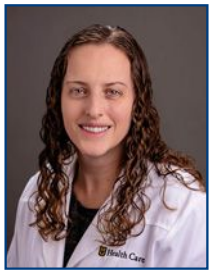
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Obesity and Anesthesia: Challenges in the Perioperative Period

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The anesthetic management of morbidly obese patients remains a challenging problem in anesthesia across the spectrum of the perioperative period.



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Abstract

The obesity epidemic has significant implications for all aspects of healthcare. The physiological changes of obesity affect every area of perioperative medicine. In this article, we discuss several anesthetic concerns regarding obesity. We will specifically discuss preoperative evaluation, perioperative challenges, and postoperative pain control and monitoring.

Introduction

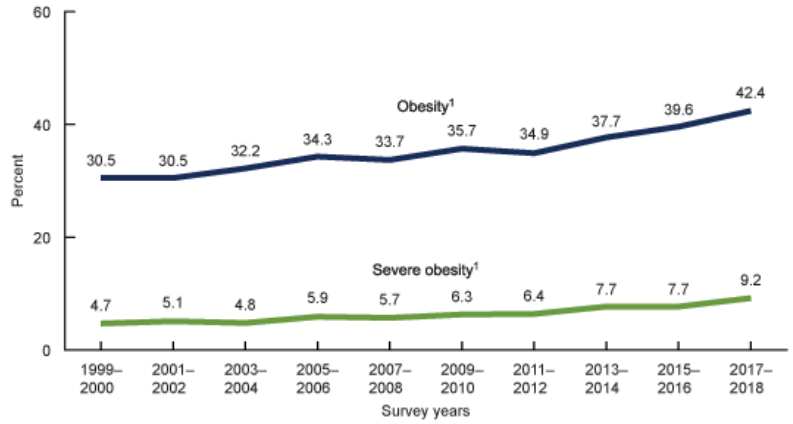
Obesity is a common comorbidity that affects all areas of medicine including anesthesiology. According to the Missouri Department of Health and Senior Services "almost two out of every three adult Missourians are overweight or obese, impacting all genders, all races and ethnicities, and all socioeconomic groups." (Figure 1).[1] The Centers for Disease Control categorizes obesity as anyone who has a body mass index (BMI) of greater than 30, and further subdivides obesity into three categories. Those individuals with the most severe form of obesity (type III obesity) have a body mass index (BMI) of 40 or greater.[2] The American Society of Anesthesiologists (ASA) recognizes that severe obesity is a "severe systemic disease with substantive functional limitations".[3] Evaluation and understanding how obesity interacts with other physiological, pharmacological, and anatomical factors is necessary to appreciate and assess perioperative risk more fully.[3] Appropriate perioperative plans and potential interventions can then be made to minimize risks in the perioperative period for these patients.

Physiologic Changes with Morbid Obesity

Cardiovascular

Perioperative cardiovascular risk is increased in patients with class III obesity. Physiological changes include increased cardiac output of 20-30 ml/kg of excess body fat.[4] This is accomplished by LV dilation and increased stroke volume, which can lead to LV hypertrophy, diastolic dysfunction, elevated LVEDP and pulmonary edema.[4] Additionally obese patients frequently have co-morbidities associated with cardiovascular disease such as HTN, dyslipidemia, myotonic dystrophy type 2, and sleep disorders.[5] Some studies suggest an increased risk of cardiovascular disease in obesity even after accounting for these co-morbidities.[6,7] A meta-analysis of over 300,000 patients with 18,000 coronary artery disease (CAD)

Figure 1. Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over: US 1999-2000 to 2017-2018.



[1]*Significant linear trend.*
NOTES: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.
DATA SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2018
REFERENCE: Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief, no 360. Hyattsville, MD: National Center for Health Statistics. 2020

events show a five-unit increase in BMI was associated with 29% increased risk of coronary heart disease (CHD).[8] Even after adjustment for blood pressure and cholesterol levels, there was a 16% increased risk of CHD relative to normal BMI 20-25.[8] Visceral adiposity is associated with the systemic and vascular inflammatory processes that lead to atherosclerosis.[9] The full extent of cardiovascular disease is often masked due to asymptomatic cardiovascular disease present due to limited exercise tolerances.[6,7]

While the 2014 ACC/AHA Guideline for Perioperative Cardiovascular Evaluation and Management of Patients undergoing Noncardiac Surgery does not specify different preoperative testing for patients with class III obesity, it is important to understand the limitations of common cardiovascular testing modalities in these patients.[5,10] ECG has a lower sensitivity and specificity in obesity, possibly due to underdiagnoses of left ventricular hypertrophy (LVH).[5] Treadmill stress testing may be non-diagnostic as many patients with BMI> 40 are unable to achieve the 80-85% age-predicted heart rate needed for diagnostically valid results.[5,11,12] Single photon emission CT (SPECT) may require two-day protocols for weights 250-350 lbs and is limited by table weight limitations above 350 lbs.[5] Stress echocardiography may be incomplete due to poor acoustic windows secondary to obesity, though contrast does improve sensitivity and specificity in obese patients preparing for bariatric surgery.[5,13,14] Stress cardiac MRI had 89% diagnostic quality in a study of 285 participants with average BMI of 34 kg/m^2; however, there are still table weight and waist circumference limitations.[5,14,15] As MRI tables have weight limits, CT calcium scans and cardiac CT coronary angiography are similarly limited with obesity.[5] Image quality also degrades as BMI increases due to increased background noise and decreased signal-to-noise ratio.[5]

Respiratory

Obesity is known to decrease chest wall and lung compliance which leads to decreased functional reserve capacity (FRC), vital capacity (VC), and total lung capacity (TLC).[4] The decrease in FRC is mostly due to a reduction in expiratory reserve volume (ERV). With general anesthesia, patients with obesity may have up to a 50% reduction in FRC compared to a 20% reduction in FRC in non-obese patients.[4] Excess fat is metabolically active leading to increases in oxygen consumption and carbon dioxide production in patients with obesity.[4] The decrease in FRC and increase in oxygen consumption reduces the tolerated apnea time during induction of anesthesia.[4] Surgical techniques such as pneumoperitoneum can negatively combine with morbid obesity further worsening underling pulmonary compliance by up to 30% compared to normal-weight individuals with increase in inspiratory resistance.[16]

Obesity is a risk factor for obstructive sleep apnea (OSA).[17] Untreated OSA can lead to chronic hypoxemia, hypercapnia, pulmonary hypertension, systemic hypertension, and polycythemia.[17] These physiologic changes increase risk of cardiovascular disease, cerebrovascular disease, and right ventricular failure. While OSA screening and diagnosis has increased, nonadherence to positive airway pressure treatment is common, either due to discomfort of

the CPAP mask, insurance issues, or various other reasons.[17] Patient's with OSA and obesity are at higher risk for difficult airway management and postoperative pulmonary complications.[4] Obesity hypoventilation syndrome (OHS) is chronic hypoventilation secondary to obesity and is often underdiagnosed. OHS occurs in 5-10% of patients with class 3 obesity and increases risk of postoperative complications and death.[4,18] These patients are more sensitive to the respiratory depressant effects of anesthesia than even patient's with OSA and should have close post-operative monitoring.[4,18]

Airway Challenges

Mask ventilation and tracheal intubation are more likely to be difficult in patients with class III obesity.[4] This is especially concerning in patients with OSA and/or a short, thick neck. Even with good preoxygenation, these patients are more likely to desaturate with apnea due to their decreased FRC. This can be improved by positioning the patient in reverse Trendelenburg. Mean arterial oxygen levels improve with 25-degree ramp, which can also help minimize the risk of aspiration of gastric contents.[4] The ramp positioning with head extended helps to align the oral, pharyngeal, and laryngeal axes while improving FRC to optimize intubation. Awake intubation should be considered in patients with a history of, or anticipated, difficult mask ventilation and difficult intubation. Accessing a surgical airway may still be particularly challenging for obese patients in an emergent 'can't ventilate, can't intubate' situation despite optimal positioning.

Close monitoring of ventilation and oxygenation is critical in obese patients undergoing sedation. Obese patients with OSA are more susceptible to the respiratory depressant effects of benzodiazepines, opioids, and propofol; and it may be difficult to mask ventilate or intubate them as a rescue.[4] Closed claims analysis shows an increase in malpractice claims related to adverse events during monitored anesthesia care (MAC) compared to respiratory complications during general anesthesia.[4]

Other Organ Systems

Obesity is associated with increased residual gastric volume (>25 mL despite 8 hours NPO) and low gastric fluid pH (<2.5) compared to non-obese individuals.[4] Abdominal obesity increases intragastric pressure, increasing risk of GERD and/or hiatal hernia formation, both of which increase the risk of aspiration. Fatty liver is commonly associated with obesity which is often a precursor to liver disease such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Up to 33% of obese patients may have abnormal liver function tests; however, drug clearance is usually not reduced.[4]

Metabolic syndrome is common in obese patients and increases risk of type 2 diabetes, doubles risk of death from myocardial infarction and stroke, and increases risk of perioperative complications including cardiovascular, pulmonary, renal injury, and wound infection.[4,19] Type 2 diabetes, hyperglycemia, and insulin resistance predispose patients with obesity to surgical site infection.[4,20] Obesity is also associated with increased renal blood flow due to increased cardiac output and increased glomerular filtration rate. This activates the renin-angiotensin system and can impair natriuresis.[4] Perioperative thromboembolic risk (DVT and PE) is higher in patients with class III obesity compared to non-obese patients.[4] On a positive note, bariatric surgery resolves metabolic syndrome in 95% of patients who achieve the expected weight loss.[4,19]

Perioperative Concerns

Blood Pressure Monitoring

Noninvasive blood pressure monitoring (NIBP) is the most commonly used blood pressure monitor for anesthetic cases, and accurate measurement depends on appropriate sizing of the cuff. Undersized cuffs will overestimate blood pressure while an oversized blood pressure cuff will underestimate blood pressure. Even with an appropriately sized cuff, the conical shaped upper extremity commonly seen in obese patients can compromise accuracy of NIBP readings. Practitioners often choose to use the forearm when faced with the conical upper extremity. However, forearm measurements are known to overestimate systolic and diastolic blood pressure in patients with obesity.[4,20,21] Historically, the alternative for blood pressure monitoring was placement of an arterial line. There are newer continuous noninvasive monitors such as ClearSite (Edwards Lifesciences, Irvine, CA) and continuous

noninvasive arterial pressure (CNAP, CNSystems Medizintechnik, AG, Graz, Autria) that use finger cuffs. These monitors are consistent with NIBP and invasive blood pressure measurements in many studies for non-obese patients; however, there have not been enough studies including patients with class III obesity.[20–22]

Alterations in dosing medications

Dosing of anesthetic medications are typically weight based, though appropriate dosing depends on understanding volume of distribution for loading dose, maintenance and drug clearance.[4] Highly lipophilic drugs have an increased volume of distribution in obesity, whereas drugs with weak or moderate lipophilicity do not and can be dosed on lean body weight.[4] Drugs that are equally distributed between adipose and lean tissue should be dosed based on total body weight. Drugs that undergo phase I metabolism (oxidation, reduction, hydrolysis) are not affected by obesity, whereas phase II reactions (glucuronidation, sulfation) are enhanced due to increased GFR and may require a higher maintenance dose.[4]

Positioning Challenges

Intra-operative patient positioning is one challenge that confronts the anesthesia team and that must be carefully and thoughtfully handled if adverse outcomes are to be avoided. First, proper equipment and instruments with sufficient weight specifications must be available and used judiciously. For example, OR tables with a weight rating of 450 kg or higher may be needed.[4,23] They should be equipped with detachable side arm supports and restraints. They must be adjustable along several different axes to facilitate optimum patient physiology and physical safety as well as to maximize surgical exposure. Often, these goals run counter to each other.[24,25] As an example, changes in respiratory and cardiovascular physiology of the obese patient favor the head-up position, sometimes requiring as much as 45 degrees or more. This promotes ventilation, oxygenation, cardiac output, and airway management.[24,25] Most operations, however, require a supine, head-down, lateral, or even prone position all of which complicate patient management.[25] Thus, the OR table is critical to a successful operation. In addition to compromised cardiopulmonary status, surgical positioning of the obese patient raises the risk of physical trauma. An obese patient's risk for peripheral nerve injury is greater than the general population not only due to the challenging positioning, but also due to their more common pre-existing co-morbidities, neuropathies, and longer surgical times.[23–25] Further, pressure ulcers and sheer trauma are more common. In severe cases, rhabdomyolysis and kidney failure have been reported.[24] The use of padding and support devices to distribute weight over as large an area as possible will help to mitigate these risks.[25]

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Additional Concerns

Often overlooked is that operative times are longer in patients with class III obesity. This can be due to technical difficulties from increased retracting, requiring longer surgical instruments, and suboptimal ergonomics for the surgeon. Prolonged

operative times means longer exposure to anesthesia and/or may eliminate the possibility of regional anesthesia as a primary anesthetic. Multiple specialties have demonstrated that patients with obesity require higher radiation exposure during fluoroscopy, either from increasing power for each shot or from additional shots needed.[26–28]

Challenges with Regional and Neuraxial Anesthesia

Regional anesthesia in the obese may be beneficial in helping avoid difficult airway manipulations, decreases aspiration risk, and is associated with earlier mobilization and shortening of hospital length of stay.[29] Peripheral nerve blocks in the obese may have difficulties in proper patient positioning, landmark identification, and need for longer needle.[30] There may be need for phrenic nerve sparing in upper extremity blockade, since there may be obesity related respiratory physiological changes that demand avoiding diaphragmatic paralysis. Continuous catheter techniques may have problems due to dislocations and possible increased incidence of infection. Ultrasound guidance may help overcome many difficulties in regional techniques, but targets are more deeply situated in obese patients and the ultrasound beam is weakened as it travels a greater distance through tissue layers, artifact may be present, and the resulting imagery may obscure the underlying anatomy.[30]

Difficulties in central nerve blockade (epidural or spinal) placement may be due to patient positioning, difficult landmark identification, catheter dislocation, and need for longer needle; neuraxial placement is done as a "blind" procedure.[29] Increasing weight is associated with the depth of placement of an epidural at all epidural sites (lumbar, lower, and upper thoracic) and with all approaches (midline, paramedian); the sitting position is the optimal position for placement.[31] After the epidural catheter is inserted and secured, the catheter position can change and actually be withdrawn from epidural space during repositioning to the lateral decubitus or supine positions. Ultrasound has been used to assist epidural needle placement in morbidly obese patients in both pain medicine and obstetric patients.[32] Despite these risks and challenges, regional/neuraxial anesthetics are successful and beneficial to these patients for surgical blockade, to labor analgesia, to mode of post-operative and opioid sparing pain control.

Post-Operative Concerns

Important postoperative analgesic goals for the management of obese patients should include maximal comfort, early mobilization, maintenance of respiratory function and avoidance of over sedation.[33] Obese patients, due to a high incidence of OSA, are predisposed to airway obstruction, hypoxia, and hypercarbia.[33] Because opioid induced respiratory depression is a concern, a multimodal approach to pain control should be employed.[34] This approach should include techniques which potentially decrease the total opioid dosage requirements. Both central and peripheral nerve blockade with local anesthetics utilizing single shot or continuous infusion catheters to reduce use of opioids. Further, the analgesic regimen should be supplemented with scheduled doses of NSAIDs and acetaminophen. Other medications to consider are the NMDA receptor blocker ketamine and the alpha-2 receptor agonists clonidine and dexmedetomidine. Also, a continuous infusion of intravenous lidocaine for up to 72 hours has been shown to be effective in reducing total narcotic requirements.[34]

If postoperative narcotics are needed, a patient-controlled option is best. Avoid basal rate dosing. Opioid dosing should be based on lean body weight.[34] Dosing schedules for all medications should be adjusted to individual patients and their unique comorbidities. Perioperative enhanced recovery care pathways (ERAS) have been developed and adopted by many healthcare facilities. They help standardize and optimize the approach to postoperative analgesia to decrease opioid requirements, increase patient safety and improve surgical outcomes. ERAS pathways do not only address pharmacologic therapies. They might include other interventions too, such as noninvasive ventilation and oxygenation, early mobilization, elevated head position and sedation scoring. They might also establish thresholds for pulse oximetry and CO_2 monitoring as well as when to adjust a patient's level of care.[35] ERAS pathways have proven especially useful for reducing untoward outcomes and increasing patient satisfaction and should continue to be used and refined as new data becomes available.

Special Considerations

Bariatric surgery continues to be the gold standard in surgical options for the obese population.

As pharmacologic treatments for obesity continue to advance, a new class of weight loss medications has emerged, the Glucagon-like Peptide-1 agonists (GLP-1 agonists), used in the treatment of type 2 diabetes and obesity. GLP-1 agonists have been shown to inhibit gastric emptying resulting in a reduction of appetite and food intake lowering glucose levels. The benefit of weight loss for obese patients results in increased perioperative risks associated with the side effects of these medications. Nausea, vomiting, and diarrhea can lead to volume contraction and may predispose a patient to acute kidney injury or hemodynamic instability perioperatively; close monitoring of volume status must occur.[36] More concerning has been the recognition of a significant decrease in gastric emptying associated with these medications, often associated with a "full stomach" despite proper NPO times and parameters. This potentially predisposes patients to an elevated risk of pulmonary aspiration perioperatively.[37]

Given these concerns, in June 2023 the American Society of Anesthesiologists (ASA) Task Force on Preoperative Fasting released a press release suggesting the following guidelines for elective procedures:[38]

Day(s) Prior to the Procedure

1. For patients on daily dosing consider holding GLP-1 agonists on the day of the procedure/surgery. For patients on weekly dosing consider holding GLP-1 agonists a week prior to the procedure/surgery.
2. This suggestion is irrespective of the indication (type 2 diabetes mellitus or weight loss), dose, or the type of procedure/surgery.
3. If GLP-1 agonists prescribed for diabetes management are held for longer than the dosing schedule, consider consulting an endocrinologist for bridging the antidiabetic therapy to avoid hyperglycemia.

Day of the Procedure

1. If gastrointestinal (GI) symptoms such as severe nausea/vomiting/retching, abdominal bloating, or abdominal pain are present, consider delaying elective procedure, and discuss the concerns of potential risk of regurgitation and pulmonary aspiration of gastric contents with the proceduralist/surgeon and the patient.
2. If the patient has no GI symptoms, and the GLP-1 agonists have been held as advised, proceed as usual.
3. If the patient has no GI symptoms, but the GLP-1 agonists were not held as advised, proceed with 'full stomach' precautions, or consider evaluating gastric volume by ultrasound, if possible and if proficient with the technique. If the stomach is empty, proceed as usual. If the stomach is full or if gastric ultrasound inconclusive or not possible, consider delaying the procedure or treating the patient as 'full stomach' and manage accordingly. Discuss the concerns of potential risk of regurgitation and pulmonary aspiration of gastric contents with the proceduralist/surgeon and the patient.
4. *There is no evidence to suggest the optimal duration of fasting for patients on GLP-1 agonists.* Therefore, until we have adequate evidence, we suggest following the current ASA fasting guidelines.[39,40]

The previously stated guidelines are a work in progress and will evolve as our knowledge about and anesthetic/surgical interactions with these medications grows.

Conclusions

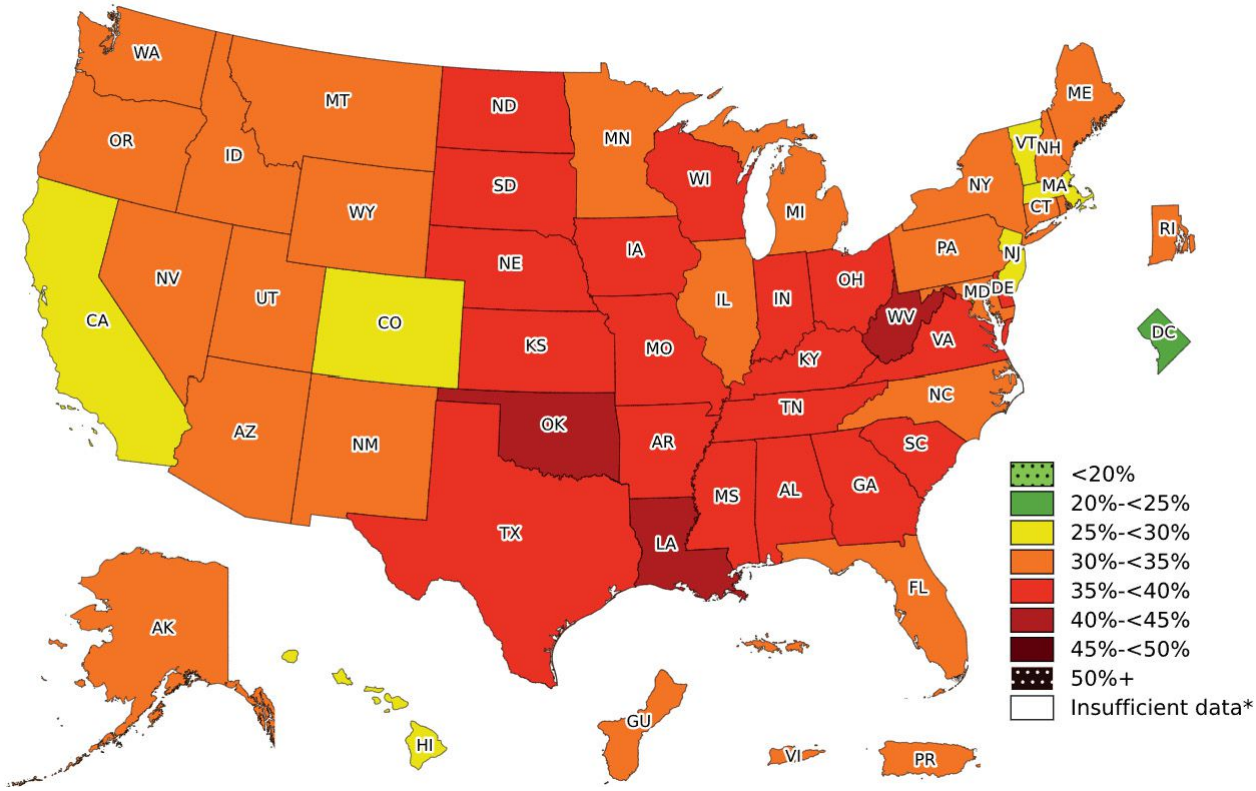
The anesthetic management of morbidly obese patients remains a challenging problem in anesthesia across the spectrum of the perioperative period. This discussion has given a generalized examination of these challenges, but the details remain numerous in the anesthesiologist's daily practice. With the increasing prevalence of obesity, each patient may present unique challenges with additional comorbidities combined with morbid obesity. We as anesthesiologists strive to remain knowledgeable and vigilant in these challenges to provide the best care to this increasing population and educate our fellow physicians about the perioperative implications.

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1 Picture = 1,000 Worrds

Prevalence† of Obesity Based on Self-Reported Weight and Height Among U.S. Adults by State and Territory, BRFSS, 2022



Source: Behavioral Risk Factor Surveillance System
**Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.*

†Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

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Telehealth Visits have Lower Non-attendance than Traditional Orthopaedic Clinic Visits

by Bradley S. Spence, MD, Mark J. Lambrechts, MD, Zhengye Si, MA, Emily V. Leary, PhD & Sumit K. Gupta, MD, MPH

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This study showed consistently lower cancellation rates for scheduled telehealth clinic visits compared to in-clinic visits.



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Abstract

The use of telemedicine has rapidly expanded in the wake of the COVID pandemic, but its effect on patient attendance remains unknown for different clinicians. This study compared traditional in-clinic visits with telehealth visits by retrospectively reviewing all scheduled orthopaedic clinic visits. Results demonstrated lower rates of cancellations in patients scheduled for telehealth visits as compared to in-clinic visits, during the initial COVID pandemic. In general, physicians can expect a lower cancellation rate than non-physician practitioners.

Introduction

The COVID pandemic forced many rapid changes in the way medicine is practiced in the US. Hospitals and clinics were required to find innovative ways to deliver care, while minimizing physician-patient contact to mitigate COVID spread. The use of telemedicine quickly expanded as a powerful platform for both physicians and advanced practitioners to deliver safe and effective healthcare while maintaining continuity of care. Our understanding of the effects of this rapid transformation in the way we deliver care continues to evolve as orthopaedic clinicians' experience with telemedicine increases.

Patient nonattendance of clinic visits is a frustrating and common problem that disrupts clinic flow, poses a significant cost to healthcare systems, and places patients at risk of receiving suboptimal care.[1–3] Reported rates of nonattendance at scheduled outpatient clinic visits, due to cancellation or no-shows, range from 5% to 39% for orthopaedic subspecialties and are more frequently associated with patients attending follow-up visits compared to new patients.[4,5] While previous literature has extensively reported on the predictors of non-attendance in traditional clinical settings, there are no clear solutions to improving these rates.[4,6]

The advantages of telemedicine are well known and supported from both clinical and economic standpoints.[7-12]

Telemedicine offers a safe and convenient alternative to in-clinic visits. Recent literature demonstrates improved geographical outreach, reduced costs, and shorter visit times with patient satisfaction comparable to in-clinic visits for patients.[7–11,13,14] However, literature pertaining to the application of telemedicine in orthopaedic surgery is limited with most studies reporting on visit times, and/or patient satisfaction.[7,8,14,15]

Furthermore, there has been little evidence comparing cancellation and no-show rates in orthopaedic surgery telehealth visits (THVs) to in-clinic visits.[10,16] The purpose of this study was to compare the rate of missed appointments in THVs to in-clinic visits among all orthopaedic surgery specialties. We also assessed the effect the beginning of the pandemic played on no-show and cancellation rates between in-clinic visits and THVs.

Methods

With IRB approval, all orthopaedic surgery appointments scheduled from July 2018 to June 2020 at a large academic health center were included in the analysis. The clinicians included orthopaedic surgeons, non-operative physicians, and mid-level clinicians (advanced practice nurses and physician assistants). The patient volumes were recorded for nine orthopaedic specialties: foot and ankle, oncology, pediatrics, spine, sports, general, total joint, trauma, and upper extremity. For each subspecialty, patients had two methods to complete a visit, either in-clinic or using telehealth. Telehealth visits were scheduled by sending an email to the patient that included a link to a secure, HIPAA-compliant video or audio-only conference using the Zoom platform. Patients were provided with the opportunity to schedule a telehealth or in-clinic appointment for both new and return clinic visits. Patients were expected to use their own device and have an internet connection. If patients did not have internet access or a device to perform the telehealth visit, arrangements were made at local hospitals or clinics to perform the telehealth visit.

Each visit, whether in-clinic or THV, was recorded as arrived, cancelled, or no-show. Cancelled appointments represented those patients that had confirmed that they wish to cancel their appointment at any time prior to the actual appointment time. This could be done either online through a patient portal, or by phone call. All patients receive an automated phone call or text message 48 hours prior to their appointment asking them to confirm or cancel. No-show patients were those that did not attend their appointment and did not cancel prior to their scheduled time. Non-attendance at appointments was also recorded as all patients who did not arrive at a scheduled appointment (the sum of cancelled and no-show).

The COVID pandemic caused significant disruption of normal schedules and procedures starting in the middle of March 2020. At our institution, patients were encouraged to schedule telehealth visits when possible and appropriate during the April to June 2020. Each appointment that did not require an imaging study, or other procedure (such as an injection or manipulation), were contacted by staff and offered a THV. For those patients who either required, or chose, an in-clinic visit, they were limited to the patient only without accompanying family members or other support persons. One accompanying caregiver was allowed for pediatric or disabled patients. Everyone entering any healthcare facility was also required to answer screening questions about COVID related symptoms and undergo a temperature check.

Statistical Analysis

Data were summarized and validated. Chi-square tests were used to test significant differences in rates among more than two groups. Odds ratios were calculated with corresponding 95% confidence intervals. To control the false discovery rate, the Holm method was applied and pre-adjustment significance was set at $p<0.05$.

Our data were analyzed to consider differences in attendance in subspecialty clinics, between in-clinic and telehealth visits and differences between physician visits and mid-level clinician visits. We also analyzed our data to evaluate any potential impact from the initial COVID lockdown or mitigation strategies, compared to pre-COVID visits. The pre-COVID time frame was defined as July 2018-February 2020, which corresponds to prior to local mitigation/lockdown initiation. The post-COVID time frame included all data

Table 1. Cancellation frequency and rates for in-clinic and telehealth methods, by orthopaedic specialty

Specialty	In-clinic			Telehealth			p-value
	Total	Cancellation	Cancellation rate (%)	Total	Cancellation	Cancellation rate (%)	
Foot and ankle	27937	8542	30.58	124	31	25.00	0.2123
oncology	3677	1226	33.34	177	56	31.64	0.6978
pediatrics	26397	7516	28.47	379	122	32.19	0.1250
spine	**37188**	**14123**	**37.98**	**964**	**227**	**23.55**	**<0.0001**
sports	**51533**	**15577**	**30.23**	**462**	**83**	**17.97**	**<0.0001**
general	**8472**	**2484**	**29.32**	**98**	**17**	**17.35**	**0.0131**
total joint	**29631**	**9972**	**33.65**	**139**	**30**	**21.58**	**0.0035**
trauma	**21471**	**6605**	**30.76**	**204**	**46**	**22.55**	**0.0141**
upper extremity	**18554**	**6211**	**33.48**	**216**	**49**	**22.69**	**0.0011**
Overall	**224860**	**72256**	**32.13**	**2763**	**661**	**23.92**	**<0.0001**
Pre-pandemic	174832	52048	29.77	206	74	35.92	0.1882
Post-pandemic	**25089**	**8848**	**35.27**	**1358**	**313**	**23.05**	**<0.0001**
	p-value* < 0.0001			**p-value* = 0.0036**			

*p-value for the comparison between pre/post pandemic rates within each type of visit

Table 2. No-show frequency and rates for in-clinic and telehealth methods, by orthopaedic specialty

Specialty	In-clinic			Telehealth			p-value
	Total	No show	No show rate (%)	Total	No show	No show rate (%)	
Foot and ankle	27937	1628	5.83	124	7	5.65	1.0000
oncology	3677	133	3.62	177	5	2.82	0.7286
pediatrics	26397	1464	5.55	379	14	3.69	0.1458
spine	37188	2152	5.79	964	63	6.54	0.3621
sports	**51533**	**2932**	**5.69**	**462**	**41**	**8.87**	**0.0046**
general	8472	404	4.77	98	1	1.02	0.1338
total joint	29631	1288	4.35	139	7	5.04	0.8501
trauma	21471	1708	7.95	204	12	5.88	0.3371
upper extremity	18554	1037	5.59	216	18	8.33	0.1113
Overall	224860	12746	5.67	2763	168	6.08	0.3740
Pre-pandemic	174832	11176	6.39	206	6	2.91	0.0715
Post-pandemic	**25089**	**605**	**2.41**	**1358**	**103**	**7.58**	**<0.0001**
	p-value* < 0.0001			**p-value* = 0.0294**			

*p-value for the comparison between pre/post pandemic rates within each type of visit

Table 3. No show and cancellation rates for physicians and non-physician practitioners for traditional and telehealth visits.

Rate type	Visit Type	Physician	Non-physician	p-value
No-show	Traditional	**5.17%**	**7.69%**	**0.001**
	THV	5.96%	8.33%	0.066
Cancellation	Traditional	**31.21%**	**34.23%**	**<0.0001**
	THV	**22.51%**	**27.38%**	**0.025**

Table 4. No-show and cancellation rates for physician and non-physician practitioners for pre-and-post pandemic periods

Type of visit	No-show rate			Cancellation rate		
	Pre	Post	p-value	Pre	Post	p-value
Physician traditional	**5.80%**	**2.17%**	**<0.0001**	**28.97%**	**34.01%**	**<0.0001**
Physician THV	3.15%	7.22%	0.1252	**32.28%**	**22.18%**	**0.0154**
Non-physician traditional	**8.94%**	**3.10%**	**<0.0001**	**31.69%**	**37.77%**	**<0.0001**
Non-physician THV	2.13%	11.36%	0.0921	**46.81%**	**24.18%**	**0.0024**

from April-June 2020. The data from March 2020 was not included since it was not possible to differentiate pre- and post-COVID appointments within that month.

Results

In-clinic vs. Telehealth Visits

Included were 227,623 clinic visits seen across nine subspecialty areas of orthopaedics. Of these, 224,860 were in-clinic visits, and 2,763 (1.2%) were telehealth visits.

Tables 1 and 2 show the cancellation and overall no-show rates for in-clinic and THV visits by subspeciality, and pre- and post-Covid.

The cancellation rates for the entire clinic for in-clinic visits were higher than THVs (32.1% vs. 23.9%; p-value<0.0001) with the corresponding odds of cancellation 1.51 times greater for in-clinic cancellations compared to THVs (OR=1.51, 95% CI 1.38, 1.64). However, six out of the nine subspecialty clinics demonstrated significantly lower cancellation rates for THVs.

There were no statistically significant differences in the overall no-show rate between in-clinic visits and THVs (5.7% vs.6.1%; p-value 0.3740, Table 2). During the initial stages of the COVID pandemic and lockdown, the odds of no-shows for in-clinic visits were 2.28 times greater than for THVs (OR=2.28, 95% CI 1.01, 5.13).

Physician vs. Non-Physician Practitioners

Table 3 shows the cancellation and no-show rates for physicians and non-physican practitioners. In general, cancellation and no-show rates were higher for non-physician practitioners. Table 4 shows how the rates differed during the pre-pandemic time, compared to those conducted during the pandemic (post-COVID – April-June 2020).

Discussion

While telemedicine has provided clinical and economic benefits[7–12] to both patients and healthcare providers, there is limited data comparing the rate of non-attendance due to cancellations and no-show in THVs and traditional in-clinic visits among orthopaedic surgery clinics. These missed appointments represent a significant problem in healthcare with rates ranging between 5 and 39%.[4,5] The non-attendance rates for in-clinic visits at our institution were between 34-43% across different sub-specialties, which is similar to prior reported rates at other institutions.[4,5]

Our results showed significantly lower cancellation rates for THVs, and these became even lower after the initial COVID pandemic mitigation measures. Several factors may contribute to this decrease. It is easier for patients to attend a clinic from their own homes or workplaces, than to spend the time and money to travel. Wait times are generally lower for THVs,[8,10-12] and furthermore, the waiting can be done in a place of comfort rather than in a physician's office. This may allow patients to perform other tasks simultaneously. Interestingly, the opposite relationship was observed for no-shows. The authors postulate that patients may be less concerned about missing THVs than in-clinic visits due to the perceived flexibility.

Our results demonstrated differences in cancellation and no-show rates amongst orthopaedic subspecialties. While the cancellation rates were lower throughout the majority of orthopaedic subspecialties, in our Pediatric, oncology and foot and ankle practices no differences were observed in cancellation rates. We hypothesize that this is likely due to the populations that these specialties care for. In general, parents and those patients with possible cancer diagnoses are less likely to cancel these important appointments. These clinic visits are "vital" to this subset of patients. Our foot and ankle providers did observe a lower cancellation rate in THVs, however this value did not reach statistical significance. This finding may be the result of lack of power within in the specialty, as these practitioners did not offer as many THVs during the pandemic.

Prior studies have clearly outlined the notable benefits of telemedicine as they relate to cost and patient satisfaction in orthopaedic surgery patients. Sultan et al.[11] demonstrated high satisfaction scores in pediatric spinal deformity patients as compared to general pediatric orthopaedic visits using telemedicine visits. In addition, they demonstrated markedly reduce wait times with THVs, which is similar to prior studies. Moreover, Atanda et al.[14] found an average savings of $50 in travel costs when patients utilized their telemedicine services. While our study did not measure reasons for cancellations or no-shows, patient satisfaction or cost savings with THVs, we found that patients greatly appreciated the ability to see their healthcare providers remotely. In several instances, THVs allowed family members, who were physically in different locations, to attend clinic visits together. This is an additional advantage in the care of our pediatric and geriatric patients. Many patients commented on the fact that they felt much safer during the pandemic and would not have come for an in-person visit.

The COVID pandemic affected every aspect of daily life for people across the world, and orthopaedic practices and their patients were no exception. Healthcare systems were forced to rapidly adapt to the new reality of reducing exposure and providing safer ways to see patients. Telehealth seemed to be ideally suited for this situation and as expected, a large increase in the number of telehealth visits was observed in our included post-pandemic time period. Despite overall increase in cancellation of clinic appointments, the rate of cancellation specifically for THV visits decreased during this time. This suggests that patients are not only willing to schedule telehealth visits but are also more likely to attend these visits once they are made, especially during times of restricted travel. Reasons for no-show and cancellation for telehealth visits may include unfamiliarity with the telehealth platform, and technical (software and hardware) problems for both the patients and practitioners. Future studies may be necessary to determine if this trend hold true as patients and practitioners become more familiar with the integration of telehealth platforms.

Our study has some important limitations. We did not have data on patient demographics and social determinants of health, and we do not know if the impact is the same for different population cohorts. Understanding which patients are at a higher risk of non-attendance would allow clinicians to develop mechanisms to improve follow-up for those at-risk patients. Due to the retrospective nature of the study design, we could not elucidate the reasons for cancellations and no-shows.

In addition, while the overall patient numbers are very large, the number of THVs comprise a small proportion of the total visits (1.2%). As such, there may be some systemic differences between the groups that we could not identify. The data was also more limited in the post-COVID time frame. As we gain more experience during this pandemic, further trends may be apparent with greater number of patient visits. Furthermore, certain orthopaedic visits may not be amenable to telehealth – such as ones requiring imaging studies, office-based procedures, or hands-on physical examination to help guide diagnosis. Finally, the availability and quality of telehealth resources varies greatly across health systems and populations, and was not evaluated in this study. At our institution, we serve a large rural population and therefore our patients may be more affected by the ability to access internet services. It is still unknown whether patient satisfaction, and ultimately patient outcome, will be affected by transition to telehealth.

Our study found that THVs provided a feasible alternative to in-clinic visits that may allow orthopaedic clinics to improve patient attendance rates. Future studies that evaluate the effectiveness of THVs should measure patient satisfaction, quality of care provided, and cost analysis.

In conclusion, this study showed consistently lower cancellation rates for scheduled telehealth clinic visits compared to in-clinic visits. This difference was more pronounced during the COVID pandemic. This data provides further justification for the use of telehealth to improve patient adherence to clinical follow-up. This study also supports expansion of telehealth capacity by health systems as a means of improving clinic efficiency.

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Disclosure

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CRISPR Advancements for Human Health

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CRISPR-based genome editing technologies offer unprecedented capabilities for precise genetic modification.



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Abstract

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has emerged as a powerful gene editing technology that is revolutionizing biomedical research and clinical medicine. The CRISPR system allows scientists to rewrite the genetic code in virtually any organism. This review provides a comprehensive overview of CRISPR and its clinical applications. We first introduce the CRISPR system and explain how it works as a gene editing tool. We then highlight current and potential clinical uses of CRISPR in areas such as genetic disorders, infectious diseases, cancer, and regenerative medicine. Challenges that need to be addressed for the successful translation of CRISPR to the clinic are also discussed. Overall, CRISPR holds great promise to advance precision medicine, but ongoing research is still required to optimize delivery, efficacy, and safety.

Introduction

The CRISPR system is comprised of a CRISPR-associated (Cas) endonuclease along with a single guide RNA (sgRNA) designed to target a specific DNA sequence. Cas nucleases are enzymes that can bind and create double-stranded breaks in DNA. sgRNAs contain a scaffold structure that complexes to the Cas protein and also includes a uniquely engineered segment that can be designed to direct the Cas protein to a specific DNA sequence of interest. CRISPR technology enables precise targeting of nearly any genomic location simply by altering the nucleotide sequence of the sgRNA. This targeted approach can help to correct disease-causing mutations or suppress genes linked to the onset of diseases.[1] CRISPR has been adapted for deleting gene function (knockout), adding new gene function (knock-in), activation or repression of endogenous genes, and genomic diagnostic screening techniques.

Advanced CRISPR approaches such as base editing and prime editing use modified Cas enzymes which can induce precise single nucleotide changes in the genome without creating double-strand DNA breaks.[2] CRISPR can also be used to activate genes (CRISPRa) or inactivate genes (CRISPRi) by targeting modified sgRNA/Cas complexes to the gene's promoter region, recruiting transcription factors for increased gene expression or repressors for decreasing gene expression.[3]

While CRISPR-Cas technology has demonstrated immense potential as a genome editing tool, its use in clinical applications is still in the early stages. As of January 2024, only 89 clinical trials employing CRISPR are currently underway, highlighting that much work remains to translate this

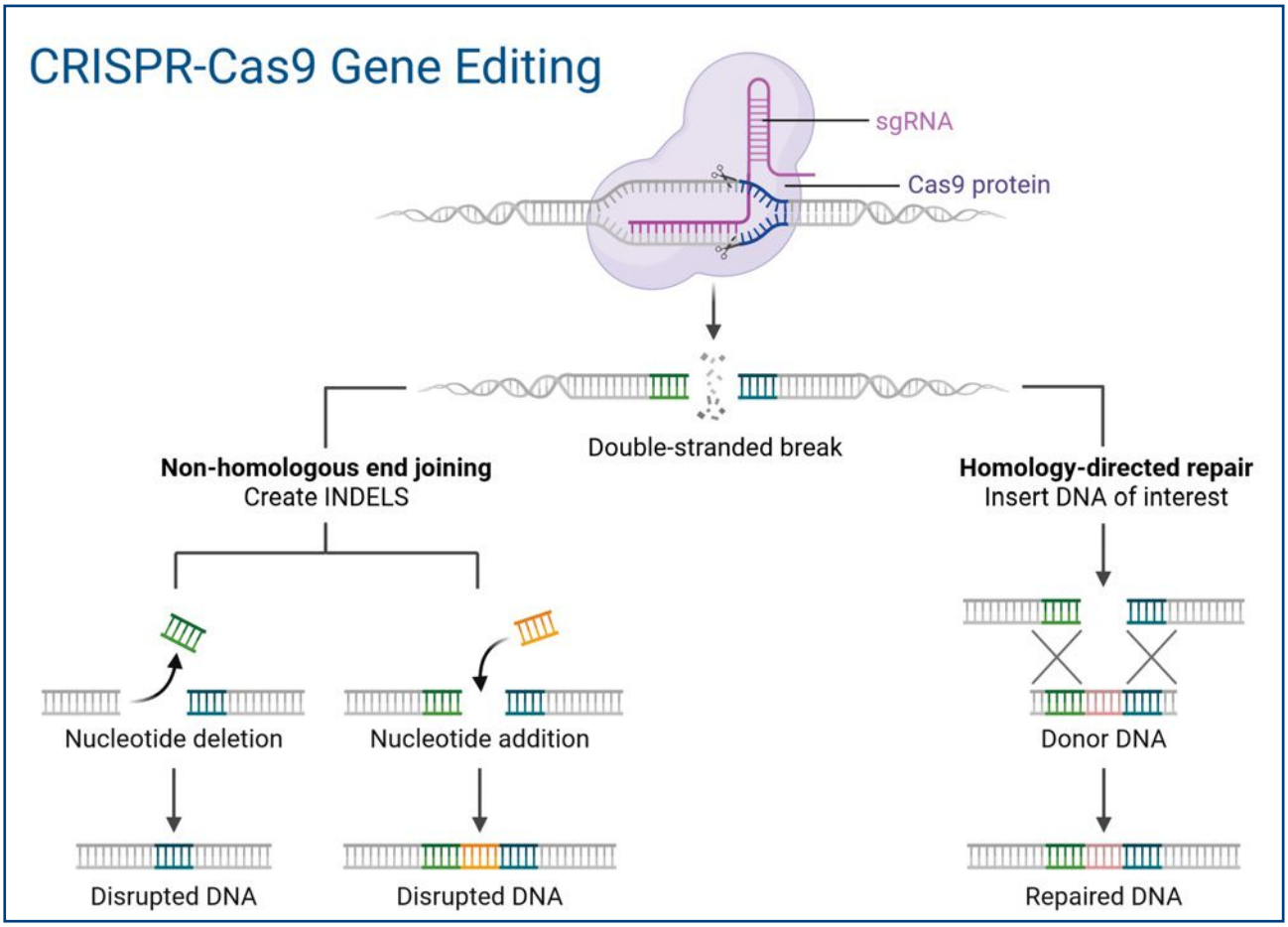


Figure 1.
Traditional CRISPR-Cas9 genome editing. The sgRNA contains a scaffold structure that complexes to the Cas9 protein and also includes a uniquely engineered segment that can be designed to direct the Cas9 protein to a specific DNA sequence of interest. Once bound to the DNA at the target location, the Cas9 protein creates a double-stranded break in the DNA. The cell naturally heals this double-stranded break using one of two main repair mechanisms. Non-homologous end joining (NHEJ) is the most common mechanism typically resulting in indel formation. Homology-directed repair (HDR) is a less efficient repair mechanism that allows for introduction of exogenous DNA through the use of a donor DNA repair template.

technology into approved gene therapies.[4] Notably, unintended alterations in DNA can occur through the utilization of CRISPR, and the long-term consequences of these modifications on patient health remain uncertain. However, given the considerable benefits that CRISPR offers, it is plausible to anticipate that these challenges will be overcome in the foreseeable future.

CRISPR Modifications and Advancements

CRISPR-based genome editing technologies have rapidly progressed, enabling more precise and versatile modifications to DNA sequences. Since wildtype Streptococcus pyogenes Cas9 (SpCas9) nucleases cause double-stranded DNA breaks that can result in unwanted nucleotide insertions or deletions (indels), scientists have developed modified Cas9 proteins such as a nickase Cas9 (nCas9) and a catalytically dead Cas9 (dCas9). nCas9 only produces a single-stranded "nick" in the DNA rather than cleaving both strands. dCas9 is able to bind DNA but does not create a break in the DNA at all. By fusing either nCas9 or dCas9 to DNA modifying enzymes, scientists can alter specific nucleotides without the risk of introducing indels.

Base editors, comprised of modified nCas9 or dCas9 fused to a deaminase, precisely convert C-to-T or A-to-G nucleotide substitutions without creating a double-stranded break in the DNA.[5] One of the limitations of base editing is that the system cannot be used to alter every possible nucleotide combination. A more recent advancement, prime editing, has further broadened the range of editable genetic sites. Prime

editing involves a fusion of nCas9 to an engineered reverse transcriptase and a prime editing guide RNA (pegRNA). The pegRNA guides the nCas9 to the region of interest, and also includes a segment that consists of the desired nucleotide sequence for repairing the DNA after the single-stranded nick has been generated.[6] Since prime editing is designed to fix single base pair changes and other small mutations, it is predicted to be capable of treating up to 89% of genetic mutations in humans. Whereas the other 11% of human mutations include larger disruptions such as having too many copies of a gene or when an entire gene is missing.[7,8]

As an alternative to modifying DNA, an RNA editing system has also been developed. This system utilizes a modified CRISPR effector protein, Cas13b, combined with an adenosine deaminase domain to edit adenosine-to-inosine accurately and effectively in RNA molecules. This approach also holds promise for correcting many mutations that contribute to specific human diseases.[9] Compared to DNA-based methods, editing RNA offers a safer therapeutic profile due to the transient nature of RNA edits.

While delivering these complexes remains a challenge, Cas molecules can be introduced into the cell as a synthetic gene sequence using adeno-associated virus (AAV), where the viral vectors carry the genetic instructions for the Cas protein. However, the large size of wildtype SpCas9 poses limitations for delivery with AAV vectors. To overcome this, researchers have engineered a compact CRISPR enzyme called Axidibacillus sulfuroxidans Cas12f (AsCas12f) that has comparable gene editing activity to the wild type SpCas9, while being one-third the size of commonly used Cas9. This modified AsCas12f was successfully delivered in vitro in mice using AAV, demonstrating its potential for more efficient CRISPR-based genetic therapies.[10]

Together, these engineered CRISPR systems and new approaches mark significant advances in precision genome editing capabilities, including more specific on-target edits, the ability to modify a broader range of sites, and enhanced delivery options like AAV-compatible AsCas12f. Continued engineering of compact yet efficient Cas nucleases and novel effector fusions will help drive the next generation of precise, versatile and deliverable genome editing tools.

Delivery of CRISPR Reagents

One of the key challenges for using CRISPR in the clinic is ensuring safe and effective delivery of the CRISPR components to the targeted tissues and minimizing off-target effects. New viral vector delivery systems like AAV are being engineered to overcome this obstacle. Extensive in vitro and in vivo animal model testing is being done to evaluate on-target editing and safety.

Multiple approaches are being explored to deliver CRISPR-Cas components into cells within the body for therapeutic editing applications. These can be categorized as viral vector-based delivery strategies or non-viral carrier-based methods.

Viral vectors may integrate into host cells and cause problems such as mutations, carcinogenesis, and immune responses.[11] However, recombinant AAVs are non-replicating and tend to remain episomal without integrating into the genome, except in rare cases. These advantages allow their use for packaging CRISPR reagents into the AAV genome for cell editing.[12] AAVs can also provide tissue-specific tropism due to the cell-specific serotypes of AAVs, have reduced immunogenicity compared to other viral vectors, and enable transient gene expression.[13] However, challenges remain regarding efficiency and safety.

Non-viral delivery methods include the use of nanoparticles or liposomes to encapsulate ribonucleoprotein complexes.[14-16] Nanoparticles made from engineered lipids or polymers can improve cell uptake, increase editing potency beyond what is achievable by protein alone, expand delivery beyond the liver, and potentially reduce immunogenicity compared to viral approaches.[17] Another non-viral method uses messenger RNA (similar to RNA vaccines) to encode the CRISPR components, achieving transient and controlled expression without needing to deliver DNA.[18]

Lastly, the CRISPR system can be used without delivering the CRSIPR components directly into the body. Ex vivo therapy involves removing cells from the patient, editing them outside the body, and then returning them to treat genetic disorders like sickle cell anemia or enhance immune responses for cancers.

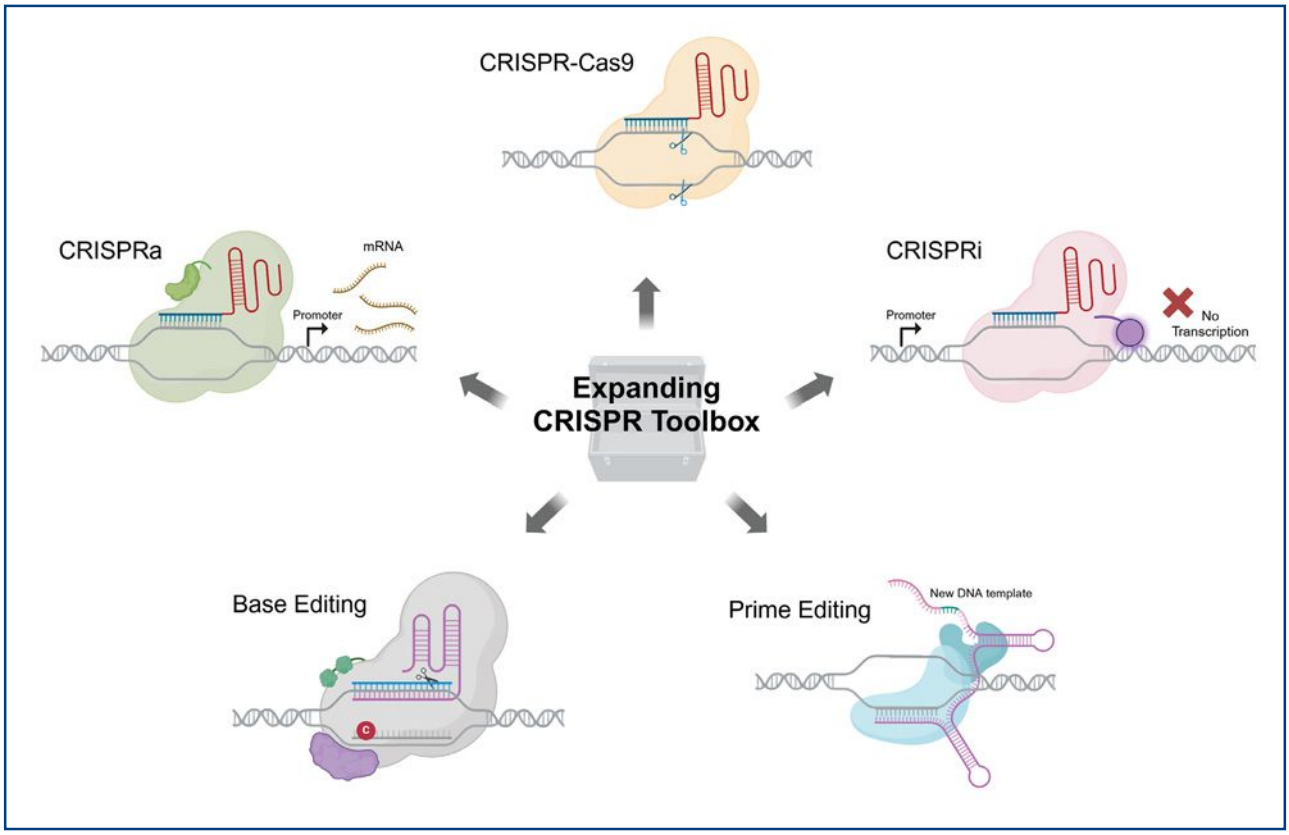


Figure 2
Expanding CRISPR toolbox. CRISPR-based genome editing technologies are rapidly progressing. CRISPRa and CRISPRi can be used to recruit transcription factors for increased gene expression or repressors for decreasing gene expression. Base editors have been designed to convert C-to-T or A-to-G nucleotide substitutions without creating a double-stranded break in the DNA. Prime editing includes a small, engineered segment of new sequence that is used for precisely repairing the DNA after a single-stranded nick has been generated. Continued advancement of CRISPR-based tools will help drive the next generation of precise, versatile and deliverable genome editing tools.

Potential Clinical Applications

Genetic Disorders

The introduction of CRISPR technology brings a hopeful new phase in treating genetic diseases. This powerful gene-editing tool offers amazing potential to directly address the root causes of many different genetic disorders. Recent clinical trials have demonstrated the potential of CRISPR-Cas gene editing to treat blood disorders like sickle cell disease (SCD) and beta-thalassemia. In a phase 1/2 study, individuals with transfusion-dependent beta-thalassemia received autologous $CD34^+$ hematopoietic stem and progenitor cells modified using CRISPR-Cas9 to disrupt the BCL11A erythroid enhancer and induce fetal hemoglobin production. Participants experienced significant and sustained increases in fetal hemoglobin levels after receiving the gene-edited cells.[19] The FDA recently approved the first CRISPR therapy for sickle cell anemia.[20] Additionally, strategies to rectify the sickle cell mutation in the beta-globin gene or compensate by overexpressing gamma-globin are actively under investigation.[21] Cystic fibrosis patients stand to benefit from CRISPR interventions aimed at correcting mutations in the CFTR gene, such as the prevalent F508del allele, and restoring proper CFTR channel function.[22] In the case of Duchenne muscular dystrophy, approaches involving exon skipping or direct correction of dystrophin mutations through CRISPR hold the potential to restore dystrophin protein production in muscle cells.[23] Leber congenital amaurosis, which is primarily attributed to CEP290 mutations, is being targeted with CRISPR strategies that seek to repair specific disease-causing mutations.[24]

Hemophilia, characterized by deficiencies in Factor VIII or Factor IX, is being addressed through CRISPR editing of liver cells to restore normal blood clotting mechanisms. A novel dual gene editing strategy using CRISPR has been shown to provide long-term phenotypic correction in a mouse model of hemophilia B, offering a promising new approach for the treatment of this disease.[25] Studies in Huntington's Disease pig models have shown that disease treatment can be optimized by lowering mutant huntingtin protein levels via the targeting of expanded CAG repeats in the HTT gene.[26] Additionally, CRISPR shows promise in difficult to treat mitochondrial diseases by modifying the gene expression through targeted knock-in or directly editing mutations in the mitochondrial DNA.[27]

Infectious Diseases

The CRISPR-Cas system has the potential to aid in diagnosing diseases, preventing their spread, and contributing to potential treatments. CRISPR-based systems have shown tremendous potential for ultrasensitive detection of pathogens. Novel assays couple isothermal amplification with CRISPR mediated DNA cleavage for single-copy detection of viral or bacterial nucleic acids within 1-2 hours.[28] These assays can be readily adapted to detect emerging outbreak pathogens. CRISPR can also improve sequencing-based detection of rare antimicrobial resistance genes by removing abundant human gene sequences or blocking background DNA to enrich pathogen signals.[29] CRISPR has shown the potential to prevent or cure various viral and bacterial diseases. HIV requires CCR5 receptors to enter the cell. Knocking out the CCR5 gene results in cell resistance to HIV and the absence of HIV infection in patients. In humanized mouse models, CRISPR delivered via AAV to knock out the receptor CCR5 prevented HIV infection.[30] In clinical trials, CRISPR-based gene therapy is being utilized to treat HIV in humans. This approach targets the viral DNA of HIV that is integrated in the host genome, aiming to disrupt its ability to replicate and maintain infection.[31] CRISPR can be used to treat infectious diseases by targeting the pathogenic nucleic acids. For instance, the Cas13d nuclease was able to target and destroy SARS-CoV-2 RNA in vitro and also reduce influenza viral load in respiratory epithelial cells.[32] CRISPR has been used to successfully targeted human papillomavirus genes E7 and E9 in cell lines, which could help treat HPV-associated cancers.[33] Additionally, modified CRISPR nucleases such as Cas3 paired with phages have been able to target antibiotic-resistant bacteria to overcome infections.[34]

Cancer

CRISPR technology is showing significant promise in cancer therapy. It is being actively used in several clinical trials, which focus on various strategies of knocking out oncogenes, correcting mutations in tumor suppressor genes, and enhancing the efficacy of T-cell therapies. These trials are exploring CRISPR's potential in different types of cancer and its ability to improve immune system responses against cancer cells. For example, in vitro studies have shown that CRISPR can be used to inactivate oncogenic KRAS, which is mutated in many cancers like lung and pancreatic cancer.[35] Researchers have also shown that CRISPR can be employed to correct mutations in tumor suppressor genes, particularly the TP53 gene.[36]

In conjunction with chimeric antigen receptor (CAR) T-cell therapy to target cancer antigens, CRISPR mediated gene editing technology has allowed for the potential to target a wide range of cancers. CRISPR-Cas9 gene editing has been utilized to knock out the immune checkpoint receptor PD-1 in tumor-specific T-cells.[37-39] Disruption of the PD-1 signaling axis in PD-1 knockout T-cells enhanced anti-tumor immunity, as evidenced by increased tumor infiltration and cytotoxicity of PD-1 knockout T-cells compared to control T-cells in murine tumor models.[40,41]

In addition to engineering patient's own T-cells (autologous T-cells), there is increasing interest in using T-cells from healthy donors (allogeneic T-cells) as an off-the-shelf cell therapy product.[42] Gene-edited allogeneic T-cells, with mechanisms to reduce graft-vs-host rejection, have shown promise as a strategy to broaden access to engineered T-cell therapies.[43] Recent studies have demonstrated the feasibility of disrupting genes such as PD-1 and TCR using CRISPR-Cas9 in allogeneic T-cells before adoptive transfer into patients.[44,45] Allogeneic CRISPR-edited T-cell therapies are now being evaluated in early-phase clinical trials, with the goals of maintaining anti-tumor potency while minimizing the risk of graft-vs-host disease.[46]

Regenerative Medicine

CRISPR technology is revolutionizing regenerative medicine, especially stem cell-based treatments,

by addressing immune rejection challenges. This is primarily achieved by editing the major histocompatibility complex-human leukocyte antigen (MHC-HLA) genes in donor cells to match those of the recipient, creating immune-tolerant cells.[47] This breakthrough significantly reduces the need for immunosuppressive drugs, mitigating their adverse effects and long-term risks. A notable application is in diabetes treatment, where CRISPR-edited stem cells could offer a durable cure without continuous immunosuppression.[48]

Ethical Considerations

CRISPR-based genome editing technologies have revolutionized the field of genetic modification, allowing for precise and targeted modifications to the genome. However, these technologies also raise significant safety and ethical concerns, specifically off-target effects and potential germline editing. Off-target effects refer to unintended editing at sites other than the intended target locus. Studies have shown that CRISPR nucleases can induce mutations at off-target sites that differ from the target sequence by a few nucleotides.[49] These off-target effects can potentially lead to unpredictable and deleterious mutations. To address this issue, various strategies are being developed to improve targeting specificity, predict potential off-target sites using computational algorithms, and analyze off-target effects through whole genome sequencing.[50] Human germline editing, which involves modifying the genetic material of embryos or germline cells, is highly controversial. Concerns include the potential for these heritable modifications to have unknown and irreversible effects on future generations.[51] While the intention behind germline editing is to eliminate genetic disease traits, there is a lack of consensus on whether it should be permitted given the current limitations in terms of knowledge and technical capabilities. The ongoing ethical debates revolve around arguments supporting parental reproductive freedom and the prevention of heritable diseases, versus concerns about permanently altering the human genome in ways that could have far-reaching unknown consequences. Moving forward, it is crucial to minimize off-target effects and restrict applications to somatic cells until safety and consensus can be firmly established regarding human germline modifications. Careful regulations and transparent public discourse are essential to govern the responsible advancement of CRISPR-based genome editing technologies.

Conclusion

CRISPR-based genome editing technologies offer unprecedented capabilities for precise genetic modification. However, the ethical concerns surrounding off-target effects and human germline editing necessitate careful consideration and regulation. Efforts are being made to improve delivery techniques and targeting specificity minimizing off-target activity, while the debate regarding human germline editing continues.

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