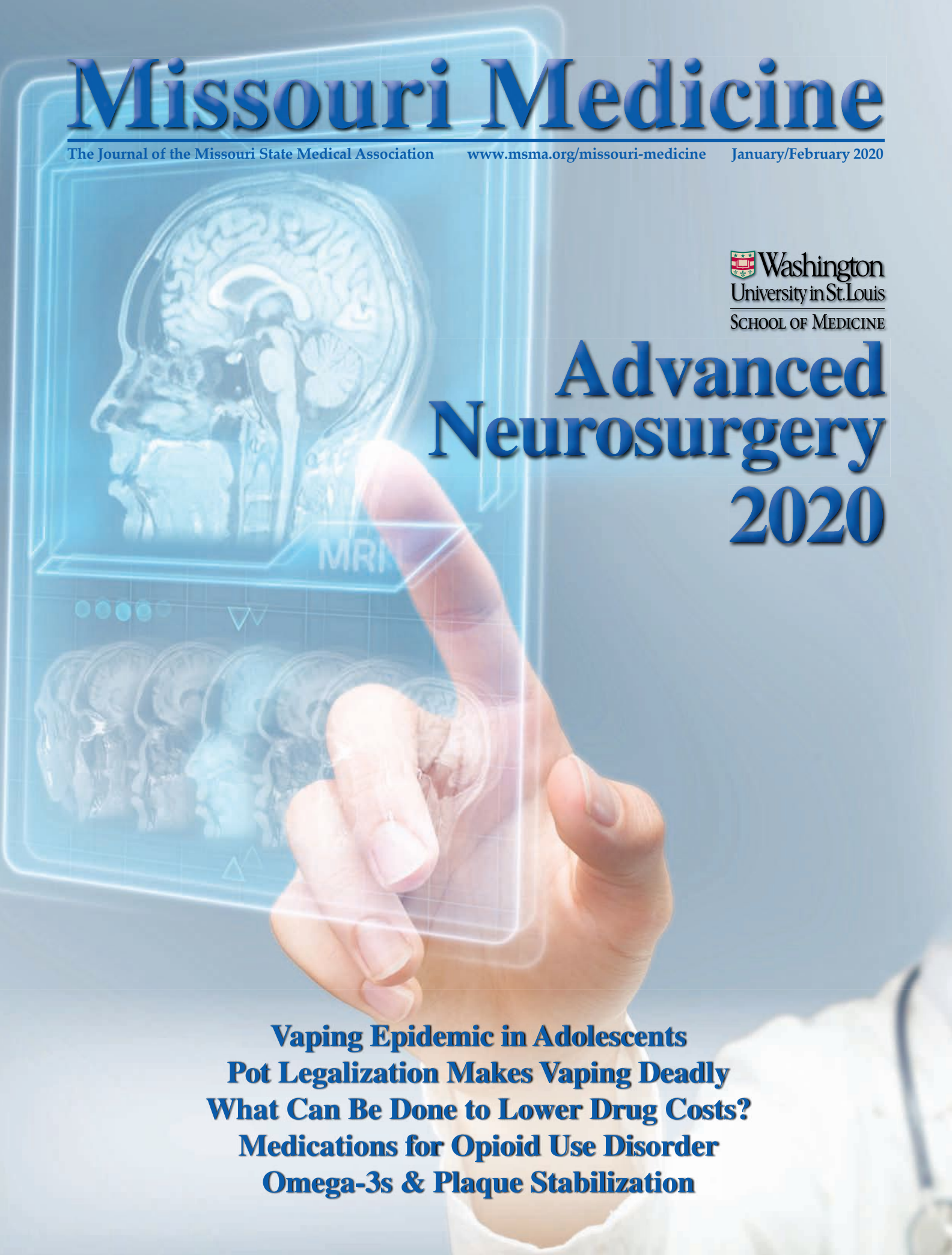
Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine January/February 2020



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Question:
Why So Much Time, Disease, and Death to Recognize a Toxic Substance?

Answer:
Addiction and Profit

by John C. Hagan, III, MD

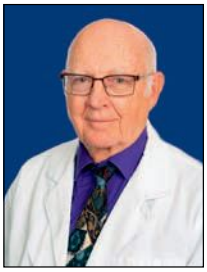
The odds of a suicide attempt were almost 3.5 times higher in youthful pot smokers versus those who didn't use marijuana.[6]

QUESTION: What do these deadly poisons have in common: arsenic, radium, mercury, thallium, cyanide?

ANSWER: At one time they were all considered by physicians and the public as useful medications and/or healthy supplements. They were taken in a wide variety of lotions, potions, notions, tinctures, tonics, and pills. These poisons were recommended, sold, and prescribed freely by physicians.[1] It took thousands of deaths and many decades before the harmful nature of these substances was perceived by physicians and the general public.

QUESTION: What disease causing carcinogenic substance was once widely used and recommended by physicians for coughs, sore throats, nervousness, and believed by the public to be harmless or salubrious?

ANSWER: Tobacco. More than half of physicians in 1940s smoked cigarettes and many recommended them to patients.[2] Smoking was considered by the public as socially sophisticated. They believed the doctors and dentists who told them tobacco was good for heath. It took millions of deaths and many decades before the harmful nature of nicotine was widely perceived by physicians and the general public.



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QUESTION: What class of drugs was widely touted by segments of the pharmaceutical industry and 'thought-leaders,' like Russell Portenoy, MD, in the late 1980s and early 1990s as a non-addicting panacea for pain? Physicians were told by these often industry-paid pain experts that if they did not prescribe these drugs they were not meeting the standard of care, subject to malpractice claims and perhaps committing a felony. Physicians responded by writing prescriptions for billions of these pain pills.

ANSWER: Opioids. It took hundreds of thousands of deaths and over a decade before the harmful nature of opioids was perceived by physicians and the general public. Dr. Portenoy, 'The Evangelist of the Opioid Epidemic,' is under a mountain of litigation, and now testifying against the opioid companies that paid him handsomely for his endorsement of their products.[3] The opioid epidemic is one of our largest contemporary health care problems.

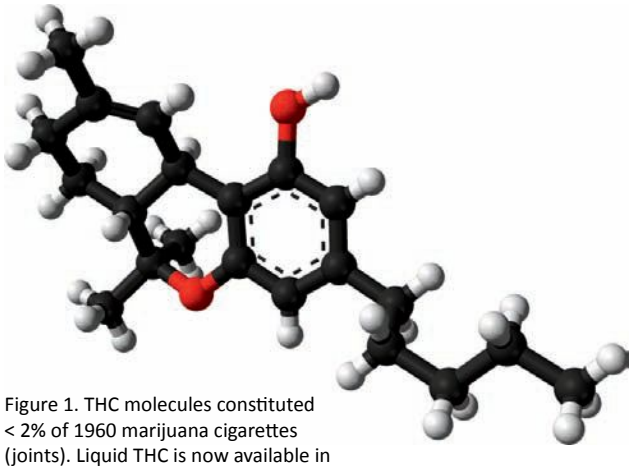


Figure 1. THC molecules constituted < 2% of 1960 marijuana cigarettes (joints). Liquid THC is now available in concentrations > 90% and can produce heroin-like high. THC is routinely found in illegal amounts in CBD products.

Source: Ben Mills.https://commons.wikimedia.org/w/index.php?curid=4759840

LAST QUESTION: What chemical substance is widely perceived by the public as medically useful or at worse, a relatively innocuous intoxicant? It's called "a medicine" in many states, and in others is as legal and available as wine, beer, and liquor? This substance is freely prescribed by a disappointing number of physicians to anyone with the cash to purchase a green, leafy 'medical' card?

LAST ANSWER: Cannabis. Sham 'medical' marijuana at its core is all about the euphoria, high-producing, and habituating THC (tetrahydrocannabinol) molecule (Figure 1). Unlike the aforementioned health destroying chemicals, evidently not enough time has passed or deaths occurred for it to be obvious to physicians, the general public, law makers, and product liability lawyers how devastating this exploding public health cannabis epidemic is becoming. As I write this editorial, millions of dollars and scores of paid activists are flowing like a noxious green river from its Big Weed source into Missouri to get recreational marijuana on our state November ballot. "'Big Weed' is the derisive name for the unseemly and avaricious conglomerate of cannabis growers, processors, distributors, dealers, Mexican drug cartels, users/abusers, investors, and other hangers-on bent on making billions on medical, and inevitably recreational, marijuana."[4]

You don't have to be an ophthalmologist to know that 'hind-sight' is the clearest of all types of vision. We now ask how erstwhile physicians and back-in-the-day public could have been so ignorant as to believe that deadly poisons and noxious substances and habituating cancer causing nicotine would be good for them. But most of us were in practice when the purveyors of opioids for everything and everyone were enticing physicians to prescribe opioids and threatening us if we did not. Still it happened then; it's happening now. We must look at the pronouncements of physician thought-leaders much more critically as well as consider who is paying them money.[5] When was the last time you heard an industry-sponsored thought-leader say anything critical about the drug that supplements their income? Me neither!

The percent of suicide incidents in which toxicology results were positive for marijuana has increased from 14 percent in 2013 to 23 percent in 2017."

https://rmhidta.org/files/D2DF/FINAL-Volume6.pdf

At first, addiction is maintained by pleasure, but the intensity of this pleasure gradually diminishes and the addiction is then maintained by the avoidance of pain.

-Frank Tallis

Missouri Medicine has chronicled and published as many scientific and social perspective articles on the detrimental effects of cannabis/THC products as any state medical journal in the United States. This began in earnest in the March/April 2012 issue (Figure 2). I will not reference all articles, but many are posted on msma.org/marijuana-education-resources and also in the index of previous issues available at msma.org/missouri-medicine-library. Our Journal has referenced the social, legal, educational, domestic, and law enforcement devastation that medical/recreational marijuana has wreaked in once healthy Colorado. While legal marijuana taxes have only generated 0.9 of 1% of the Centennial State's annual budget, cannabis has created far in excess of that amount in added Colorado expenses, taxes, and social costs. See rmhidta.org/files/D2DF/FINAL-Volume6.pdf.



Physicians can write prescriptions for three FDA approved cannabidiol-based (CBD) pure drugs with individual indications for nausea and vomiting of chemotherapy, or childhood seizures or weight loss/poor appetite (Marinol®, Epidolex®, and Cesamet®) All of Missouri's major physician organizations opposed uncontrolled sham medical marijuana but supported legitimate true-science research on cannabis in the 2018 state elections. The introduction of medications by legislation and public referenda outside of FDA mandated pathways is unprecedented, unlawful, unscientific and frankly frightening.

The country is going to pot. We are losing the battle in Missouri and the United States. Our profession, the media, and the public are failing to note the parallels between rising violent crime and suicide in youth and the corresponding escalating use of cannabis products it largely reflects.[6] The tsunami of money from both legal and illegally sold cannabis by Big Weed and the advocacy of growing numbers of users both habituated, addicted, or the scientifically misinformed is guaranteeing that cannabis will be the next and perhaps among the largest and most devastating public health crises in our nation's history.

I don't have any answers or easy solutions. Likely this will also take decades and hundreds of thousands of deaths before the public, legislators and healthcare professionals 'get it.' There will be little satisfaction and no solace in retrospectively saying, "I told you so."

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MM

Questions and Answers for Physicians on Medical Marijuana

by Lowell Pearson, JD

In November 2018 the People of Missouri adopted Constitutional Amendment 2, enacting a new constitutional chapter permitting medical marijuana use, and authorizing growing marijuana, manufacturing of marijuana products and the dispensing of marijuana. The best estimate from the industry is that dispensaries will be open and selling products in the summer of 2020.

There are many issues facing the medical community. This article addresses some common questions. Both Chapter XIV of the Constitution and the Department of Health and Senior Services rules (health.mo.gov/safety/medical-marijuana/rules.php) should be consulted for more detail.

Did Amendment 2 adopt a constitutional right that affects physicians?

Yes, article XIV, Section 1 defines a new right for "patients with qualifying medical conditions . . . to discuss freely with their physicians the possible benefits of medical marijuana use" and a new right for physicians "to provide professional advice concerning the same." Finally, patients have a new right "to use medical marijuana for treatment under the supervision of a physician."

Since the patient has the constitutional right to use medical marijuana, can the patient make a physician authorize medical marijuana use?

No. The patient right does not carry with it any ability of the patient to compel physician conduct.

Can a physician sell marijuana from his/her office?

Only a licensed dispensary can sell marijuana or marijuana products.



Lowell Pearson, JD, is a partner in the Jefferson City office of Husch Blackwell. He heads the Firm's Missouri cannabis practice group. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are encouraged to consult their own attorney concerning their specific situation and specific legal questions.
Contact: Lowell.Pearson@huschblackwell.com

Does Amendment 2 include a waiver of physician liability?

Yes, article XIV, Section 1 says that the intent is to protect physicians from civil and criminal penalties. Having said that, caution is warranted because it is unclear how courts will interpret that language in the context of professional licensing, malpractice, and other cases. It is no secret that Missouri courts have been creative in permitting lawsuits where there is any ambiguity in an applicable statute or constitutional provision.

What is the primary role of the physician under Amendment 2?

Physicians can issue a "physician certificate" stating that, in the physician's professional opinion, the patient suffers from a qualifying medical condition.

What is a qualifying medical condition?

Cancer; epilepsy; glaucoma, migraines unresponsive to other treatment; a chronic medical condition that causes severe, persistent pain or spasms; debilitating psychiatric disorders, if diagnosed by a state-licensed physician; human immunodeficiency or acquired immune deficiency syndrome; terminal illness; "a chronic medical condition that is normally treated with a prescription medication that could lead to physical or psychological dependence, when a physician determines that medical marijuana could be effective in treating that condition and would serve as a safer alternative to the prescription medication;" "any other chronic, debilitating or other medical condition."

If a patient informs the physician that he/she is going to use medical marijuana instead of a prescribed medication, can the physician discharge the patient without liability?

The physician can explain his/her concerns to the patient and, if the patient refuses to accept the physician's advice, the physician should document that and then explain to the patient that because of the physician's concerns, he/she can no longer provide care to them and arrange to transition them to another appropriate caregiver.

If a patient has a qualifying medical condition, can a physician be forced to issue a certification?

No. This remains within the professional judgment of the physician.

Does a physician who issued a certification have a risk of liability for adverse effects from marijuana use by the certified patient?

Maybe. Amendment 2 purports to limit liability, but it remains to be seen how courts will interpret it.

Are there special concerns about certifying patients who work in industries that prohibit use?

The physician's certification is limited to the existence of a qualifying condition, and not the suitability of use. Having said that, the physician is never required to certify, so he/she can refuse to certify for whatever reason he/she takes into account.

Can minors obtain a physician certification?

Only a parent or guardian who holds a primary caregiver card issued by the Department of Health and Senior Services can obtain medical marijuana for a minor, unless the minor is legally emancipated. **MM**

Medical Marijuana, Opioids & Prescribing Controlled Substances



MSMA's website (www.msma.org) has dozens of resources on medical marijuana law, answers to frequently asked questions, medical treatment, public health and education, reducing opioid abuse and misuse, opioid education resources, and guides to prescribing controlled substances.

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Pot Legalization Makes Vaping Deadly

by Scott Gottlieb, MD

Recent injuries and deaths demonstrate the need for Washington to take control over cannabis policy.



Doctors have linked a tragic wave of lung injuries and deaths to the vaping of tainted marijuana concentrates. The episode reveals the dangers created by the federal government's decadelong refusal to challenge state laws legalizing pot and promoting risky uses of its derivatives.

The Obama administration announced in 2013 that it wouldn't enforce federal drug laws in states that had legalized pot use. The following year, Congress started attaching legislative riders to budget bills to prevent the Justice Department and other agencies from enforcing federal laws banning marijuana use in the 33 states that have made weed legal. The Trump administration has tried to reverse some of these policies. In 2018, then-Attorney General Jeff Sessions rescinded Obama administration guidance giving U.S. attorneys discretion not to enforce federal drug law in states that have legalized marijuana. But the White House has been reluctant to challenge popular state policies directly. As a result a large pot industry has bloomed in recent years, and a dangerous market in cannabis concentrates, such as the ones responsible for the vaping deaths, has proliferated.

According to an analysis by health officials in Wisconsin and Illinois, about 87% of those recently injured said they had vaped tetrahydrocannabinol, or THC, the main psychoactive ingredient in marijuana, from prefilled cartridges purchased from "informal sources" during the three months before they developed symptoms. A majority of the victims said they used THC every day.

Data from state marijuana dispensaries show that inhalation of these liquid concentrates from a vaping device is now the second most common way to consume THC, exceeded only by the old-fashioned way. Because the vape cartridges are prefilled, users don't know what they're getting. To prepare the concentrates, dodgy suppliers are known to add ingredients to thicken the liquids, since viscosity is seen as a measure of the concentrate's potency. But these emulsifiers, including vitamin E acetate, can be deadly if inhaled into the lungs. The liquids can also contain pesticides and other contaminants that, when heated, produce gases that can directly injure the lungs.

Yet the Justice Department remains unwilling or unable to enforce existing federal laws, even on matters not specifically mentioned by the congressional budget riders. The feds are also reluctant to regulate this market. Exerting partial oversight over the riskiest products would effectively signal the end of federal marijuana prohibition. Justice officials see such a step as politically controversial, even as it becomes clear that a blanket ban is no longer politically practicable.

The result is an impasse. Federal agencies exert little oversight, and regulation is left to a patchwork



Scott Gottlieb, MD, a resident fellow at the American Enterprise Institute, served as Commissioner of the Food and Drug Administration, 2017-19. He consults with and invests in drug makers.
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of inadequate state agencies. The weak state bodies sanction the adoption of unsafe practices such as vaping concentrates, while allowing an illegal market in cannabis to flourish.

The Food and Drug Administration might be able to exert oversight on some vaping hardware. The FDA has jurisdiction over "components and parts" used to vape derivatives of tobacco. Manufacturers selling devices for cannabis often make vague claims that their products are intended for use with extracts and leaves, which could include nicotine and tobacco. This might give the FDA a hook over the THC vaping pens that are enabling most of the harm.

But such an assertion of authority might be hard for the FDA to sustain without clear laws and firm political support. So many state legislatures have legalized marijuana that the U.S. is well past the point of blanket prohibition. But mounting evidence of the public-health consequences from regular marijuana use, especially among children and expectant mothers, should give politicians pause. Studies show that regular use of THC affects memory, executive function and psychological well-being. The recent lung injuries and deaths confirm the market has become a Wild West of potent and shadowy products.

THC is currently illegal under federal law. Right now there's no middle ground allowing federal agencies to scrutinize these compounds for their manufacturing, marketing and safety.

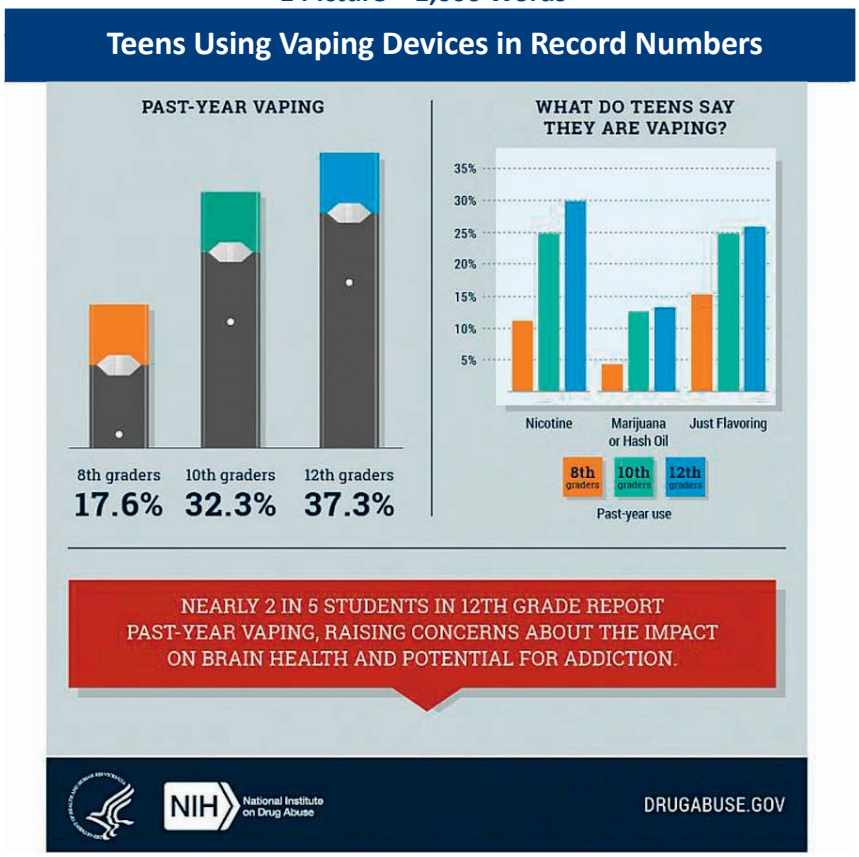
A feasible compromise would require Congress to take marijuana out of the existing paradigm for drug scheduling, especially if Congress wants to allow carefully regulated access for uses that fall outside FDA-approved drug indications. The ship has probably sailed on legalization for recreational use. But regulation of the potency of THC compounds, the forms they take, how they're manufactured, and who can make purchases ought to be possible.

Research challenging bogus medical claims or establishing legitimate clinical uses for THC is thin on the ground. Getting legal access to marijuana for federally sanctioned drug research requires cumbersome registration and record-keeping. The supply also has to come from a tightly regulated source controlled by the feds. Scientists say the product is substandard. It's also meaningfully different—in potency and other features—from what most people use in states where pot is legal.

Any federal regulation would need to be backed up with oversight and vigorous enforcement to keep a black market from continuing to flourish and causing these lung injuries. Expanding access to marijuana for legitimate medical research would allow more scientists either to validate or dispel the myriad claims about marijuana's therapeutic usefulness. Whatever medical claims are made should be subject to the same federal standards applied to other drugs.

The protracted hand-wringing over federal cannabis policy must stop. The tragic spate of fatalities related to vaping of pot concentrates means the time has come for Congress and the White House to stop blowing smoke and clear the air. **MM**

1 Picture = 1,000 Words





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Generic Drugs: A Treatment for High-Cost Health Care

by Steve Miller, MD



Generic medications, which have saved billions of dollars over the past 30 years, remain vitally important as patients and payers wrestle with access and affordability in health care.

The cost of medications continues to be one of the fastest-growing health care expenses, due to increases in both price and volume: Innovative new medicines bear higher prices, while at the same time our country's use of prescription drugs is growing in response to higher rates of chronic disease, such as diabetes and high cholesterol.

Benefit payers – the employers, labor unions, and government programs that share healthcare costs with insured individuals – can keep drug spending in check by ensuring their proper use, eliminating waste, and adopting formularies that prefer generics. Pharmacy Benefit Managers (PBMs), such as Express Scripts, a Cigna company, bring together the buying power of payers and negotiate with pharma manufacturers to include the most clinically effective and cost-effective medicines. To create the financial headroom for innovative new products, leveraging the use of generics – comprising about 90% of all prescriptions – is critical.

Beyond generic utilization, formulary management can drive dramatic savings. Express Scripts' National Preferred Formulary, which covers more than 25 million people, has saved clients $14.5 billion in annual, incremental savings since 2014. Overall, the company's clients spent just 0.4% more on drugs in 2018 than the prior year – and half of them spent less.

That's despite steady increases in the cost of brand-name drugs. The average price for the most commonly used brand drugs experienced list price inflation of 62.1% between 2014-2015, more than eight times higher than the rate of inflation on a market basket of commonly used household goods. During the same period, prices for the most commonly used generic medications declined by 36.9%.

The benefits also accrue to patients. In 2018, people with Express Scripts drug coverage paid an average of $11.55 for a 30-day prescription, just 6 cents more than in 2017. And the savings realized by payers help them avoid dramatic increases in the cost to members of health care benefits.

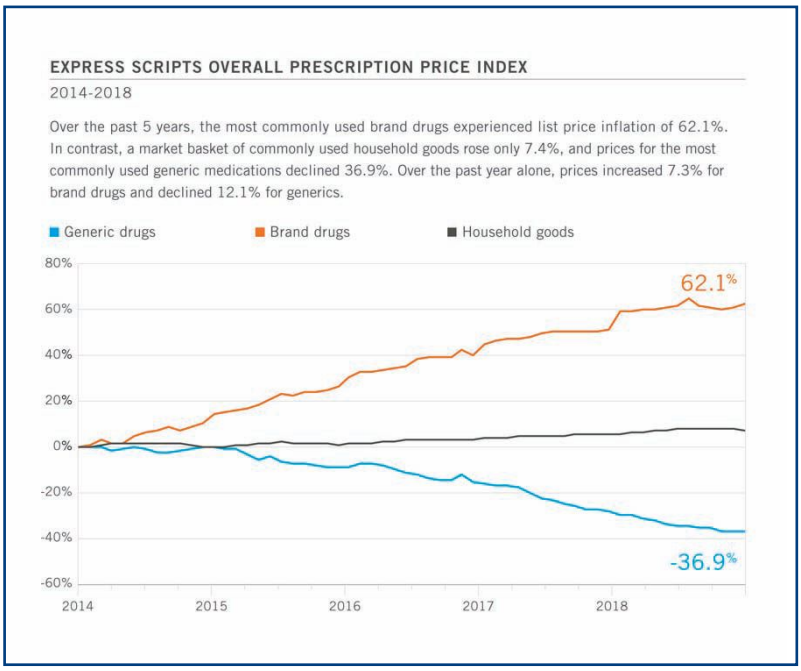
Hurdles to Overcome

Yet the generic medication landscape does have challenges. As prices fall, so do profits for manufacturers. Generic drugs that aren't sold in high volume are a particular challenge to the supply chain – especially when manufacturing facilities require new investments to keep up with safety standards or maintenance. Manufacturers may drop out of the market, rather than invest, leaving production of a particular drug in the hands of a single company.

In some cases, profiteers have purchased the manufacturers of single-source drugs and dramatically hiked prices.



Steve Miller, MD, serves as Cigna's Chief Clinical Officer, and leads the company's clinical policy, quality, and performance efforts. He formerly served as Senior Vice President and Chief Medical Officer for Express Scripts and received his medical degree from the University of Missouri-Kansas City, Kansas City, Missouri.



The most notorious of these is Martin Shkreli, whose now-defunct Turing Pharmaceuticals in 2015 raised by more than 5,000% the price of a medication, Daraprim, which is used to treat a parasitic infection found in pregnant women, babies, and HIV patients. Express Scripts worked with compounding pharmacies to make an alternative generic medication for just $1 per dose, compared with $750 charged by Turing; and later implemented a program to protect payers and patients from market price shocks. Shkreli was convicted in 2017 of criminal fraud for other business practices.

Another consequence of declining generic drug manufacturing capacity is drug shortages.

In an October 2019 report, the U.S. Food and Drug Administration found that the number of ongoing drug shortages has recently been increasing, after declining from a peak in 2011, and that they are lasting longer. It analyzed 163 drugs that went into shortage between 2013 and 2017, and found that drugs most likely to run low are both older and sold at relatively low prices.

These included vital medications, such as treatments for a childhood cancer, septic shock, and palliative care in a number of forms of cancer.

Recognizing the fragility of the supply chain, Express Scripts uses proprietary algorithms to predict drug shortages, allowing the company to strategically purchase and contract for drugs from manufacturers and avoid impacts to its patients.

As overall market dynamics come into play, prices should increase to levels of sustainability for manufacturers. Global drug production also can mitigate shortages. And the FDA is recommending steps to reward manufacturers which have mature quality management systems.

The Next Generic Wave

It is important to not only protect the supply of existing generic drugs, but to encourage and support development of even more lower-cost alternatives to brand medications. A host of high-cost specialty drugs is losing patent protection, creating new opportunities to drive value and savings.

A wave of specialty oral solid generics is emerging, with FDA generic approvals representing about $14 billion in U.S. drug spending already approved and another $24 billion in opportunity expected through 2023. Prices will fall as competition is introduced into therapeutic categories long dominated by high-cost brand drugs.

Likewise, advocates including Express Scripts support the approval of biosimilars, which are clinically equivalent alternatives to injectable biologic drugs. These medications are used to treat some of the most complex and chronic disease, including rare and orphan conditions, and are among the most expensive. While the U.S. has not yet gained a significant benefit from biosimilars, it is important to note that in Europe, the biosimilar market is robust and safe, cost-effective alternatives are more broadly used. The opportunity in the U.S. is important in the overall drug pricing picture.

Biosimilars could reduce direct spending on biologic drugs by $54 billion in the next decade, according to estimates by the Rand Corporation. However, realizing that value will require regulatory changes to recognize biosimilars as interchangeable with brand originator drugs and able to compete as generics do with branded oral solid medications.

As more generics come to market, and when the potential of biosimilars is realized, payers will realize savings in drug spending that can create headroom for them to afford more new, innovative and life-saving treatments, such as gene therapy.

The U.S. spends $3.7 trillion on health care. Our challenge isn't in finding more dollars to spend, but in using our money more wisely to afford the treatments that people need to get and stay healthy. Generic drugs are an important tool for doing so. **MM**



How to Reduce Prescription Drug Prices: First, Do No Harm

by Scott Atlas, MD

Top-down controls restrict access. Instead, encourage patients to shop around among pharmacies.

Everyone wants to reduce prescription drug prices, but how? First, do no harm. It's true that Americans pay more for medication than just about anyone else: A 2018 report from the White House's Council of Economic Advisers found that, as of 2009, the price per dose of patented drugs was five times as high in the U.S. as in foreign markets.

Yet Americans get something in return—early access to lifesaving medications. Between 1995 and 2005, 12 new cancer drugs were first introduced in the U.S., versus 13 in Canada, France, Germany, Japan, Switzerland, and the U.K. combined. Of the 45 novel drugs the Food and Drug Administration approved in 2015, 29 were available in the U.S. first. And a 2017 study found that all 45 approved new cancer drugs were covered by Medicare in the U.S., compared with public insurance coverage of only 26 in the U.K., 19 in France, 13 in Canada, and 11 in Australia. America has superior treatment results for virtually all serious diseases reliant on drug treatment, including cancer, heart disease, stroke, high blood pressure and diabetes.

Price controls would jeopardize that advantage. A 2014 study of 642 drug launches in 76 countries found that price regulation "strongly delays" them. A 2005 study estimated that drug price controls would have led to 198 fewer new drugs in the U.S. market from 1981 to 2000, at a societal cost of about $20 trillion, or more than 28 times the estimated savings from those price controls.

Pegging drug prices to those of foreign countries, as both Bernie Sanders and Donald Trump have proposed, would ultimately lead to the same consequences Europeans endure—reduced access to critical drugs and worse outcomes, including more deaths from disease.

Price negotiation by Medicare sounds logical. Economists have noted, however, that a single dominant buyer would lead to supply shortages and fewer new products. But there's a more serious problem. Only the patient, not the negotiator, will suffer the severe penalties of sickness and death when drug availability and pharmaceutical innovation dry up.

"Government negotiation" would generate restrictions based on political budgets rather than clinical benefit. The U.K.'s National Health Service launched its 2017 Budget Impact Test to delay introducing any new drug up to three years, if projected spending exceeded £20 million during any of the first three years, regardless of cost-effectiveness. NHS patients would be forced to wait years for the "acceptable price" to kick in. By this formula, the more widely a drug is needed, the more likely it is to be delayed. The Alzheimer's Society calculated that a drug costing as little as £23.50 a year per patient (less than 9 U.S. cents a day) would be subject to the new restriction.

So how can policy makers bring drug prices down? By empowering consumers, not insurers or other intermediaries.

The Trump administration has announced a proposal to do away with rebates paid by drug manufacturers to pharmacy-benefit managers, replacing them with discounts to beneficiaries at the point of sale. PBMs are middlemen that control "formularies," the lists of drugs covered by a plan. Rebates from drug companies to PBMs are payments for influence—either



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to position a drug on the formulary as "exclusive" or to give it preferred status over competitors.

PBMs act counter to patient interests while aggravating the lack of price transparency. These complex behind-the-scenes payments—$179 billion in 2016—reward inflated list prices, on which patient premiums are often based. This prevents patients from taking account of price. Some PBMs even use contractual gag clauses to prohibit pharmacists from volunteering that a medication may be less expensive if purchased for cash—as it was in more than 20% of cases, according to a 2018 study.

The Trump measure is necessary but not sufficient. Patients have neither the power nor incentive to shop around and put downward pressure on drug prices, even though prices vary greatly for the same drug. In a Consumer Reports study, the national average price ranged by a factor of 20 for a one-month supply of a given generic. In a single city, the cost of a 30-day supply varied by a factor of 10 to 17, depending on the drug. For the 15 million seniors taking five or more medications daily, the monthly savings from comparison shopping could amount to many hundreds of dollars. Yet insurance tends to minimize the patient payment. I use two prescription drugs, for which my pharmacy charges $12.49 and $31.49 for a month's supply. My copayments are 95 cents and zero, respectively. Why would I care if the "retail prices" are lower elsewhere?

Go-betweens like PBMs should be eliminated. And rather than broaden coverage, it would be better to require patients to pay directly for more of their drugs and reward them for saving money. Cheaper, higher-deductible drug insurance, coupled with larger, liberalized-use health savings accounts, would accomplish both goals—especially for seniors, who make up about 12% of the population but account for over 34% of prescription-drug use. HSAs are currently prohibited for seniors.

Government also should tear down barriers to the supply of new and competing drugs. Bureaucratic excesses must be streamlined, including overlong clinical trials that require more than 14 years and $2.5 billion on average, a cost that has multiplied 10-fold in the past decade. The FDA has already made progress: 2017 saw 68 new drugs and biologics approved and a 60% increase in generic approvals over the previous year.

Drugs are the most significant reason for the past half-century's unprecedented gains against deadly and debilitating disease. But policies that aim to reduce drug prices—price regulation and weaker patent protection—are also associated with delayed availability, less innovation, and limited access. Legislators must avoid replicating misguided policies that have harmed patients elsewhere, and instead rely on competition for empowered patients, the ones with the most to lose.

MM



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TOP WORK PLACES 2019

Medicine's Challenges: Vaping and Coronavirus

by James DiRenna, DO

What does 2020 mean to me? This new year has arrived with a positive attitude, a great reflection of the travels and meeting physicians in numerous states, as well as renewing collegial friendships. But most importantly FOOTBALL FEVER! At the time of this printing, the Chiefs are the Super Bowl LIV Champions, breaking a 50-year drought. YAY CHIEFS! I also have been blessed with invitations to attend annual membership, business, and educational meetings. I find a sincere feeling of dedicated physicians continuing to meet their organizations' and associations' missions and successes.



The last several weeks have included annual meetings, inductions of new officers and boards of governors for the Missouri Society of the American College of Osteopathic Family Physicians, the Regional Osteopathic Medical Society (which is the reformed Jackson County Osteopathic Medical Society), the St. Louis Metropolitan Medical Society, and the Boone County Medical Society. My presence and role as an induction officer has been both inspiring and educational. I recognize how valuable it is for physicians to unite through these associations. Regardless of our specialty or geographic location many of us are facing the same problems, including burdensome EHRs, opiate use in our communities, caring for an uninsured population, and the constant monitoring of physician health programs.

We face an increasing number of individuals and groups who oppose vaccinations —to the detriment of public health, a spike in illnesses related to vaping, as well as physician burnout, which I believe has deeper roots in the growth and development of morale injury for the individual physician.

This year your MSMA advocacy team dedicated many resources to address the legislative aspects of these and other issues. Our team met throughout the state with groups of physicians, which proved that the face-to-face dialogue and quality of conversation is imperative for our legislative agenda.

I want to update you on our continual efforts to combat the vaping epidemic. As I reported in my last article in the November/December issue of *Missouri Medicine* (Combatting the Vaping Epidemic), MSMA sent a letter to Governor Mike Parson asking to consider actions designed to reduce youth access to vaping products and to change how vaping products are marketed, especially toward younger populations. Within two weeks, Governor Parson announced an Executive Order directing several state agencies to use existing resources to develop a statewide campaign to educate, warn, and deter the use of vaping devices among Missouri's youth. The "Clear The Air" campaign launched shortly after, and the state is working to ensure teens and others get the message that vaping is not a safe alternative to smoking nor is it safe. Vaping is "the new addiction," and should be regulated and marketed appropriately by our country's standards.

More recently, I have been advised about the statistics concerning the Novel Coronavirus from China. I implore all physicians to keep a vigilant lookout for the new virulent infection that is now hitting the U.S. It's very likely that we haven't fully clarified the true identity of the strain of this coronavirus according to the CDC.

Through its Foundation MSMA awards $240,000 in MSMA scholarships during the academic year. The $4,000 scholarships are presented to students at each of the state's six medical schools. That is sixty MSMA scholarships in all. This is a true example of MSMA's commitment to medicine.

My next priority this year is to invite you (and I appreciate your involvement) to Jefferson City on Tuesday, March 3, for MSMA's White Coat Day. Hundreds of physicians, residents, and medical students plan to flood the Capitol to support our patients and profession. More information about the White Coat Day can be found at msma.org/white-coat-day.

As always, help us help you!

MM



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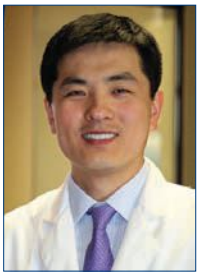
Things To Do to Get Involved in Advocacy That Don't Require Money

by Jonathan Patterson, MD

As a second-year legislator I've learned quickly about how things get done in Jefferson City. It's not complicated. It is 197 elected members who are trying to learn about all the issues that are put before them and then vote in a way that would best serve their constituents. There's no way to know everything about every one of the thousand bills that are filed every year. That is why advocacy matters. Ten people emailing their representative about a specific issue might be the only thing she hears about on that particular subject. Physicians need to advocate for medicine in Missouri. Here are ten easy ways to get politically involved:

1. Look up your legislators at www.house.mo.gov and www.senate.mo.gov. Know their names. Write down their email addresses. Write down their phone numbers.
2. Email your representative about an issue that you care about. Write your phone number and address on the email so that they know you are a constituent. They should at least read and respond to your email.
3. Meet your representative back in your district. Go to one of their town halls. Call them and ask them to come speak to a group of doctors at your office or hospital. Build a relationship with your state legislators. Politicians are human. This doesn't mean you have to become hunting buddies. Just don't have the first time you meet your legislator be the time you call her to encourage her to vote one way on a certain bill.
4. Go to your legislator's official website and sign up for their Capitol reports. They'll email you every week about the issues that they are working on.
5. Sign up to be MSMA Physician of the Day at the Capitol. Both your representative and senator will go out of their way to meet with you. You'll be introduced and thanked on both the House and Senate floor. You'll be providing a public service. There will be little to no actual doctoring required.
6. Take time to learn about issues that affect physicians in Missouri. Read the weekly update emails from MSMA. Read the brief bill summaries online. All the bills have one page summaries that are written in non-legalese and posted on the House and Senate websites.
7. Get upset sometimes. It's okay to disagree. If you strongly disagree with your representative about an important issue, let them know. Respectfully tell them you're a constituent and you disagree with them, and tell them why. They are paid to represent you. It's part of the job to hear from their voters.
8. Take time to write your legislator thanking them for a vote you agree with. Legislators receive dozens of emails and letters a week, mostly from constituents that are unhappy with their vote. Be the bright spot in their day.
9. Get your colleagues involved. Talk with people in your specialty about issues that affect you directly. If it's a really important issue get a group of you together for coffee and invite your representative.
10. Join your local medical society. They have people who are tied in politically and will get you more involved if you want.

This past year the House once again passed a prescription drug monitoring (PDMP) bill. We voted on it once and then left for the weekend. By the next week when it was time to finally vote on the bill and send it over to the senate, eight members had changed their "yes" vote to a "no." Why? Because over the weekend they received emails from some constituents telling them they disagreed with their vote. Political advocacy matters. It's not hard. Get involved. **MM**



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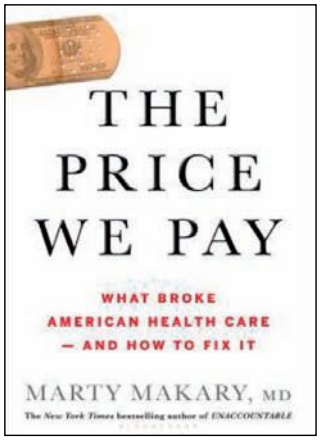
The Price We Pay - What Broke American Health Care and How To Fix It

by Marty Makary, MD

Reviewed by Arthur Gale, MD

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A recent book titled "The Price We Pay- What Broke American Health Care and How To Fix It" by Marty Makary, MD, MPH, is a highly critical analysis of the U.S. health care system. Several features of this book make it unique.



First it is written by a practicing gastrointestinal surgeon who performs long tedious operations such as pancreatic cancer surgery and islet cell transplantation. The author is the youngest person ever to hold an endowed professorship at Johns Hopkins Medical Center. He also holds a Masters Degree in Public Health (MPH) and has a team of doctors and other professionals help him conduct his research on health care.

Secondly, the author focuses on the exorbitant charges of hospitals and the financial toll they take on patients. He and his team are not just armchair analysts poring over statistics. They go out into the field interviewing administrators, physicians, and patients, and just about anyone associated with health care including business owners who are forced to pay high insurance premiums for their employees.

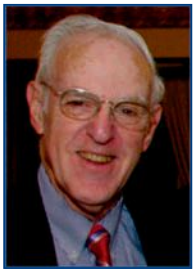
Thirdly, Makary does not think "Medicare For All" is the solution to the problem. He believes transparency will solve the health care cost problem by allowing the free market to work. Despite what hospital and insurance company executives say he does not believe we have a competitive free market in health care today.

Welcome to the Game

"Welcome to the Game" is the title of one of the book's chapters and aptly describes what is transpiring between hospitals and insurance companies in America today. Makary writes hospital prices are notoriously inflated. Different hospitals charge different prices for the same operation which do not relate to quality. Makary notes that researchers from the University of Iowa called 101 U.S. hospitals on prices for the same type of heart bypass operation. Only 53 provided the price which varied from $44,000 to $448,000. Makary asks whether the hospital that charged ten times more was the hospital with the best outcomes. The answer is no. Makary states "heart outcomes are publicly available. Research shows no correlation between surgery prices and outcome." He states the same is true of joint replacement surgery and other major operative procedures.

At a meeting attended by Makary and the major stakeholders in health care which included representatives of hospitals, insurance companies and payers all acknowledged that they know how the game is played. "Hospital officials confessed they inflate bills each year in order to generate more revenue since the insurance companies pay only part of the sticker prices. Insurers confessed they demand bigger and bigger discounts in their contracts with hospitals in order to keep up. Both admitted that they pass on higher bills to the public in the form of higher insurance premiums."

So a reasonable question is why are hospitals and insurance companies able to continue these games which are essentially scams that extort health care



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consumers. A hospital employee whom Makary confronted on behalf of a patient who received an exorbitant hospital bill provides the answer:

"The law allows us to charge whatever we want. If we want to charge a million dollars she has to pay it."

This is not free market competition. It is monopoly pure and simple. How did this state of affairs come about? The answer is revealed in Elisabeth Rosenthal's book "An American Sickness: How Health Care Became Big Business and How You Can Take It Back." I reviewed this book in *Missouri Medicine*, March /April 2018. The business consulting firm Deloitte and Touche travelled around the country and told members of hospital boards to stop their tradition of billing based upon the cost of an item or service. Instead Deloitte told the hospitals "you can increase the amount you bring in just by manipulating how you bill." This is called strategic pricing.

Free market competition simply does not exist in health care. Imagine what would happen if a grocery charged four times what another grocery charged for a carton of milk or a loaf of bread. It would shortly be out of business.

Hospitals and insurance companies game the system by colluding. Insurance company administrative costs under Obama Care and other private insurance run close to 18%. It follows that the higher the hospital bill is the more the insurance company profits. There is no incentive to voluntarily lower overall costs to the health care consumer by either the insurance companies or the hospitals.

Throughout the book Makary describes the harmful effects that high prices charged by hospitals have on patients. He cites a study that shows "Half of patients with metastatic (Stage 4) breast cancer in the United States report being pursued by a collection agency for medical bills." Makary confesses that "as a cancer surgeon, hearing the details made me sick to my stomach. Is this what the noble profession of cancer care has become? Is this how our society now treats breast cancer patients at the end of their life?" Not only are these patients dying from breast cancer they are also facing financial ruin.

Many hospital leaders say that they do not sue patients and garnish their wages. Yet, when Makary checks out the facts he finds that many of these same hospitals do sue patients including his own hospital, Johns Hopkins.

Makary devotes an entire chapter to reporting on the billing practices of the only hospital in Carlsbad New Mexico a town with a population of about 25,000. He and his team found that about one fifth of the town's population has been sued by Carlsbad Medical Center. Many have had their wages garnished. Carlsbad Medical Center is part of a for profit hospital chain.

Makary then went to the courthouse in Carlsbad where he discovered that about 95% of all civil cases have been filed by Carlsbad Medical Center going after patients. He is "shocked" when the judge handling these cases told him that "My husband and I have both been sued by the hospital…"on separate occasions for different bills." Makary then spoke with the head surgeon at the hospital who is well regarded and serves on the hospital's board. Like most doctors he had no knowledge of the hospital's billing practices.

In addition to reading his book I heard Dr. Makary give two lectures. He opposes "Medicare For All" as the solution to the cost crisis in health care. He strongly believes that transparency and true free market competition not the game playing we have today can bring prices down. He is vague on how this goal can be achieved. As noted he has met with various stakeholders in the business communities as well as the hospital and insurance industries. They are all well aware of the games being played by hospitals and insurance companies. The big question is can they do anything about it.

Makary spends several pages in his book making the plea that medical authors avoid writing in medical jargon and write in plain English, even in scientific journals. He certainly follows his own recommendations as his book is written in simple plain English for the average citizen as well as for the medical professional.

Regardless of what one feels about the solution to the high cost of America's health care system Makary's book presents a unique perspective on the games that hospitals and insurance companies play in increasing costs. "The Price We Pay" is one of the best books ever written on America's dysfunctional health care system. **MM**

Correspondence

Increased Traffic Fatalities Associated with Recreational Marijuana Legalization

In the September/October 2019 issue of *Missouri Medicine*, author Alex Berenson criticized a study for claiming that recreational marijuana legalization had no effect on traffic fatalities. He stated that a more accurate conclusion would have been that there was a trend towards increased fatalities, but more data was needed.[1] In a different study, Aydelotte et al. also found a statistically non-significant, though potentially meaningful, trend toward increased fatalities in the first two states to legalize (Colorado and Washington).[2]

Using data from two more years and two more states (Alaska and Oregon) from the National Highway Transportation Safety Administration Fatality Analysis Reporting System dataset,[3] I re-examined the question. The first four states to legalize recreational marijuana were compared with all 21 states that did not have medical or recreational marijuana (control states) as of 2017. For each state, the change in the traffic fatality rate (TFR) was calculated by subtracting the average TFR for a two-year baseline period (2010-2011) from the average TFR for most recent two years available (2016-2017). The baseline period consisted of the two years immediately preceding the vote to legalize recreational marijuana in the first state to legalize. The final period consisted of the most recent two-year period available and contained at least two years of commercial sales from four recreational marijuana states. Numbers were analyzed using the SigmaStat program.

The TFR in recreational marijuana states increased 19.8% (± 5.1), while control states saw an increase of only 1.3 % (± 2.2) (Figure 1). This 18.5 percentage point (95%CI, 7.2-29.7) difference between recreational marijuana and control states was statistically significant [$t(23) = 3.4$, $p = 0.002$], and adequately powered for the comparison (0.89).

Had the state of Missouri followed the path to recreational marijuana legalization set by the four states in question, the excess traffic deaths in Missouri would have ranged from 67 to as high as 277 deaths per year. National recreational marijuana legalization would have been associated with approximately 6,000 increased roadway deaths each year.

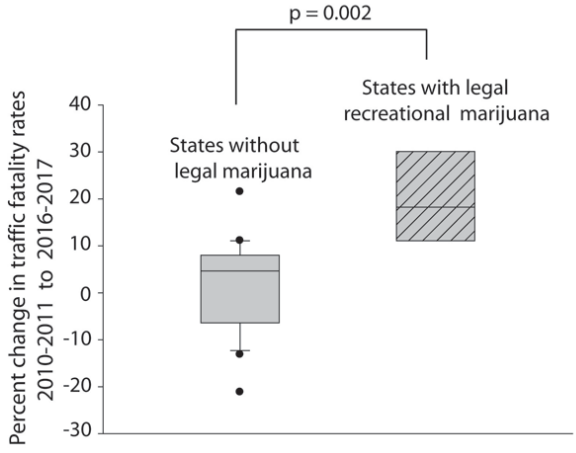


Figure 1. Percent Increase in Traffic Fatality Rate in States without Legal Marijuana vs. States with Legal Recreational Marijuana. The boxes contain the middle 50% of the data, except where there are five or fewer values as in the right plot. In that case, the box includes all data points. The 95% confidence intervals are represented by the short horizontal bars at the end of the vertical line. On the right plot, the confidence intervals fall within the box. The median values are marked by horizontal black lines within each box, and any outliers are denoted by small black circles.

This letter suggests that more data from longer observation periods are needed to adequately assess the effects of legalization. Consequences of legalizing marijuana may not be apparent immediately after enactment, but only become clear after the establishment of a commercial market.

States that have already established legal commercial marijuana sales should take heed of these findings and employ measures to mitigate the dangers of stoned driving. States that haven't legalized should consider the likelihood of increased traffic fatalities as they decide whether to embark on their own social experiments.

References

1. Berenson A. Weeding out dubious marijuana science. Missouri Medicine. 2019; 116(5):352.
2. Aydelotte JD, Mardock AL, Mancheski CA, et al. Crash Fatality Rates After Recreational Marijuana Legalization in Washington and Colorado. Am J Public Health. 2017; 107(8):1329-1331. doi:10.2105/AJPH.2017.303848
3. National Highway Traffic Safety Administration's Fatality Analysis Reporting System. https://www-fars.nhtsa.dot.gov/States/StatesFatalitiesFatalityRates.aspx Accessed November 22, 2019.

Russell Kamer, MD
Internal Medicine, White Plains, New York

Does Talc Used in the Genital Area Cause Ovarian Cancer?

On the heels of Johnson & Johnson's latest defense verdict in a talc ovarian cancer case in St. Louis City in December 2019[1] – the fourth consecutive verdict in its favor[2] – comes another study that supports Johnson & Johnson's long held position. Published in the *Journal of the American Medical Association*, the article entitled Association of Powder Use in the Genital Area With Risk of Ovarian Cancer found no statistically significant association between the use of powder in the genital area and incident ovarian cancer.

The study examined data pooled from four previous studies and included 252,745 women of whom 38% self-reported using powder in the genital area. Of the pooled women, 2,168 developed ovarian cancer during a median of 11.2 years of follow-up, which amounted to 58 cases/100,000 person-years. Among women who had ever used powder in the genital area, the incidence of ovarian cancer was 61 cases/100,000 person-years while women that reported never using powder in the genital area had an incidence of 55 cases/100,000 person-years.

The analysis showed a 1.08 hazard ratio for the association between self-reported ever use of powder in the genital area vs. never use and incident ovarian cancer. Though the authors found no significant association between powder use and incident ovarian cancer, they included a caveat that the study could have been underpowered to identify a small increase in risk.

Assuredly, expert witnesses in talc/ovarian cancer litigation will continue to disagree on whether talc causes ovarian cancer, the extent asbestos or other contaminants are present in talc-containing products, and whether those contaminants cause ovarian cancer. This latest study, though, again calls into question the claim that powder use in the genital area causes ovarian cancer.

References

1. *Forrest v. Johnson & Johnson*, No. 1522-CC00419 (Mo. Cir. Ct. Dec. 20, 2019).
2. Robson, N. Johnson & Johnson Gets Second Talc Defense Win in a Week, Law.com. https://www.law.com/2019/12/21/johnson-johnson-gets-second-talc-defense-win-in-a-week/. Accessed Jan. 19, 2020.

Tim Larkin, JD and Grant Ford, JD
Associate Attorneys, Husch Blackwell
St. Louis, Missouri

MM



Letters to the Editor
Submissions reflect readers' opinions and may be edited for length.

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- As I See It - A forum of general interest.
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www.msma.org/missouri-medicine

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Missouri Medicine in the News

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

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

Patricia I. Dickson, MD, MSMA member since 2019, is the new Editorial Board member for Medical Genetics.



She replaces Gary S. Gottesman, MD, who we thank for his service on the Board for nearly two decades. Dr. Dickson is Division Chief, Genetics and Genomic Medicine, and Professor of Genetics, Department of Pediatrics, at the Washington University School of Medicine in St. Louis, Missouri. She has edited, lectured, testified, and published widely on pediatrics, genetics, and genomic medicine.



Jacqueline L. Reiss, MD, MSMA member since 1998, is the new Editorial Board member for Allergy and Immunology. She replaces Susan Berdy, MD, who we thank for her service. Dr. Reiss is an Allergist and Immunologist with Allery Associates, Inc., in Chesterfield, Missouri. She is board certified in both Internal Medicine and Allergy/Immunology. She is also an Instructor of Clincal Medicine at Washington University in St. Louis, Missouri.



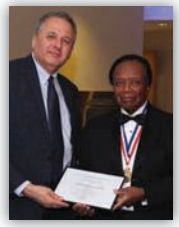
Congratulations to MSMA members, from left, above, Drs. Patrick Dawson, Michael Wurm, Lisa Gorry-DiStefano, and Shirley Harris on being recognized for their many years of service by Mosaic Life Care - Maryville. Combined, these physicians also represent more than 50 years of MSMA membership.



Scott H. Hardeman, MD, left, received the Arthur Gale Writer's award from Dr. Gale at the Saint Louis Metropolitan Medical Society Gala. Dr. Hardeman has been an MSMA member since 2003.



William H.Huffaker, MD, left, received the President's Award for service to SLMMS and organized medicine. Dr. Huffaker has supported MSMA since 1978. SLMMS 2019 President Ramona Behshad, MD, is at right.



Nathaniel H. Murdock, MD, right, was among eight physicians honored for 50 years of membership in SLMMS. Dr. Murdock has been an MSMA member since 1977. At left is Dave Nowak, SLMMS Executive Vice President.



St. Louis County Executive Sam Page, MD, received the Robert A. Schlueter Award from SLMMS for his achievements in elected office, including the creation of the St. Louis County Prescription Drug Monitoring Program. Dr. Page has been an MSMA member since 1989.

Congratulations to longtime MSMA member Stephen



L. Reintjes, Sr., MD, who will begin serving as President and Chief Executive Officer of North Kansas City Hospital and its physician network subsidiary, Meritas Health, in April. Dr. Reintjes, a neurosurgeon, joined MSMA in 1990.



Congratulations to MSMA member Michael J. Richardson, MD, on his appointment as the City Physician for the City of Washington. In this role, Dr. Richardson, an MSMA member since 2016 and graduate of UMKC School of Medicine, will monitor issues impacting public health.

Missouri Medicine would like to acknowledge and thank Fran Draper, MSMA Office Receptionist, for her dedicated work and administrative support with the Journal. Fran retired from MSMA on December 29, 2019. **MM**



New MSMA Members!

(Joined between October 10, 2019-January 15, 2020)

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fMatthew C. Aboudara, MD - Kansas City
Samir Abu-Amer, MD - Kansas City
Patrick Akin, DO - Kansas City
Ashley Ali, MD - St. Louis
Mohannad M. Al-Samarraie, MD - Columbia
Jason B. Amato, MD - St. Louis
Michael B. Anreder, MD - Lenexa
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Samuel H. Barry, MD - Columbia
Daphne Bascom, MD - Overland Park
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PRELIMINARY PROGRAM

Pre-Convention Meetings

Thursday, April 2

2:30 pm	MSMA Insurance Agency Board Meeting
3:30 pm	MSMA Executive Committee
3:30-6:00 pm	Convention Registration
3:30-6:00 pm	Exhibitor Setup & Registration
5:00 pm	**MSMA Council Meeting**
6:30 pm	**MSMA Council Reception & Dinner**
7:00 pm	Alliance Cabi Fashion Fundraiser

Convention Meetings

Friday, April 3

6:30 am-4:00 pm	Convention Registration
6:45 am	Moneta Group Investment Advisors Breakfast
7:00 am	**Exhibit Hall Opens/Breakfast for all Attendees**
8:00 am	**Opening Session**
	MSMA House of Delegates
9:00 am	Alliance Board Meeting
9:30 am	Alliance General Assembly - Session I
10:00 am	**Reference Committee A**
10:30 am	**Reference Committee B**
11:00 am	Missouri Physicians Health Luncheon & Meeting
Noon	"Spirit of the Alliance" Awards Luncheon
Noon	SLMMS Caucus & Luncheon
Noon	KCMS Caucus & Luncheon
1:30 pm	**MSMA General Session**
2:30 pm	Alliance Past President's Reception
3:30 pm	**MSMA General Session**
5:00 pm	Organized Medical Staff Section Business Meeting
5:00 pm	Medical Student Section Business Meeting
5:30 pm	Medical School Alumni Receptions
7:00 pm	Alliance Foundation Fundraiser/Dinner
7:00 pm	Resident and Medical Student Mixer

Saturday, April 4

6:30 am-4:00 pm	Convention Registration
7:00 am	**Breakfast for all Attendees**
7:00 am	International Medical Graduate Section Meeting
8:00 am	**MSMA General Session**
8:30 am	Alliance General Assembly - Session II
10:00 am	**MSMA General Session**
10:00 am	MMPAC Meeting
10:15 am	Resident and Fellow Section Business Meeting
Noon	Alliance Installation Luncheon
1:00 pm	AMA Issues
1:30 pm	**MSMA General Session**
2:00 pm	Alliance Board Meeting
2:30 pm	Missouri State Medical Foundation Meeting
3:00 pm	Component/Specialty Society Leaders Meeting
3:30 pm	**General Session**
5:15 pm	Reception: 50-Year Pin Recipients & MSMA Past Presidents
6:30 pm	**MSMA Presidential Inauguration**
7:30 pm	**MSMA Presidential Reception**
	Entertainment, Hors d'oeuvres & Cash Bar

Sunday, April 5

7:00 am	District Breakfasts & Caucuses
8:15 am	**Second MSMA House of Delegates**
Immediately Following Closure of the HOD	MSMA Council Meeting

REGISTER/RESERVATIONS

www.msma.org/annual-convention

Call the Renaissance St. Louis Airport Hotel at 1-800-468-3571 and mention "MSM." Group rates available until March 11, 2020. Rates start at $100 per night plus charges and taxes.

Program subject to Change. Refer to Convention Official Program for times and meeting locations. For more information, contact MSMA's Benita Stennis, at 800-869-6762 or bstennis@msma.org.

162nd Missouri State Medical Association Annual Convention

April 3-5, 2020 | Renaissance St. Louis Airport Hotel www.msma.org/annual-convention

GENERAL SESSIONS



Friday, April 3 | 1:30 pm

MO HealthNet Update

Todd Richardson, JD
Director, MO HealthNet
Jefferson City, Missouri



Saturday, April 4 | 10:00 am

Vaping: Public Health Scourge or Safer Way to Use Nicotine?

Donald Bohnenkamp, MD
Associate Professor, Psychiatry
Washington University School of Medicine
St. Louis, Missouri



Friday, April 3 | 3:30 pm

To CBD or Not to CBD? That is the Question for Medical Practitioners

Merrill Norton, PharmD., DPh, ICCDP-D
Clinical Associate Professor
University of Georgia
College of Pharmacy
Athens, Georgia



Saturday, April 4 | 1:30 pm

Stop the Bleed/ Trauma First Aid

Laurie J. Punch, MD
Associate Professor of Surgery
Washington University School of Medicine
Acute and Critical Care Surgery
Barnes-Jewish Hospital
Co-Director, Stop The Bleed STL
St. Louis, Missouri



Saturday, April 4 | 8:00 am

Artificial Intelligence and Machine Learning in Health Care

Kent Bottles, MD
Thomas Jefferson University
College of Population Health
Philadelphia, Pennsylvania



Saturday, April 4 | 3:30 pm

State Legislative Update

Jeff Howell, JD
Director of Governmental Relations
Heidi Geisbuhler
Director of Legislative Affairs
Missouri State Medical Association
Jefferson City, Missouri

FREE CME TO MEMBERS

CME procedures, sessions available for MOC points, how to obtain CME credit, disclosures, and evaluations will be described in the Official Program. For more information, contact Benita Stennis at 800-869-6762 or email bstennis@msma.org.

REGISTER/RESERVATIONS

www.msma.org/annual-convention

Call the Renaissance St. Louis Airport Hotel at 1-800-468-3571 and mention "MSM." Group rates available until March 11, 2020. Rates start at $100 per night plus charges and taxes.

Program subject to Change. Refer to Convention Official Program for times and meeting locations. For more information, contact MSMA's Benita Stennis, at 800-869-6762 or bstennis@msma.org.

2019 Contributors to Missouri Physicians Health Program

The Missouri Physicians Health Program is proud to recognize the following organizations and individuals who contributed to our annual fund drive. We are truly grateful for their generosity which helps provide crucial support as we strive to provide high quality physician health care services and meet the demand for our services statewide. Many of our participants are physicians-in-training who are unable to pay for services rendered. Your contribution helps us to defray those costs. We encourage you to generously contribute to our 2020 campaign. Thank you for your compassionate support.

Please note that the donors that are (*) are those who made donations to honor Robert Bondurant, RN, LCSW, who retired December 31, 2019, after 25 years of dedicated service to physicians.

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Mercy Hospital Joplin
Mercy Hospital St. Louis
Missouri Baptist Medical Center
Mosaic Life Care
NE Regional Medical Center
Nevada Regional Medical Center
No. Kansas City Hospital
Progress West Medical Center
Research Medical Center
Southeast Hospital
SSM Health Cardinal Glennon Children's Hospital
SSM Health DePaul Health Center
SSM Health St. Clare Hospital
SSM Health St. Joseph Hospital Lake St. Louis
SSM Health St. Louis University Hospital
SSM Health St. Mary's Hospital, St. Louis
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St. Luke's Hospital – Kansas City
St. Luke's North Hospital
St. Mary's Medical Center, Blue Springs
Truman Medical Center

2019 MPHP Contributors continued

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Foundations (matching grant)
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A Tribute to Bob Bondurant, Retiring Executive Director



Robert Bondurant, RN, LCSW, Executive Director of the Missouri Physicians Health Program (MPHP), resigned December 31, 2019, after 25 years of dedicated service. He decided to step down to focus on his health following a diagnosis of non-hodgkins lymphoma. We would like to pay tribute to Mr. Bondurant's passion to his life's work, and his commitment to physician health.

Mr. Bondurant was tireless in traveling the state to provide educational presentations to medical staffs. When he first began, the program was quite small, but with his efforts the program expanded over time. He often would leave on a Monday and return on Friday after his travels. He particularly enjoyed presenting programs to medical students and residents and teaching them about avoiding some of the pitfalls that could derail their careers. The relationships he established with medical staff leadership as well as administrators were vital in sustaining the program and providing necessary donations. (The MPHP is a 501(c)3 not for profit organization and is totally independent of the Board of Healing Arts.) He firmly believed in the organization maintaining its independence so the clinical staff could advocate for clients without concern for any repercussions.

Mr. Bondurant authored numerous articles on physician health, one of which is the following article which presents the history of the MPHP as well as the successful outcomes of the program: www.ncbi.nlm.nih.gov/pmc/articles/PMC6188337.

He also volunteered his time as a dedicated member of the Federation of State Physician Health Programs serving on committees spearheading efforts for national policy and support on behalf of the profession. His devotion and passion to this cause was obvious to anyone who attended his educational sessions or enjoyed his presence on committee calls.

Among his many laudable accomplishments, Mr. Bondurant recently presented at the American Medical Association Interim Meeting on the evolution of physician health and the role of physician health programs (PHPs) in creating awareness and access for physicians in need of confidential assistance for their substance use, mental health needs, and behavioral issues.

Please join us in recognizing Mr. Bondurant. If you would like to send a note of appreciation or wish to make a donation in his honor, please send it to: MPHP, 1023 Executive Parkway, Suite 16, St. Louis, MO 63141. **MM**

Alliance Channels 007 James Bond for Annual Convention Fundraiser

by Gill Waltman

Celebrities often grace us with their presence as an attraction at fundraising events, and although the Alliance was not able to invite in person the iconic figure who prefers his martinis shaken, not stirred, James...James Bond will feature strongly at the MSMA's Annual Convention Alliance Dinner/Fundraiser on Friday, April 3, 2020, at the Renaissance St. Louis Airport Hotel.

Alliance VP for Foundations Kathy Weigand has planned a follow-up event in keeping with her British theme from last year. Chosen in honor of the current Alliance president (yours truly), Kathy's theme for last year was *The British Invasion*. The evening was filled with English touches, such as an appearance by Her Majesty Queen Katherine, and an array of bid items and prizes of typically English fare. Fawlty Towers and English tea were well represented.

In keeping with last year's focus (as this president is completing a second term), Kathy and her committee will continue the British theme and present *Alliance Celebrates James Bond - 007.* It is hard to imagine that 007 has been around for over 50 years. (In good company with other famous fictional characters such as Mickey Mouse and Winnie-the-Pooh who have been around even longer!)



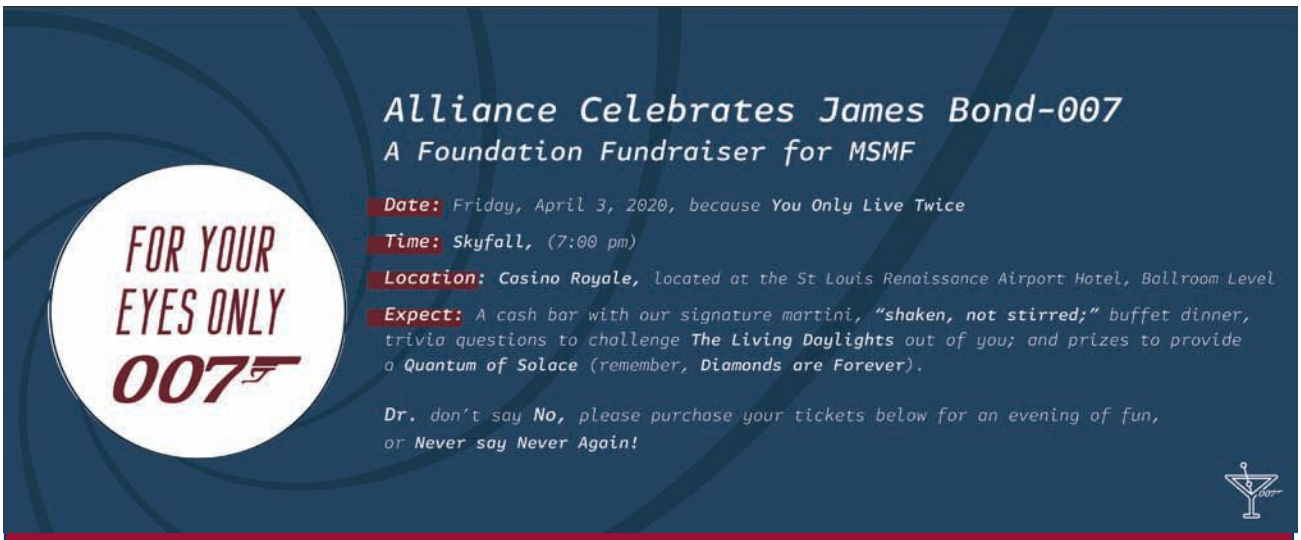
Gillian Waltman is the 2019-2020 MSMA Alliance President and Professor, Ophthalmology, Saint Louis University, St. Louis, Missouri.
Contact: gillian.waltman@gmail.com

Just in time for the twenty-fifth James Bond film, *No Time To Die*, release on April 10, 2020, the evening will be filled with James Bond trivia, music, drink specials, and perhaps even James Bond, himself. Please join us! You can register for the event online at msma.org/alliance.

There are many creative individuals in the MSMA Alliance who are never at a loss for clever ideas for these fundraising events. Some previous themes for the Friday night fundraiser at the state meeting have included casino nights, a mystery party with sleuths and suspects, *Running with the Roses* (a mock Derby), and various musical programs including *An Evening of Blues*, featuring Dr. Joe Corrado's band.

The Alliance has always had a strong tradition of fundraising for good causes. These events have evolved over the years into a variety of different formats at the local and state level. Funds are raised to donate to charities or community programs supported by the Alliance dealing with topics such as breast cancer awareness, illiteracy, autism, impaired physicians, and newborns in crisis. The Alliance offers school programs that address prevention of violence, *Smoking is Not for Me*, and the current *Drugs are Not for Me* program, which now includes opioid awareness and the new horrors of electronic cigarettes, or vaping. These anti-smoking and anti-drug programs used by the Alliance were developed in Greene County, spearheaded by Barbara Hover. The program has been presented in many other states and at the national level, even winning the prestigious HAP Award.

Women's shelters and food banks are routinely supported by Alliance counties across the state. A new initiative by the AMA Alliance this year invites participants to arrive at a local or state meeting armed with jars of peanut butter. These are donated to the local food banks by one of the hosting members. For many years, the Alliance in Cape Girardeau has funded a *Backpack for Fridays* program so children in the local elementary school have food and other items for the weekend.



Alliance Celebrates James Bond-007

Register NOW for the Annual Convention Fundraiser/Dinner Benefiting MSMF

Friday, April 3, 2020

Renaissance St. Louis Airport Hotel

msma.org/alliance

Alliance members in Buchanan County raise funds at their holiday event with the medical society and purchase anti-bullying books for the St. Joseph School District. Kansas City and St. Louis also combine their annual holiday parties with charitable fundraising and donations.

The Alliance contributes to medical student scholarships through donations to Missouri State Medical Foundation throughout the year, but the Holiday Sharing Card and the annual meeting fundraiser are the main sources of Alliance funding for MSMF. The Alliance provides additional gifts to graduating medical students at the Match Day events. St. Louis donates gift cards and luggage to students in a drawing at Match Day. An innovative idea, conceived by Angela Zylka, raised money for these gifts by renting out an independent movie theater and showing classic movies such as *Breakfast at Tiffany's*, *Casablanca*, *Gone with the Wind*, *Meet me in St. Louis*, *Singin' in the Rain,* and more. This took place annually for several years until the theater ownership changed hands.

Wine tastings, fashion shows over lunch (Neiman Marcus) or in the evening (The Vault) or a direct sales fashion event (Cabi) at someone's home, are always popular ways to raise funds.

If you are coming to the MSMA Annual Convention in St. Louis April 3-5, please mark your calendars for Friday, April 3 at the Renaissance. We will be celebrating James Bond's 50-plus years in many ways – there will be a signature drink (guess!), a DJ playing the familiar songs and soundtrack music and videos from the Bond movies during the evening, a drawing for Bond-worthy gifts, a trivia competition (hint - start re-watching all those movies!) and a couple of surprise guest appearances.

Funds raised will benefit MSMF. Please join us for a fun evening for a good cause.

For more information go to msma.org/alliance or contact Kathy Wiegand at daffodil4302@yahoo.com or call 816 387-7264. **MM**

KANSAS CITY
MEDICAL SOCIETY

Many Successes Result From Merged, Stronger Kansas City Medical Society

by Michael L. O'Dell, MD & Jim Braibish, APR

Medicaid expansion in Missouri and Kansas is top priority.

During 2019 and moving into 2020, the Kansas City Medical Society is reaping the benefits of the 2018 merger that created one medical society serving our entire Kansas City metropolitan region.

As this larger, unified, bi-state society, we are now laying the groundwork for organized efforts to support Medicaid expansion in both states. In Missouri, we are joining forces with Healthcare for Missouri, the lead statewide group promoting expansion, to gain signatures to place Medicaid expansion on the November 2020 ballot. In Kansas, we are working with Alliance for a Healthy Kansas, that state's lead group, to help advocate for expansion legislation. There is much momentum in Kansas for expansion in this 2020 session, with bipartisan support in the Legislature and a pro-expansion governor.

KCMS will be creating pro-expansion materials, including physician testimonial videos, for use on our website, social media and other communications, as well as by Healthcare for Missouri and Alliance for a Healthy Kansas. During 2019, our KCMS president sent letters endorsing expansion to the governors and state house and senate members in Missouri and Kansas.



Michael L. O'Dell, MD, MSHA, FAAFP, (left), is chair of the Department of Community and Family Medicine at the University of Missouri-Kansas City School of Medicine, and associate chief medical officer for the Truman Medical Centers Lakewood campus. He is editor of *Kansas City Medicine*. Jim Braibish, APR, is principal of Braibish Communications and managing editor of *Kansas City Medicine*.
Contact: Michael.O'Dell@tmcmed.org

Guiding Priorities

The endorsement of Medicaid expansion originated as a result of our new two-tier governance structure created through the merger. Expansion was among several priorities identified in January 2019 by the KCMS Leadership Council, our 42-member advisory group comprising broad representation of physicians across Kansas City-area hospitals and independent physicians. Our board of directors in May 2019 approved Medicaid expansion as a priority of the Society.

Other priority issues pinpointed by the Leadership Council—all of which will be acted upon in some way by the Society—include:

- Improving access to care for the uninsured and underserved.
- Advocating effectively in the legislative arena as well as with payers and insurance companies.
- Relieving administrative burdens such as prior authorization.
- Addressing mental health care, including a shortage of providers and the integration of behavioral health into primary care.
- Responding to the opioid crisis, including effective addiction treatment, achieving a Missouri PDMP, and a recognition of appropriate use of opioids in chronic pain management.
- Relieving physician burnout.
- Reducing vaping and e-cigarette use by young people.

Donated Care for the Uninsured

Also a result of the merger, the KCMS Foundation now operates a combined charitable care program serving both states. We are among a small number of medical societies across the United States that run charitable care programs. Our members have always believed in the need to preserve access to care for those without resources.

Through this program—known as Metro Care in Missouri and Wy Jo Care in Kansas—local physicians donate specialty care to patients who are uninsured and who could not otherwise afford needed treatment. Services range from cancer surgery and treatment, to orthopedic surgery and diabetes care, all provided at no charge by specialty physicians who desire to help those in need. Hospitals and other partners also donate facilities and services.

KCMS Foundation staff work with local safety net clinics to refer and screen patients, then we provide care coordination to help make sure that any barriers to care are overcome, and the patient's needs can be met.

During 2019, the KCMS Foundation served 613 patients who received 2,913 donated medical services valued at over $8 million. In addition, 27 specialty care practices joined our network of practices donating care.

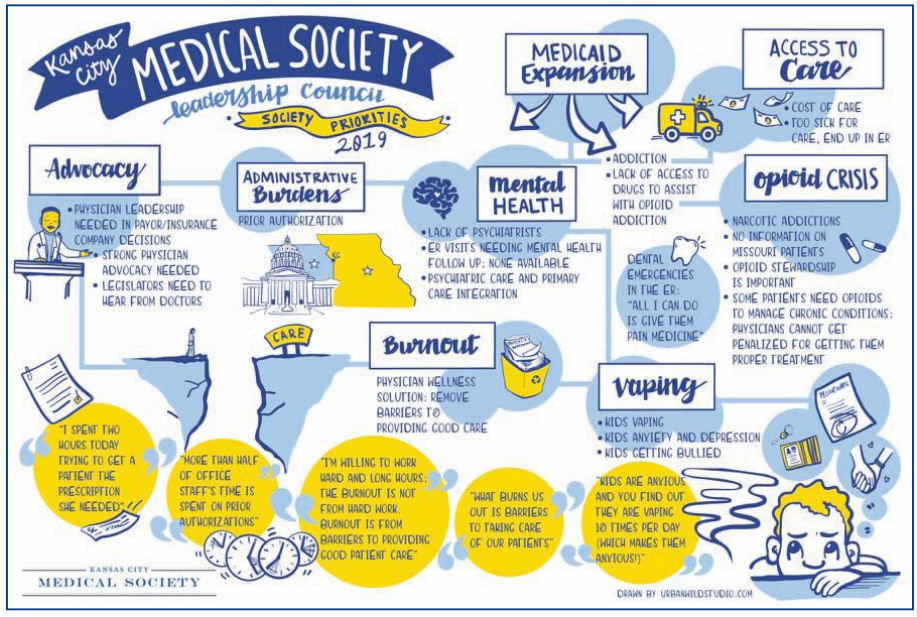
We also are very pleased that the Foundation in 2019 received the "Reviewed" designation from the Greater Kansas City Community Foundation. This designation provides an endorsement of the integrity and transparency of the Foundation's operations, and is highly regarded in the Kansas City philanthropic community.



Charles B. Wheeler, Jr., MD, JD, received the Lifetime Achievement Award for his years of service as a physician in elected office, including two terms as mayor of Kansas City, from KCMS President Mark Brady, MD.



Collecting signatures for the Missouri Medicaid expansion ballot measure are KCMS members Beth Andes, MD, and Michael O'Dell, MD, along with UMKC resident Crystal Brown-Vredenburg, MD. (photo courtesy Healthcare for Missouri)



KCMS priorities identified by the Leadership Council.

More Highlights

Here are some other highlights of 2019:

Our September 26 annual meeting drew more 250 physicians and partners. Our keynote speaker was Vanila M. Singh, MD, MACM, of Stanford University. She served as a chief medical officer in the U.S. Department of Health and Human Services from 2017 to 2019, and chaired a federal inter-agency task force that released a major report on opioids and pain management in May 2019.

We presented our Lifetime Achievement Award to Charles B. Wheeler, Jr., MD, JD, who served two terms as mayor of Kansas City during the 1970s and later as a Missouri state senator. He has been a role model for physicians in elected office.

Our August 21 Summer Social at the home of President Mark Brady, MD, was attended by 16 Kansas state legislators and over 20 KCMS physicians. This event was enjoyed by all as a time for informal networking and relationship-building between physicians and legislators.

Thanks to MSMA for the August 27 "Medicine's Muscle" presentation in Kansas City that attracted a large audience and helped prepare us as advocates. **MM**

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Therapeutic Role of Gamma Knife Stereotactic Radiosurgery in Neuro-Oncology

by Rupen Desai, MD & Keith M. Rich, MD

Washington University in St. Louis
School of Medicine

Stereotactic radiosurgery offers improved treatment options for patients with brain metastatic disease, introducing a major shift away from the use of whole brain radiation in many patients.



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Abstract

The Gamma Knife Center of St. Louis has established itself as a key facility offering stereotactic radiosurgery (SRS) for a variety of neuro-oncologic disorders. Since the Gamma Knife unit was first brought to Washington University in 1997, we have treated 5,696 patients. In this review, we discuss the effective role of Gamma Knife SRS in the treatment strategies for patients with neuro-oncologic disorders including brain metastases, meningiomas, pituitary adenomas, and acoustic neuromas. While there is active ongoing research evaluating the most effective treatment for patients with these disorders, it is clear that best management practices may be tailored for individual patients utilizing SRS either alone or in conjunction alternative treatment strategies including open neurosurgical procedures, laser thermos-ablative surgery, and even new medical oncological treatment strategies.

Introduction

The concept and development of stereotactic radiosurgery (SRS) was initially proposed by Dr. Lars Leksell incorporating his Leksell stereotactic frame to guide radiation to precisely irradiate selected targets within the brain.[1] Radiosurgery accomplishes this by delivering multiple convergent beams of gamma radiation emitted from cobalt-60 directed toward a central point to provide the conformal delivery of high dose radiation to a specific tumor volume within the brain and to avoid delivering high-dose irradiation to normal brain tissue. The prototype Gamma Knife unit utilizing gamma radiation was initially developed in 1968 at the Karolinska Institute in Stockholm, Sweden.[2,3]

The widespread use of Gamma Knife stereotactic radiosurgery was made possible by the development of CT and MR stereotactic imaging techniques and corresponding development of computer technology and software that allow for creation of treatment plans unique for each patient that are extremely accurate and efficient, allowing most patients to be treated as outpatients. During frame-based SRS, the patient is initially placed in a Leksell stereotactic frame. The patient undergoes neuro-imaging with MRI or CT studies that permit generation and definition of image-guided Leksell stereotactic coordinates. The Gamma Knife software allows the creation of three-dimensional treatment plans to simulate radiation isodose lines and allow the neurosurgeon and radiation oncologist to define a prescription dose of radiation at the tumor target. Ultimately, the treatment plan simulates the delivery of high radiation in a conformal manner with a single treatment fraction. The radiation dose falls rapidly outside the volume of the tumor target and avoids delivering significant radiation doses to normal brain. (Table 1).

Table 1. Quantification of all SRS completed at a single institution, Washington University in St. Louis

Lesion		**Sample size** (n=5201)
Astrocytoma		112
Acoustic/trigeminal schwannoma		439
Functional		
	Trigeminal neuralgia	739
	Glossopharyngeal neuralgia	5
	Tremor	12
Vascular		
	Arteriovenous fistula	10
	Arteriovenous malformation	347
	Cavernoma	4
Meningioma		525
Metastases		2502
	Melanoma	277
	Breast	369
	Lung	1387
	Renal	142
	Colon	55
	Other	272
Sellar Lesions		
	Pituitary adenoma	290
	Craniopharyngioma	7
Other		734

Current radiosurgery units may utilize frameless radiosurgery techniques that allow repeated treatment fractions, or hypo-fractionated radiosurgery. While earlier Gamma Knife radiosurgery units have solely utilized single fraction treatments, the most recent models with an attached CT scanner (ICON Gamma Knife unit) allows frameless SRS techniques and hypo-fractionated therapy. Figure 1 shows the Gamma Knife ICON unit (a) with a schematic representation of the central core allowing collimation of multiple beams of gamma radiation delivered to stereotactic target (b).

Gamma Knife Stereotactic Radiosurgery in Treatment of Metastatic Brain Disease

Metastatic disease represents a prevalent form of brain tumors, comprising 9-17% all intracranial neoplasms.[4] Most commonly, intracranial metastases represent secondary lesions from lung cancer, breast cancer, or melanoma cumulatively representing approximately 75% of brain metastases.[5] Although untreated brain metastases are associated with a median survival as low as one month, standard of care treatment significantly improves outcomes.[6] Positive prognostic factors include high Karnofsky Performance Status (KPS), age $<$ 65 years, control of systemic disease, response to steroid treatment, and lack of neurocognitive impairment. In retrospective analyses examining patients with a variety of systemic cancer, up to 41% were found to have greater than three intracranial lesions.[7]

Current guidelines for treatment of metastatic brain disease include a multi-faceted treatment approach variably incorporating stereotactic radiosurgery, whole brain radiation therapy (WBRT), and surgery. Dexamethasone at a dose up to 4 mg 4x/day is frequently prescribed for symptomatic treatment of cerebral edema, with a majority of patients demonstrating neurological improvement within 72 hours of treatment. Anti-epileptic medications are used both prophylactically and therapeutically to reduce the incidence of seizures. Systemic management of disease generally includes a medical oncology regimen tailored to the primary malignancy. Traditionally, intracranial metastases are often poorly responsive to standard chemotherapy. Treatment responsiveness is thought to be limited by blood-brain barrier penetration. In some intracranial tumors, radiation treatment may function synergistically to increase chemotherapy efficacy and improve progression-free survival. Selective utilization of targeted chemotherapy or immunotherapy regimens improve responsiveness of systemic disease to primary malignancies and may have a potential role in mitigating growth of metastatic lesions in the CNS. The roles of these new therapies (targeted and immune) are still being evaluated for possible efficacy within the CNS in controlling metastatic brain disease.

Traditionally, WBRT represented the gold-standard treatment for treatment of metastatic disease to the brain.[8] During the 20th century a wide number of clinical trials optimized WBRT treatment durations and regimens with current clinical practice utilizing a prescribed dose of 30 Gy over 10 fractions. Experience has demonstrated that WBRT, initially thought to represent a low-risk treatment option, is associated with significant adverse effects including delayed toxicity, most notably significant for adverse neurocognitive effects that may be both profound and permanent. The associated neurocognitive decline has a characteristic biphasic pattern, with an initial transient decline at four months post-treatments and a secondary severe decline that starts months to years after treatment, more recently quantified in a meta-analysis to represent a cognitive decline of 31-57% at 3 months and 48-89% at one year.[9] Active research includes leveraging WBRT with hippocampal sparing in an attempt to provide the treatment efficacy of WBRT while attempting to avoid its neurocognitive



Figure 1. Stereotactic Radiosurgery. Left, example of a patient within the Gamma Knife Icon system, that is able to deliver SRS with either frame-based or frameless techniques. Right, a schematic representation of a highly focused point by collimating beams of radiation from its cobalt sources to a lesion as selected by a treatment team comprised of neurosurgeons, radiation oncologists, and physicists.

effects on memory, with long-term outcomes ongoing. The significant neurocognitive effects of WBRT have spawned the advance of stereotactic radiosurgery options that provide high-dose radiation to the metastatic tumors specific and avoidance of both vital structures and normal brain tissue.

Surgery has been and continues to have a critical role in treatment of metastatic disease. A well-designed clinical trial published in the *New England Journal of Medicine* established the utility of surgical resection of single metastatic tumors demonstrating improved survival and decreased local recurrence rates compared with treatment with WBRT alone.[10] In addition, surgical resection provides both immediate relief of mass effect and treatment for lesions that might be too large for SRS therapy. Gamma Knife SRS provides an increasingly important alternative modality for treatment of metastatic brain disease in patients. With the advent of more focused radiotherapeutic options, WBRT and neurosurgical resection are often not the primary modality for treatment of patients with metastatic brain disease, but may be utilized in selected patients with extensive intracranial disease burden or with lesions characterized by large tumor volumes and significant mass effect.

In multiple studies, cumulatively with more than 6,000 patients, Gamma Knife SRS for patients with brain metastases showed an average of 84-97% local control rate. SRS can also decrease peri-tumoral edema as characterized by a decreased steroid dependence at six months post treatment. Delayed radiation effects typically develop 9-12 months following SRS in a minority of patients. Post-surgical adjuvant SRS is a necessary component of treatment for surgically resected metastases as surgical resection alone demonstrates a local recurrence rate of 46%.[11] Finally, SRS may be utilized as a primary treatment option for patients who are deemed poor surgical candidates for either medical comorbidities or location of lesions either in deep or eloquent brain locations, or for lesions less than 3 cm in maximal diameter.

Historically, SRS has also been employed in the treatment for patients with up to three brain metastases, while in the past WBRT was more often considered to treat four or more lesions. A *Lancet Oncology* observational study of nearly 1,200 patients demonstrated similar median overall survival for patients treated with SRS with two to four tumors versus those with five to ten metastases, without significant difference in neurocognitive function, therefore suggesting the possibility that SRS may be effectively utilized as a treatment option with patients with greater numbers of intracranial metastases.[12] Treatment of intracranial metastatic disease with multiple tumors with Gamma Knife SRS remains a controversial topic, and its utilization as an alternative treatment option to WBRT in these situations vary with institutional preference. There is a lack of definitive evidence to support level one guidelines for WBRT versus SRS in treatment of metastatic diseases with larger numbers of lesions. Figure 2 demonstrates the effectiveness of Gamma Knife SRS in treatment of metastatic disease.

Stereotactic Radiosurgery for Treatment of Meningiomas

Meningiomas are most often benign neoplasms arising from arachnoidal cap cells along the inner surface of the dura, and represent approximately 25% of primary

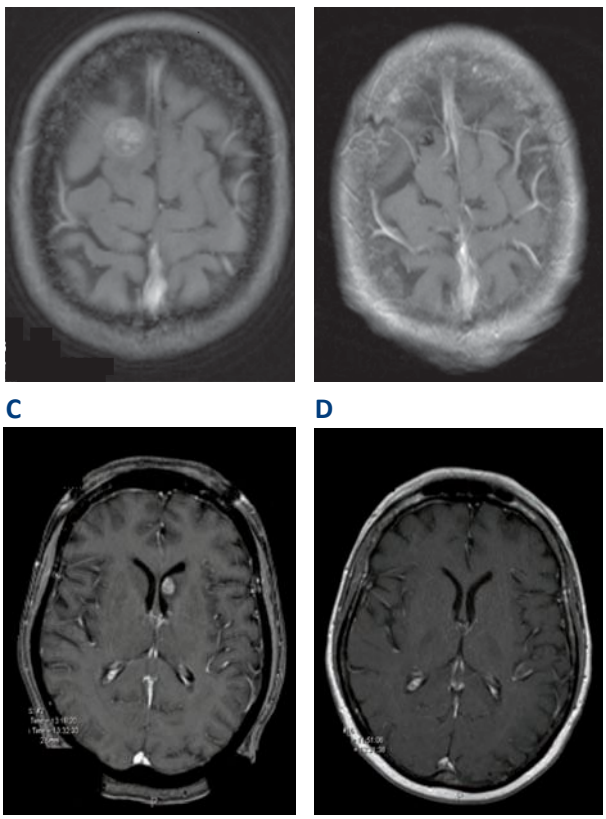


Figure 2. Stereotactic Radiosurgery Treatment of Metastatic Tumors. Metastatic melanoma pre- and post- Gamma Knife SRS (A) and (B) respectively six months after treatment. Metastatic lung carcinoma pre- and post- Gamma Knife SRS (C) and (D) respectively three months after treatment.

intracranial tumors in the United States. The large majority (~97%) of these meningothelial neoplasms are WHO grade 1 (typical) or WHO grade 2 (atypical), while the remainder may be considered anaplastic or malignant WHO grade 3. Meningiomas occur more frequently in the elderly and female patients, and usually arise from intracranial or intraspinal regions with much less common intraventricular or extradural (intra-osseous) locations. Meningiomas generally grow at a slow rate with doubling times varying from 415 days to eight years.[13,14] Symptoms generally are reflected in their size and location. Large tumors may result in headaches, secondary to increased intracranial pressure, and focal neurologic deficits such as seizures (cortical), weakness (paracentral), ataxia (cerebellar), and cranial nerve dysfunction (medial sphenoidal or petro-clival) secondary to mass effect on the adjacent brain parenchyma. Meningiomas may also produce symptoms from peritumoral edema. MR imaging of meningiomas typically show isointense lesions on non-contrast studies, and are best visualized with MR T1 contrast-enhancing studies.

Clinical management of meningiomas includes an assessment of their symptomology, growth rate, and age of patient. Indeed, many patients with meningiomas may be observed with surveillance neuro-imaging studies. This is common management strategy with incidental meningiomas in the elderly and poor operative candidates. Classic treatment of meningiomas includes surgical resection, stereotactic radiosurgery, or a combination of both modalities. Surgery has maintained a continued key role in management of meningiomas, offering effective rapid relief of mass effect, while complete or near total surgical resection result in improved long-term tumor control. The role of radiosurgery in now well-established as a key treatment modality in the management of selected patients with meningiomas. A retrospective study of 5,300 patients with meningiomas undergoing SRS from 15 centers showed a five-year and 10-year progression-free survival of 95.2% and 88.6% respectively, with morbidity of 6.6%. A similar long-term study of 290 consecutive patients showed progression-free control rates of 88.7 and 87.2% at 10 years and 20 years at follow up, respectively, with adverse radiation effects in 3.1% of patients.[15]

Meningiomas located along the skull base affecting critical structures offer a difficult management problem. Such tumors often involve the orbit, cavernous sinus, or petro-clival regions. Aggressive surgical resection of these complicated meningiomas in the past were associated with a high incidence of injury to cranial nerves, eloquent regions of the brain, or essential vascular structures. With the advent of SRS, surgical goals may be modified with plans for less aggressive surgical resections with the knowledge that radiosurgery offers on excellent option for long-term management of incompletely resected meningiomas. This is particularly exemplified for large meningiomas in surgically inaccessible locations. Such lesions may require pre-surgical planning for subtotal surgical resections, with planned adjuvant Gamma Knife radiosurgery to treat residual tumor, knowing its capability to provide excellent long-term control of tumor growth while minimizing injury associated with gross total resection of the tumor. Such a multi-modality approach offers the more efficient and safer treatment paradigm in these patients.

Stereotactic Radiosurgery in Treatment of Pituitary Adenomas

Pituitary adenomas account for approximately 10-20% of intracranial neoplasms.[16] Pituitary adenomas are classified in two main biological categories, either secretory or non-functioning adenomas, and two morphological categories, microadenomas or macroadenomas, based on size. Larger tumors are more likely to result in compression of the optic chiasm, resulting in bitemporal visual field deficit, and/or symptoms of panhypopituitarism. Secretory pituitary adenomas are associated with clinical syndromes; for example, prolactin-secreting adenomas may cause Forbes-Albright syndrome with amenorrhea-infertility in women and erectile dysfunction-infertility in men, while growth hormone-secreting adenomas cause acromegaly and ACTH-secreting adenomas cause Cushing's disease.

The initial treatment of pituitary adenomas varies depending on size and biochemical function. Conservative management may be indicated in incidental and non-functional microadenomas with observation and surveillance MR imaging. Prolactinomas are typically treated medically with dopamine agonists. Other secretory adenomas are commonly surgically treated with endoscopic, transphenoidal biopsy and surgical resection to achieve a biochemical "cure". Similarly, endoscopic resection may be employed to treat macroadenomas that cause mass effect on the optic structures, and allow rapid decompression by removing the suprasellar component of the tumor, though frequently complete surgical resections may be limited by invasion of surrounding structures like the cavernous sinus. Incompletely resected or recurrent tumors can be treated with radiation to enhance long-term control of tumor growth. Radiosurgery may have a primary or a complementary role for patients with small tumors, in patients who are poor surgical candidates, or in patients treated with partial surgical debulking to prevent tumor recurrence. In addition, SRS may be utilized to treat acromegaly or Cushing's disease in patients who have persistent secretory disease post-operatively and/or who have failed medical management.

Outcomes of Gamma Knife radiosurgery following treatment of nonfunctioning pituitary adenomas in 125 patients over 22 years showed tumor control rates of 99%, 94% and 76% at one, five, and 10 years respectively though with less effective control associated with larger tumors greater than 4.5 cm.[3,17] Similarly, secretory tumors demonstrate slower treatment responses; Pollock reported 46 patients with acromegaly treated with Gamma Knife radiosurgery, with endocrinologic normalization rate of 60% at five years.[18] Gamma Knife radiosurgery may work in a delayed fashion with remission rates occurring variably over time. Kobayashi reported in a group of patients with Cushing's Disease a normalization of ACTH levels in 35% and significant improvement in an additional 25% with a mean follow up of 64 months.[19] The role of Gamma Knife radiosurgery in patients with secretory pituitary adenomas provides an additional therapeutic modality often combined with other treatment options including surgical or medical therapy.

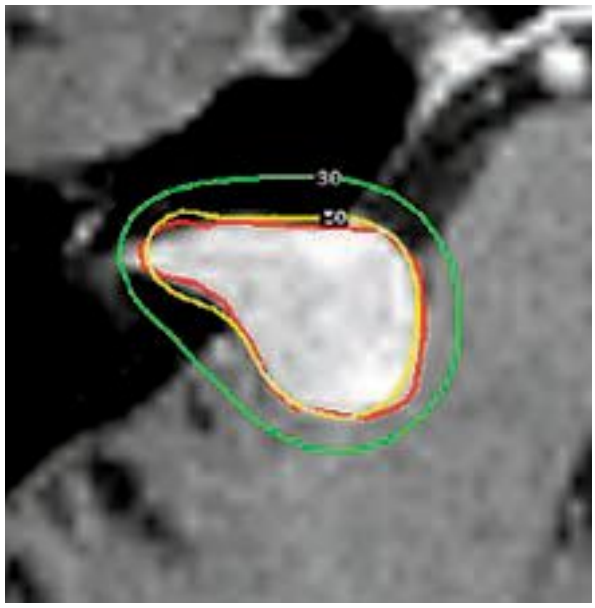


Figure 3. Radiosurgery plan for treatment of vestibular schwanomma. Red outline represents contoured tumor target, while the yellow line represents the 50% prescription isodose of radiation (12Gy), and the green line represents the 30% isodose (7.2 Gy). Radiosurgery is able to prescribe a high radiation dose inside the yellow prescription isodose line conformal with the edge of the shwannoma with rapid radiation fall off.

Stereotactic Radiosurgery for Treatment of Vestibular Schwannomas

Intracranial schwannomas are characterized as capsulated benign tumors arising from Schwann cells along cranial nerves. The most common intracranial schwannoma, acoustic, or vestibular schwannoma, accounts for approximately 10% of intracranial neoplasms and occurs in the cerebello-pontine angle typically arising from the vestibular component of the eighth cranial nerve and extending into the internal auditory canal. Less frequent intracranial schwannomas may arise from the fifth, seventh, or twelfth cranial nerve, and rarely on other cranial nerves.[20]

Prior to Gamma Knife stereotactic radiosurgery, surgical resection was essentially the only treatment option for patients with vestibular schwannomas with high risk of morbidity given the tumor's deep location near the brainstem nuclei and cranial nerves. Progress in microsurgical techniques have decreased surgical risks with improved post-operative morbidity and less frequent injury to the facial nerve resulting in facial palsy. Gamma Knife stereotactic radiosurgery is now established as a non-invasive alternative to microsurgical resection, and typically provides successful long-term control. In a retrospective study, 829 patients with a vestibular schwannoma treated with SRS demonstrated a tumor control rate without need for open surgery of 97% over a 15-year period, with facial neuropathy in less than 1% of patients.[21] Furthermore, Gamma Knife radiosurgery can be combined with partial surgical resection for treatment of previously inoperable large vestibular schwannomas. A group of 40 patients with large vestibular schwannomas (median volume of 3.3 cm^3) were underwent incomplete surgical tumor resection followed by a median dose of 12 Gy SRS at the fiftieth prescription isodose line. The patients showed an 86% tumor control rate over a 10-year follow-up.[22] Furthermore, these patients demonstrated high rate of facial nerve preservation as demonstrated by 95% of patients remaining grade 1-2 in the House-Brackmann facial nerve scale. While there is significant overlap in the efficacy of Gamma Knife radiosurgery and open microsurgical resection, judicious use of each modality in selected patients provide better treatment options in individual patients with vestibular schwannomas. Figure 3 demonstrates the highly conformal prescription isodose line in Gamma Knife SRS in treatment of vestibular schwannoma.

Conclusion

In the past few decades, stereotactic radiosurgery techniques have changed the clinical treatment paradigms in managing neuro-oncology patients. SRS offers improved treatment options for patients with brain metastatic disease, introducing a major shift away from the use of whole brain radiation in many patients. Radiosurgery has also demonstrated significant promise as an alternative minimally invasive therapy in managing patients with benign brain tumors such as meningiomas, pituitary adenomas, and vestibular schwannomas.

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Disclosure

None reported. **MM**

Image Guidance in Cranial Neurosurgery

How a Six-Ton Magnet and Fluorescent Colors Make Brain Tumor Surgery Better

by Michael R. Chicoine, MD, Peter Sylvester, MD, Alexander T. Yahanda, BS & Amar Shah, MD

Washington University in St. Louis
School of Medicine

Surgical navigation, intraoperative imaging, and tumor fluorescence are powerful modalities that advance this goal by improving brain tumor localization and visualization.



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Abstract

Maximal safe resection can improve patient outcomes for a variety of brain tumor types including low- and high-grade gliomas, pituitary adenomas, and other pathologies. Numerous intraoperative adjuncts exist to guide surgeons with maximizing extent of resection. Three distinct strategies exist including: 1) surgical navigation; 2) intraoperative imaging; and 3) tumor fluorescence. Surgical navigation involves registration of high-resolution three-dimensional imaging to the patient's cranial surface anatomy, allowing real-time localization of tumor and brain structures. Intraoperative imaging devices like intraoperative magnetic resonance imaging (iMRI), intraoperative computed tomography (iCT), 3-D fluoroscopy, and intraoperative ultrasonography (iUS) allow near real time visualization to assess the extent of resection. Intraoperative fluorescence via intravenous fluorescein or oral 5-aminolevulinic acid (5-ALA) causes brain tumors to "light up", which can be viewed through surgical optics using selective filters and specific wavelength light sources. A general overview, as well as implementation and utilization of some of these image guidance strategies at Washington University and by Siteman Cancer Center neurosurgeons at Barnes Jewish Hospital, is discussed in this review.

Introduction

Maximal safe resection of brain tumors is the "holy grail" of neurosurgical neurooncology. This applies to low- and high-grade gliomas, pituitary adenomas, brain metastases, and a variety of other pathologies. Maximizing the extent of resection has been demonstrated to improve progression free survival and overall survival for many different tumor types.[1–5] A variety of modalities have been implemented in neurosurgery to improve neurosurgeon's ability to assess intraoperatively the extent of resection in an effort maximize tumor removal and to preserve critical neurological functions. This review will discuss advances in neurosurgical guidance techniques including surgical navigation; intraoperative imaging modalities including iMRI, iCT, iUS; and tumor fluorescence. In particular, neurosurgeons of Washington University and Siteman Cancer Center practicing at Barnes Jewish and St. Louis Children's Hospitals have significant expertise with intraoperative imaging.[5–11]

Surgical Navigation

Resection of brain tumors is complicated by poor visualization,

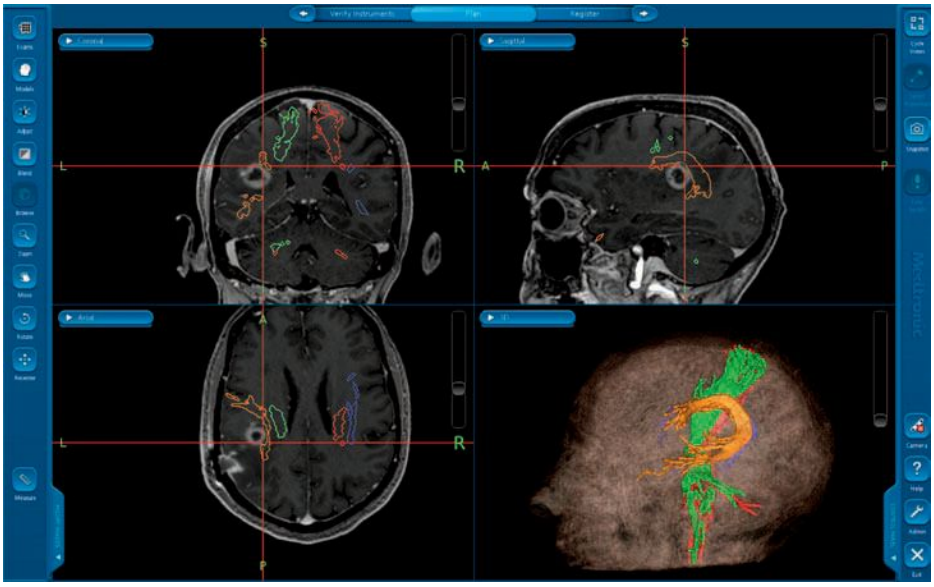


Figure 1. Surgical navigation
Surgical navigation (Stealth™ Medtronic, Inc, Louisville, CO) enables the neurosurgeon to continuously review the anatomical location during surgery using preoperatively acquired MRI studies register to the patient's surface cranial anatomy. This technique improves accurate selection of safe surgical corridors and maximizes safe tumor removal. In this example, pre-operative post-contrast T1-weighted MRI identifies a ring-enhancing glioblastoma. Pre-operative MRI DTI tractography are merged to demonstrate the relationship of the tumor to the corticospinal motor fibers (left, green: red, right) and the left arcuate fasciculus language fibers (orange).

complex three-dimensional anatomy, and the critical importance of anatomic structures. Intraoperative localization during surgical resection is critical to optimize maximal safe extent of resection. Neurosurgeons commonly utilize surgical navigation to improve localization. In the most general case, surgical navigation requires registration of the patient's surface cranial anatomy with high-resolution three-dimensional images. Neurosurgeons use optical and electromagnetic devices to create three dimensional maps of the patient's cranial surface, which can be registered with high accuracy to high-resolution pre-operative CT and MRI scans loaded on the intraoperative computer (Figure 1). Registration of the patient's cranial surface in real and imaging space allows the surgeon to place a probe anywhere within the intracranial space and see this location on the uploaded imaging. Surgical navigation techniques give the neurosurgeon a kind of "x-ray vision", allowing gross estimation of tumor borders, extent of resection, and proximity to important brain structures.

Advanced MRI modalities can be incorporated to improve surgical navigation. Diffusion tensor imaging (DTI) can identify critical white matter tracts involving motor (corticospinal fibers), language (arcuate fasciculus), vision (optic radiations), and other vital subcortical tracts. Functional imaging such as task-based functional MRI (fMRI) and resting state MRI (rsMRI, non-task based) can also be incorporating into the surgical navigation system. The fMRI identifies areas of cortical function by measuring changes in the BOLD signal during simple tasks, while rsMRI measures interactions between cortical regions to identify underlying functional networks.[12] These modalities can be registered to structural imaging to identify relationships between areas of critical function and tumor. Integration of these modalities into the surgical navigation assists with maximization of resection while preserving function.

Intraoperative Imaging

Surgical navigation techniques are highly accurate immediately after registration; however, tissue shifts caused by the operative approach, tumor resection, cerebrospinal fluid drainage, and other factors impair this accuracy. Images used for navigation can be updated and improved intraoperatively with iMRI, iCT, and iUS as will be discussed below.

Intraoperative ultrasound (iUS) has been applied in neurosurgery for over 30 years.[13,14] It is readily available and relatively inexpensive. Intraoperative ultrasound permits real time visualization enabling the surgeon the ability to estimate the margins of a lesion and the extent of resection. There are several significant advantages of iUS compared with other intraoperative imaging modalities. Of the available imaging techniques, iUS is the only true real time modality, allowing immediate assessment of tumor tissue and brain shift during surgery. It can be deployed quickly, is commonly available in the operating room, and is lower cost. Additionally, iUS (and iCT) does not impact pacemakers and other implanted devices, which is a limitation of iMRI.[14] The principle disadvantages of iUS are poor resolution relative to iCT and iMRI, as well as relatively steep learning curve. The utility of iUS has improved with advanced 3D techniques, integration into

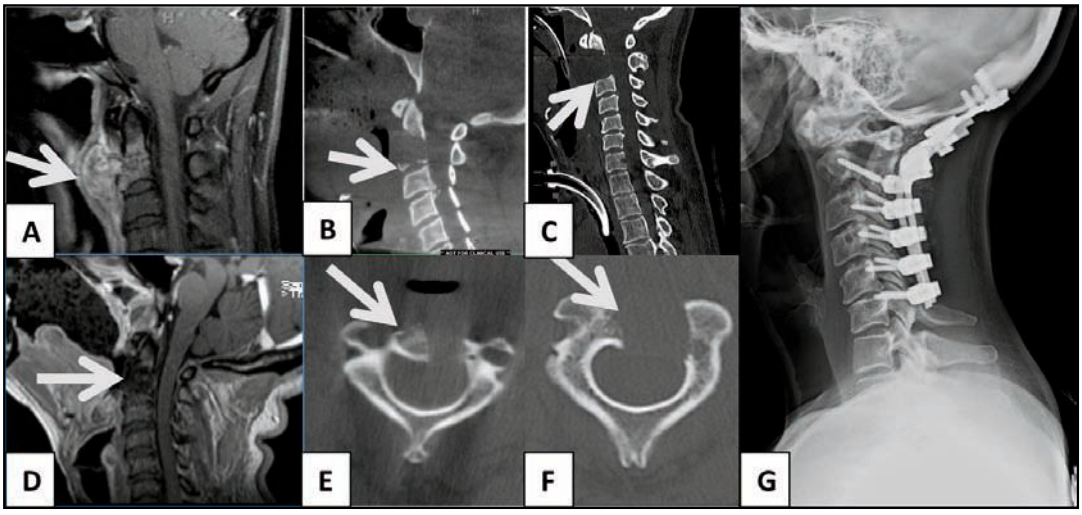


Figure 2. Intraoperative CT
Sagittal post-contrast T1 weighted MRI (a) showing patient with cervical chordoma involving C2 and the prevertebral tissues (arrow) in the posterior oropharynx. Intraoperative 3-D fluoroscopy (b, sagittal; e axial) during a transoral approach for tumor resection demonstrating some residual C2 body (arrows) involved with tumor that lead to additional resection prior to closure. Postoperative CT (c, sagittal; f, axial) demonstrating more complete resection (arrows). Intraoperative MRI (d, sagittal) demonstrating resection of the chordoma. Postoperative lateral C-spine x-ray image after posterior instrumented occipital-cervical fusion for stabilization (g).



Figure 3. Intraoperative CT
3-D fluoroscopy (O-Arm, Medtronic, Minneapolis, Minnesota) can produce "CT like" images, and has been shown to be quite useful for spinal surgery and some cranial procedures. Intraoperative CT and 3D fluoroscopy can be particularly helpful, and in fact, superior in terms of the ability to assess osseous anatomy for tumors involving the bone of the skull, skull base, and spine (see example in Figure 2).

surgical navigation platforms, and implementation of color Doppler techniques to visualize vasculature such as the internal carotid artery and its branches during brain tumor resection.[14]

Diagnostic CT imaging has become ubiquitous in neurosurgery over the last 30 years given the low cost, versatility, acquisition speed, and spatial resolution (particularly for osseous structures). Intraoperative CT is used during brain tumor resection at some centers; can be particularly helpful, and in fact is generally superior tool, for assessing osseous anatomy for tumors involving the skull, skull base, and spine.[15] (Figure 2). Intraoperative CT and 3D fluoroscopy are typically faster and relatively less expensive than intraoperative MRI modalities. However, iCT does have significant limitations in soft tissue resolution compared to iMRI. 3-D fluoroscopy, can produce "CT-like" images, and has been shown to be quite useful for spinal surgery and some cranial procedures[15] (Figure 3).

For more than 20 years, iMRI has been advancing as a modality in neurosurgical operating rooms.[16,17] Of the available intraoperative imaging modalities, iMRI offers the highest soft tissue spatial resolution. Numerous centers worldwide have implemented iMRI strategies using either high or low magnetic field devices. At Barnes Jewish Hospital, Washington University physicians have been using a movable six-ton 1.5 tesla high field intraoperative MRI device mounted on ceiling rails.[6] This device is situated in a middle storage room in between two neurosurgical operating rooms, and therefore can be used intermittently by surgeons in two different adjacent rooms during overlapping surgeries. Using this strategy, the neurosurgeon performs brain tumor resection until perceived maximal



Figure 4. Intraoperative MRI
iMRI suite at Barnes-Jewish Hospital in St. Louis with a movable iMRI device (IMRIS Inc, Minnetonka, Minnesota). After completion of standard brain tumor resection, prior to closure of the craniotomy, additional sterile drapes are applied and safety checks are completed (upper left), external 8-channel coils are applied (upper right), the doors of the magnet storage bay located in between 2 operating rooms are opened (lower left), and the movable 6-ton ceiling mounted iMRI device is moved into position (approximately 90 seconds) to enable acquisition of 1.5 Tesla high field high resolution iMRI images to assess the extent of tumor resection (lower right).

safe resection, at which point preparations are made for iMRI. Specifically designed imaging coils are placed around the patient's head, additional sterile drapes are applied, and a safety checklist is completed prior to moving the iMRI device into the operating field (Figure 4). Acquired images can then be integrated into the surgical navigation system, enabling accurate navigation to resect identified residual tumor when accessible and safe. In recent years, an iMRI modality termed continuous MR thermography has facilitated performance of laser interstitial thermal therapy (LITT), a minimally invasive technique by which a laser probe is placed within brain lesions using surgical navigation for laser ablation[18] (see related article by Kim and colleagues in this issue).

Washington University neurosurgeons have employed the iMRI strategy in more than 2,000 brain tumor surgeries, one of the largest experiences with this technique in North America. Clinical outcome studies by Washington University neurosurgeons as well as others worldwide have demonstrated that iMRI can improve the safe extent of resection increasing progression free and overall survival for patients with low and high-grade gliomas, pituitary adenomas and a variety of other pediatric and adult brain tumors. Pediatric neurosurgeons at St. Louis Children's Hospital have successfully treated children with various brain tumors using the iMRI strategy employed at Barnes Jewish Hospital.[9,11] Washington University neurosurgeons are part of a multi-center collaboration, the IMRIS Multi-Center Intraoperative MRI Neurosurgery Database, (I-MiND) which is studying the impact of iMRI and other treatment modalities on outcomes for patients with brain tumors and other complex neurological disorders across multiple centers in North America.

Tumor Fluorescence

Fluorescent agents including fluorescein and 5-ALA are being used in US centers to visualize brain tumors during surgeries. These agents help identify brain-tumor interfaces and hard to visualize residual tumor. The principle advantage of this technique is that information is immediate and continuously available to the surgeon.

Fluorescein has been utilized in medicine and other non-medical industries for decades.[19] Ophthalmology and other areas of medicine utilize intravenous or topical application of fluorescein allows better visualization of certain pathologies. In neurosurgery, intravenous administration of fluorescein can aid in visualization of blood vessels during vascular neurosurgical procedures such as clipping of cerebral aneurysms or resection or arteriovenous malformations. Modification of the technique of has been proven to enhance the neurosurgeons ability to visualize brain tumors.[19] Intraoperative imaging with fluorescein relies on the breakdown of blood brain barrier that is inherent with many brain tumors, particularly malignant gliomas.[20] Intravenous fluorescein is administered early in brain tumor surgeries. The neurosurgeon uses a microscope with selective fluorescent filters that enable enhanced visualization of the brain tumor (Figure 5). Advantages include high available of fluorescein, low cost, proven safety, and ease of use. The major disadvantage is limited to specificity, which could result in retained residual tumor, or worse, injury to critical brain structures. Extreme care is needed on the part of the neurosurgeon to understand the limits of this technology.

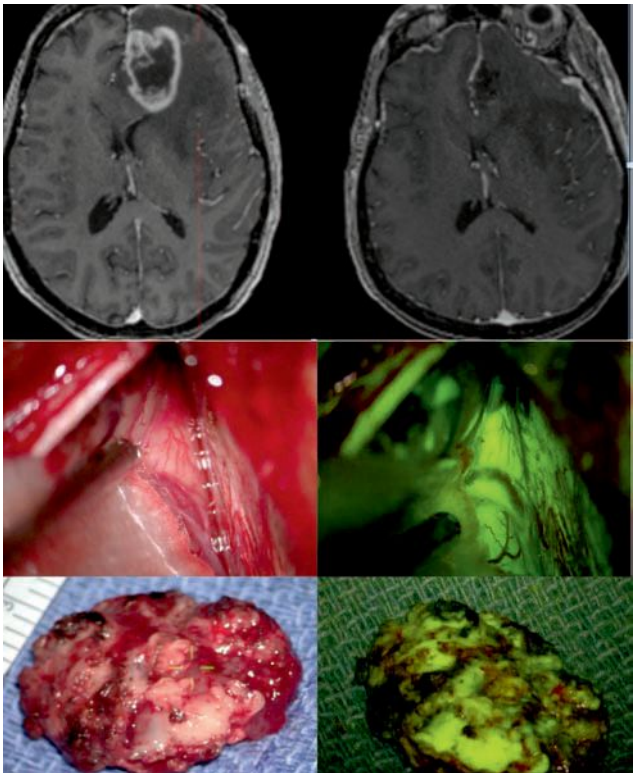


Figure 5. Fluorescein for brain tumors
Upper row: Patient with left frontal glioblastoma as seen on T1 weighted axial post-contrast MRI (preoperative upper left, postoperative upper right). Middle row: Interhemispheric intraoperative microsurgical view during resection of the tumor under standard white light (left) and under 560 nm yellow fluorescence filter after intravenous injection of fluorescein (right) using the Zeiss Pentero microscope (Carl Zeiss Meditec, Inc., Dublin, California). Note the demarcation between the green fluorescence of the tumor and the absence of fluorescence of the adjacent brain. Lower row: En bloc gross specimens with standard white light (left) and fluorescence filter (right) demonstrating the fluorescence of the tumor after the intravenous injection of fluorescein.

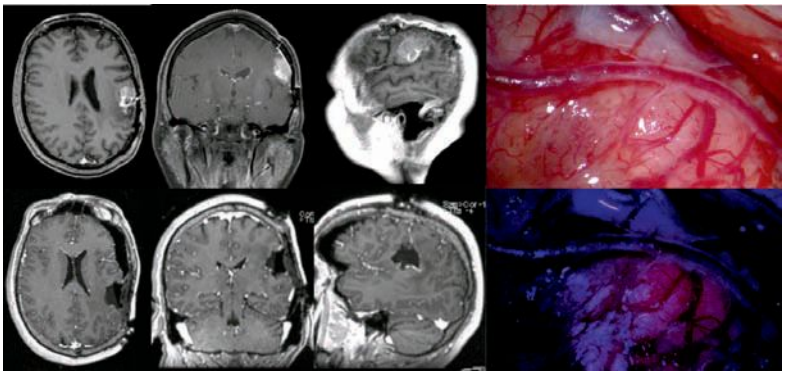


Figure 6. 5-ALA for brain tumors
Patient with recurrent left frontal-parietal glioblastoma as seen on preoperative T1 weighted axial post contrast MRI, (upper left 3 images), and on intraoperative MRI after 5-ALA guide resection (lower left 3 images). Upper right: intraoperative microsurgical view of the view during craniotomy for resection of the tumor under standard white light using the Zeiss Pentero microscope (Carl Zeiss Meditec, Inc., Dublin, California). Lower right: 400 nm blue fluorescence filter after oral administration of 5-ALA (Gleolan™) several hours preoperatively (right). The pink fluorescence signifies the presence of protoporphyrin IX, the metabolite visualized in the tumor which preferentially metabolizes 5-ALA.

5-aminolevulinic acid (5-ALA) also improves visualization of select brain tumors. Mechanistically, 5-ALA is preferentially metabolized by certain tumors to protoporphyrin IX,[21] which can be excited with a blue light and visualized using a selective blue filter through surgical optics as a fluorescent pink hue (Figure 6). The use of this fluorescent agent can facilitate detection of tumor that may not be readily apparent using surgical microscopes or other techniques. 5-ALA is more specific than fluorescein as it is metabolized preferentially by the tumor. Patients can have a mild photosensitivity for 24-48 hours after administration of this agent, but the worldwide experience with thousands of patients have demonstrated this as a very well tolerated strategy.[22] Brain tumor resection using 5-ALA has been extensively studied in Europe and other continents. A randomized prospective study demonstrated that 5-ALA improved extent of resection and progression free survival for malignant gliomas.[23] The Food and Drug Administration (FDA) in the United States approved 5-ALA in the commercial product of Gleolan (NXDC, Inc) in 2018. The neurosurgeons of Washington University and the Siteman Cancer Center at Barnes Jewish Hospital are among the first in the United States to employ this recently FDA approved agent.

Summary

Maximizing the extent of safe resection is an important goal in the removal of a variety of brain tumor types. Surgical navigation, intraoperative imaging, and tumor fluorescence are powerful modalities that advance this goal by improving brain tumor localization and visualization. These strategies can be used independently, in combination with each other, or in combination with traditional neurosurgical physiologic monitoring techniques including cortical/subcortical motor stimulation, awake craniotomy to identify and preserve areas of language, somatosensory and motor evoke potentials, and monitoring of cranial nerve electromyography. Additionally, advanced MRI techniques such as DTI tractography, fMRI, and rsMRI offer visualization of critical cortical / subcortical areas, improving safe tumor resection. Structural and functional

imaging can be performed using iMRI, and surgical navigation scans can be updated with these scans to account for brain shift during surgery. Integration of intraoperative imaging modalities, navigations tools and techniques for identification and preservation of critical function are leading to more precise and safe maximal brain tumor resection by the neurosurgeons of Washington University and the Siteman Cancer Center practicing at Barnes Jewish and St. Louis Children's Hospitals.

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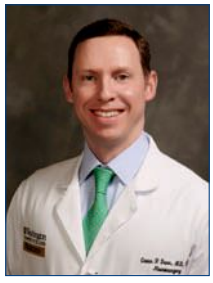
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An Innovative Immunotherapy Vaccine with Combination Checkpoint Blockade as a First Line Treatment for Glioblastoma in the Context of Current Treatments

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School of Medicine

While recent achievements in immuno-oncology have improved the prognoses of many cancer diagnoses, these benefits have not yet translated to glioblastoma multiforme.



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Abstract

Glioblastoma is a devastating disease with a dismal prognosis. While recent advancements in cancer immunotherapy have led to improvements in treating other types of cancer, patients with glioblastoma have not benefited from these new therapies and techniques. Fortunately, neurosurgeons and oncologists at Washington University School of Medicine conducting a cutting edge clinical trial are looking to overcome these persistent challenges in treating glioblastoma through combining a personalized vaccine with new immunotherapy drugs.

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor and accounts for approximately 17,000 new cases in the United States annually.[1] GBM unfortunately has the worst prognosis of primary gliomas, with a miserable median survival of 12-15 months despite aggressive treatment.[1,2] The current first line standard of care includes maximal surgical resection, adjuvant radiotherapy with concurrent temozolomide chemotherapy following resection, and six months of maintenance temozolomide after concurrent chemoradiotherapy.[1] Tumors in a large majority of patients will recur, and the lack of effective standard second-line options leads to patients rapidly succumbing to the disease; the current 5 year survival rate is less than 10%.[1] Due to the abysmal prognosis associated with GBM, new safe and effective therapies are desperately needed.

Cancer immunotherapy is a new and active area of cancer research, where various therapies are used to evoke an immune response against a tumor. Contemporary cancer immunotherapies include targeting immune checkpoint signaling pathways with inhibitory antibodies, checkpoint blockade immunotherapy (CBI), or priming the immune response with therapeutic vaccines. Therapeutic vaccinations aim to prime the immune response against tumor antigens, which can include shared tumor antigens and/or personalized tumor-specific antigens, called neoantigens. While other therapies, including cellular therapies such as chimeric antigen receptor (CAR) T cells have shown positive data in other cancer types, this review will focus on past applications of CBI and therapeutic vaccines. We will also present a pioneering clinical trial that combines a personalized therapeutic vaccine with CBI.

Checkpoint Blockade Immunotherapy in Glioblastoma

Landmark discoveries in checkpoint inhibition have revolutionized oncology treatment options for previously devastating diagnoses, resulting in a well-deserved Nobel Prize. Two major immunotherapy targets are the negative immune regulatory checkpoint proteins cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed cell death protein 1 (PD-1) or its ligand, PD-L1. Both CTLA-4 and PD-1/PD-L1 are coreceptor molecules on the surface of T-cells that inhibit T cell function and play key roles in guarding against autoimmunity.[3] The CTLA-4 pathway regulates T-cell proliferation and priming in the lymph nodes, while the PD-1/PD-L1 pathway regulates T cell response in the tissues later in the immune response.[4] CBIs targeting these pathways can improve the anti-tumor immune response.

CBI has shown efficacy in preclinical orthotopic transplantable GBM mouse models, such as GL261 and SMA-560. Mice with intracranially implanted GL261 tumors show a survival benefit when treated with either anti PD-1, anti PD-L1, or anti CLTA-4 treatment.[5,6] These effects of anti PD-1 or CTLA-4 therapy in GL261 are synergistic when combined with radiotherapy.[7,8] Anti CTLA-4 treatment also confers a survival benefit in mice with intracranially implanted SMA-560 GBM cell line tumors.[9]

Both anti CTLA-4 and anti PD-1/PD-L1 CBI antibodies have been FDA approved or have shown preliminary success in melanoma, squamous and non-squamous non-small cell lung cancer, small cell lung cancer, metastatic renal cell carcinoma, urothelial cancers, head and neck squamous cell carcinoma, and colorectal cancer.[10] The immune system can apparently control tumors in many environments as shown by the success of CBI in multiple organ systems; ongoing clinical trials are investigating the efficacy of CBI in other systems.[10]

Due to the success of CBIs in other cancer types, many clinical trials for CBI in newly diagnosed and recurrent GBM are currently underway, but none have reported convincing positive results in large patient cohorts. The Checkmate 498 open label trial for patients with newly diagnosed GBM and an unmethylated MGMT promoter comparing nivolumab (anti PD-1) combined with radiotherapy against standard of care temozolomide with radiotherapy did not meet the primary endpoint of overall survival.[11] The ongoing sister phase III Checkmate 548 (NCT02667587) trial for patients with newly diagnosed GBM and methylated MGMT will compare nivolumab versus placebo combined with standard radiotherapy plus temozolomide. While a phase II trial comparing pembrolizumab (anti PD-1) against concurrent pembrolizumab and bevacizumab appeared safe in both cohorts, it also showed minimal anti-tumor activity in the pembrolizumab only cohort, and combination therapy did not show improved outcome compared to historical bevacizumab controls.[12] A phase Ib trial of pembrolizumab in 25 patients with recurrent PD-1 positive GBM reported 1 partial response and 12 patients with stable disease.[13] In a trial of patients with recurrent GBM, neoadjuvant (pre-reresection) combined with adjuvant pembrolizumab conferred a survival benefit over adjuvant pembrolizumab alone.[14] The results from this neoadjuvant administration study suggest that a strong priming response associated with increased tumor antigen exposure may lead to a better anti-tumor response later. A trial treating 6 recurrent GBM patients with pembrolizumab and bevacizumab reported no dose-limiting toxicities and clinical benefit in 3 of 6 patients.[15,16]

In addition to CBI monotherapy, ongoing clinical trials for both newly diagnosed and recurrent GBM are investigating combination CBI of anti CTLA-4 and anti PD-1. Results from these trials demonstrate that CBI is safe and tolerable in these populations, but do not show a survival benefit. Results from the Checkmate-143 phase I study comparing nivolumab (anti PD-1) alone or in combination with ipilimumab (anti CTLA-4) in patients with recurrent GBM showed no grade 3 or greater SAEs out of 10 patients treated with nivolumab monotherapy (3 mg/kg every 2 weeks).[17] Only 2 of 20 patients in the Checkmate 143 trial treated with nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks for 4 doses followed by maintenance nivolumab at 3 mg/kg every 2 weeks experienced grade 3 or greater SAEs.[17] A lower initial 4 doses of nivolumab at 1 mg/kg with higher ipilimumab at 3 mg/kg led to a larger (7/10) proportion of SAEs without a dramatic increase in treatment response.[17] Furthermore, cohort 2 of the Checkmate 143 phase III study, which randomized GBM patients to nivolumab monotherapy or bevacizumab monotherapy, did not show any difference in median overall survival, 12 month overall survival, or progression free survival.[17]

Although the completed trials investigating CBIs in patients with GBM have established a safe treatment protocol, they have not shown a survival benefit compared to standard therapy. The GBM microenvironment and standard of care treatment conditions cause immunosuppression, and the low mutational burden does

not create an immunogenic environment present in other tumors.[18,19] The challenging tumor biology along with past negative trial results suggest that combination therapies are likely necessary to see a clinical benefit.

Therapeutic Neoantigen Vaccination in Glioblastoma

Tumor antigens distinguish tumors from normal tissue and serve as potential targets for immune system neutralization. Shared tumor antigens and neoantigens are both subsets of tumor antigens. Normal tissues or limited subsets of normal tissues express low levels of shared tumor antigens, but tumors overexpress these shared antigens. Examples include MAGE in melanoma[20] and HER2/neu in breast cancer.[21] Tumor-specific antigens, or neoantigens, are the result of somatic mutations only present in the tumor.[22] Therefore, while tumor cells may express neoantigens, normal tissue does not due to a lack of somatic mutations present. The first neoantigen described was mutated cyclin-dependent kinase 4 in melanoma.[23] Other groups have since described neoantigens in multiple other types of cancer.[24,25]

Because they are targets for immune cells, vaccinating a patient against their own tumor antigens could stimulate an anti-tumor immune response. The obvious benefit to using neoantigens over shared tumor antigens is that they are unique to the tumor, therefore mitigating autoimmune effects. Phase II clinical trials in patients with GBM using rindopepimut, a vaccine against the neoantigen EGFRvIII, combined with standard temozolomide and radiation showed benefits in overall survival and progression free survival over historical controls.[26–28] However, a phase III trial of rindopepimut with temozolomide failed to show a survival benefit.[29] Additionally, EGFRvIII is only expressed in 20-30% of GBMs, so most patients would not be candidates for this therapy.[30] While disappointing, these results warrant investigation into combining neoantigen vaccines with additional immunotherapy such as CBI. Within the past year, several publications show that personalized neoantigen vaccine therapies for glioblastoma are feasible, generate neoantigen specific T cells that infiltrate the tumor, and have favorable safety profiles.[31–33] A predictive approach to identify immunogenic neoantigens is necessary to streamline any potential therapy that would benefit more than a small subset of patients.

The Future of Brain Tumor Immunotherapy

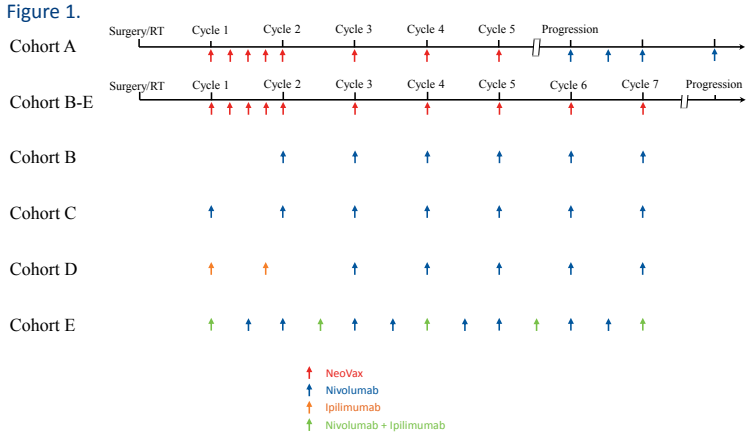
Given the favorable safety profile and different mechanisms of immune activation, combining CBI with neoantigen vaccines makes therapeutic sense. These two approaches could synergistically increase the anti-tumor immune response, using CBI to overcome the problem of immunosuppression and using neoantigen vaccination to counteract the poor immunogenicity of the tumor. Blocking CTLA-4 and PD-1 with CBIs potentially enhances anti-tumor neoantigen-specific T cell responses in melanoma[34] and NSCLC respectively.[35]

An innovative clinical trial (NCT03422094) currently recruiting patients at Washington University School of Medicine (WUSM) combines a state-of-the-art personalized neoantigen vaccine (NeoVax) with different CBIs, specifically nivolumab (anti PD-1) and ipilimumab (anti CTLA-4). Eligible patients must have newly diagnosed GBM with an unmethylated MGMT promoter. Patients who enroll in the trial receive NeoVax and their designated nivolumab or ipilimumab infusions at Siteman Cancer Center in St. Louis. This trial seeks to investigate how the timing of CBI administration combined with a personalized neoantigen vaccine affects the clinical and immunological response. Because CTLA-4 has a role in early priming and PD-1 in later local tissue response, sequentially administering different CBIs which target these separate pathways could synergistically boost the anti-tumor immune response.

Preclinical data has shown a synergistic effect of combining a vaccine with either anti PD-1[36] or anti CTLA-4[37] in mice with intracranially implanted GL261 tumors. Multiple clinical trials in various cancer types have investigated concurrent tumor antigen vaccination with checkpoint blockade monotherapy without an increase in adverse events over CBI alone.[38] These results indicate that combining a vaccine with CBIs should be safe for patients with GBM.

Creating a neoantigen vaccine specific for each tumor requires a robust, accurate, and cost-effective pipeline. Fortunately, investigators at the Siteman Cancer Center and the McDonnell Genome Institute at WUSM have developed an immunogenomics approach to identify patient neoantigens for a vaccine. Compared to cancer genome sequencing, identifying neoantigens with tumor versus normal tissue exome sequencing is robust, accurate, and conserves resources.[39] To ensure that the tumor expresses enough of the identified mutant neoantigens, RNA sequencing will measure tumor mRNA mutant allele expression levels of neoantigens identified by tumor/normal exome sequencing. An in silico prioritization algorithm then filters the mutant neoantigens to identify the top candidates that have high HLA class I or class II allele epitope binding affinity for presentation to the patient T

Figure 1.



Study schema of "A Pilot Study to Assess the Safety, Feasibility, and Immunogenicity of a Neoantigen-based Personalized Vaccine Combined with Immune Checkpoint Blockade Therapy in Patients with Newly Diagnosed, Unmethylated Glioblastoma" (NCT03422094). Note that patients in cohorts B-E will all receive the same NeoVax schedule in addition to CBI.

cells. Scientists then manufacture a vaccine against the prioritized neoantigens with a synthetic long peptide vaccine combined with a poly-ICLC adjuvant. In preclinical studies, our group successfully predicted and screened neoantigens from the GL261 and SMA-560 murine GBM models using this screening strategy.[40]

Patients who have a potential GBM and want to participate in the trial can receive surgery and treatment from experts at Barnes Jewish Hospital and Siteman Cancer Center. After surgery, patients receive the standard course radiotherapy (60 Gy over 30 treatments, Monday through Friday for 6 weeks) without temozolomide. Temozolomide is excluded due to the immunosuppressive effects and lack of efficacy in MGMT unmethylated GBM, a similar strategy adopted in Checkmate 498 to avoid the immunosuppressive effects of chemotherapy. During radiotherapy, scientists and physicians at WUSM analyze the tumor and generate a personalized neoantigen vaccine as described above. After radiotherapy, patients enter the vaccine priming phase where they receive their unique NeoVax treatment weekly for 4 weeks. After priming, patients then move to the boosting phase, where they receive NeoVax once every 4 weeks. While the NeoVax schedule is the same for all patients, the schedule for CBIs differs among the cohorts. Patients in cohort A will receive only NeoVax until progression, when they begin nivolumab infusions every other week. Patients in cohort B receive only NeoVax during the priming phase, and then receive nivolumab and NeoVax during the boosting phase. Patients in cohort C receive nivolumab and NeoVax during the priming and boosting phases. Patients in cohort D receive ipilimumab and NeoVax during the priming phase, and then switch to nivolumab and NeoVax during the boosting phase. Patients in cohort E receive all 3: nivolumab, ipilimumab, and NeoVax during both the priming and boosting phases. Figure 1 depicts the administration schedule for the NeoVax trial.

To date, only 8 other trials across various cancer types are recruiting patients for clinical trials involving a therapeutic vaccine and combination CBI. Some of the ongoing trials will begin reporting results next year. The NeoVax trial at WUSM is the only enrolling trial administering a therapeutic vaccine with combination checkpoint blockade immunotherapy for patients with glioblastoma. Our group will soon open a new clinical trial (NCT04015700) investigating a therapeutic DNA vaccine with combination CBI.

Conclusion

GBM is a uniformly lethal disease. While recent achievements in immuno-oncology have improved the prognoses of many cancer diagnoses, these benefits have not yet translated to GBM. These setbacks are likely due to the unique and immunosuppressive nature of GBM, which will require ingenuity to overcome. Despite these roadblocks, trailblazing new treatments like NeoVax and combination checkpoint blockade at Washington University are giving hope to patients with GBM and shaping the future of cancer treatment.

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Disclosure

GPD is a co-founder and Chief Scientific Officer of Immunovalent Therapeutics, Inc. TMJ has served on scientific advisory boards for Geneos Therapeutics and NovoCure. **MM**

Laser Interstitial Thermal Therapy

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Laser interstitial thermal therapy is a minimally invasive, cytoreductive surgical technique that can be used to make targeted and conformal lesions in the brain.



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Abstract

Laser interstitial thermal therapy (LITT) is a minimally invasive and cytoreductive neurosurgical technique that has gained significant momentum in the last decade. Several technological enhancements such as MRI thermometry and improved laser probe design have enabled feasibility and improved the safety of LITT procedures. Numerous reports have been published describing the treatment of lesions ranging from tumors to epileptogenic foci, but the indications for LITT continue to evolve. We describe the general physical and biological concepts underlying LITT, clinical workflow, and established and emerging indications.

Introduction

Stereotactic laser interstitial thermal therapy (LITT) is an emerging, minimally invasive and cytoreductive neurosurgical technique for a variety of central nervous system (CNS) lesions ranging from tumors to epilepsy foci. Although the technique was first described in 1983, enthusiasm for its use was limited in large part due to the inability to monitor tissue temperature during laser treatment and thus control the extent of ablation.[1,2]

In the past decade, renewed interest in LITT has been sparked by advances in intraoperative magnetic resonance imaging (MRI) techniques that now enable real-time thermometry using T1-weighted 2D images obtained during the ablation procedure.[2-4] Use of stereotactic LITT with MR thermometry has since been described for treatment of primary and metastatic brain tumors, radiation necrosis, and epilepsy foci.[5] Investigation of new uses and the limitations of LITT is currently a highly active area of research. In this review, we describe the surgical procedure, technological advances, treatment indications, and emerging uses of LITT (Table 1).

Laser Interstitial Thermal Therapy

The first experiments using laser ablation in brain tumor models were described in 1983 by Bown, who used a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.[1,2,4,5] Subsequently, animal studies and clinical trials were performed, establishing LITT as a potential treatment for intracranial neoplasms. Numerous technical advancements in laser probe design and MRI have led to the development of the modern stereotactic LITT neurosurgical procedure.

Typical LITT Surgical Workflow

Surgical technique and workflow vary by institution and LITT system in use but in general are as follows: Prior to

Table 1. Uses of LITT reported in the literature.

Tumor
Glioma (Grade I – IV)[2,4,20,27,28]
Brain metastases, especially treatment refractory[6,7,13,27]
Radiation necrosis[13]
Meningioma[12]
Epilepsy
Amygdalohippocampectomy[23,24]
Corpus callosotomy[25]
Lesionectomy (*e.g.* hamartoma)[29]

surgery, a thin section CT scan or MRI suitable for use in stereotactic surgery is performed. An optimal trajectory for ablation is then planned using a computer-based stereotactic neuro-navigation system, following the first-order principle of treating the lesion down the center of its long axis. In some cases, multiple trajectories may be required to optimally ablate the lesion. Once in the operating room, the patient is positioned to facilitate placement of the laser probe, keeping in mind the space restrictions of the MRI. This may require positioning the patient's head such that the entry point and the direction of the laser probe is more in line with the barrel of the MRI bore and not at the top of the field as in traditional open cases. The laser probe may be placed using either frameless or frame-based stereotactic techniques or using a robotic arm, such as the ROSA® system, depending on surgeon preference and resources available.

A stab incision no more than 5 mm is then made at the planned probe entry site and a drill used to generate a bur hole in the skull. A rigid guide is then affixed to the skull and the fiberoptic laser probe inserted through the bur hole, following the pre-planned trajectory. Once the probe is secured in place, the patient must be placed in an MRI scanner. This can be achieved either by transporting the patient with the probe in place to a suitable MRI scanner or by utilizing an intra-operative MRI scanner. After initial MRI images are captured to verify probe position, the ablation process is initiated. During this time, firing of the laser probe is interleaved with periodic acquisition of 2D T1 MRI images. These images are generally overlaid with a graphical representation of the temperature of the brain surrounding the probe. Once the ablation is completed, the patient is removed from the MRI scanner. If no additional trajectories are planned, the laser probe is then removed, and the surgical incision irrigated and closed. All patients undergo post-procedure monitoring for at least 24 hours before being discharged from the hospital.

LITT Technology

Significant technological advances continue to be made in the tools and techniques used to perform stereotactic LITT surgeries. In the United States, there are currently two LITT systems available: the NeuroBlate® System (Monteris Medical, Winnipeg, Manitoba, Canada), which received FDA clearance in 2009 and the Visualase® Thermal Therapy System (Visualase Inc., Houston, Texas, USA), which received FDA clearance in 2007. Detailed descriptions of both systems have previously been reported, and the underlying biological mechanism of action between the two systems is similar.[6-9]

During a LITT ablation, light energy emitted by the laser is converted into thermal energy by the surrounding tissue. This process occurs when photons emitted by the laser optical fiber are absorbed by tumor cell chromophores, resulting in chromophore excitation followed by release of thermal energy.[5,10] Once a sufficiently elevated temperature is achieved and maintained, protein denaturation, cellular necrosis, and tissue coagulation occur. Numerous factors influence the speed, pattern, and degree of tissue heating, including intrinsic properties of the target tissue and its surrounding environment, properties of the laser used, and the temperature and duration of ablation. For example, diode and Nd:YAG lasers are the two types of lasers used for neurosurgical LITT procedures. The NeuroBlate® system uses a 12 watt 1064 nm Nd:YAG laser that is cooled with carbon dioxide while the Visualase® system uses a 15 watt 980 nm diode laser that is saline cooled. The differing wavelengths and other properties of these laser probe designs may result in different degrees of tissue penetration and ablation.[5,10]

Several innovations in laser probe design have significantly enhanced the LITT procedure. For example, laser probes were initially designed with diffusion tips that emitted laser photons in all

directions from the probe tip. Subsequently, a side-fire probe was designed to emit photons in one direction, orthogonal to the laser probe. When this probe is paired with an MRI-compatible driver capable of rotating, advancing, and withdrawing the probe, a more conformal pattern of ablation can be achieved, although at the expense of increased ablation time.[2] Significant advances in probe cooling also made LITT a tractable solution for lesion ablation. Initial probe designs lacked enough cooling and insulation to protect tissue traversed by the laser probe, limiting lasers to a power of 1-5 watts. Furthermore, if temperatures at the probe tip exceed 100°C, a pseudocapsule can form around the tip with charring and carbonization of the surrounding tissue, limiting further laser penetration and reducing the treatment volume.[5] The introduction of carbon dioxide and saline cooled probe sheaths allowed for use of increased laser power, improved protection of traversed tissue, reduced treatment times, and increased treatment volume.[2,5] Temperature changes from heat conduction fall off exponentially with distance from the laser probe. Currently available probes have an effective treatment radius between 1 and 2 cm from the tip. The tip can be moved along the implanted axis of the probe to create a treatment "cylinder" approximately 3 cm in diameter for a single pass of a laser probe.[2] Depending on the shape and size of the target lesion, multiple trajectories may be used, at the expense of additional operative time.[5,8]

Both commercially available LITT systems depend on intraoperative MRI scanning. During a LITT procedure, a computer is connected directly to the MRI scanner and runs software used to integrate images acquired from the MRI scanner in real time. This integration allows for verification of the initial probe position and of any new probe position that results from advancing or withdrawing the probe, and measurement of tissue temperature using MR thermometry. The development of MR thermometry was a critical step in making LITT feasible for neurosurgical applications. MR thermometry is a noninvasive means of measuring tissue temperature to within 1°C with a spatial resolution of 1-2 mm that is based on changes in MR characteristics (primarily proton resonance frequency) of living tissue that occur with change in temperature.[3,5] Critically, MR thermometry can be used to measure temperatures distant from the laser probe, allowing surgeons to maximize ablation of the target lesion while avoiding damage to surrounding normal tissue. Several MR sequences, including T1-weighted, diffusion coefficient and water proton resonant frequency sequences can be used for MR thermometry.[5] Once firing of the laser probe begins, newly acquired MR images are compared to baseline images by the computer. The Arrhenius equation predicts cell death as a function of tissue temperature and ablation time and is used to display zones of tissue damage.[5,8,11] For example, in the NeuroBlate® system, the white line encircles the target volume that has received the thermal dose equivalent of 43°C for at least 60 minutes, the blue line surrounds the target volume that has been exposed to 43°C for at least 10 minutes, and the yellow line surrounds tissue exposed to 43°C for 2 minutes. These lines are also referred to as thermal damage thresholds (TDT). Tissue within the white line is considered to have undergone coagulation necrosis, while tissue within the blue line is considered to be severely damaged and tissue outside the yellow line is considered to have no permanent damage.[8]

Tumor

An increasing number of neuro-oncological applications for LITT have been reported in the literature, with a growing body of evidence gradually clarifying its role. Studies have described its use in brain metastases, low- and high-grade gliomas, meningiomas, and radiation necrosis.[2,4,6,7,12-15] In general, the minimally invasive nature of LITT is particularly well suited for treating deep-seated or otherwise difficult to access lesions, lesions resistant to alternative therapies such as stereotactic radiation, or lesions in patients who could otherwise not tolerate a larger, open surgical resection.

The median overall survival of GBM is 15 months in the setting of maximal surgical resection, radiation and chemotherapy with temozolamide.[16] Several retrospective and prospective studies have established that maximal cytoreduction with gross total resection of glioblastoma is associated with improved survival compared to biopsy alone.[2,17,18] While patients are generally able to tolerate radiation

and chemotherapy, surgery may not be feasible for all patients, either because the patient is too ill to tolerate a craniotomy or because the lesion is located in or adjacent to eloquent structures, making resection impossible without significant neurological deficit. Recently, a multicenter matched cohort study compared outcomes of patients undergoing LITT versus biopsy followed by standard chemo- and radiation therapy for treatment of newly diagnosed GBM. The authors reported that patients undergoing LITT with near total blue TDT-line coverage had improved survival compared to matched patients undergoing biopsy alone. Thus, as a cytoreductive, minimally invasive procedure, LITT may represent a favorable alternative to biopsy alone in patients with difficult to access tumors or who cannot tolerate a craniotomy.[15]

Recurrent GBMs have limited options available for additional therapy, and there is currently no widely recognized standard of care. At the time of recurrence, patients may have already undergone multiple prior craniotomies, fractionated radiation, radiosurgery, and/or chemotherapy, all of which increase the risk of subsequent surgeries. Prior studies have reported a significantly increased risk of systemic infection, worsening neurological status, and increased wound-related surgical complications in patients undergoing a second surgery for glioblastoma.[5] Several studies have described the safe utilization of LITT as a cytoreductive therapy in patients with recurrent glioblastoma.[19,20] In a recently published study of LITT treatment of 41 recurrent GBM lesions, the post-LITT median overall survival was found to be 11.6 months, with a 16% rate of 30-day procedure-related morbidity.[20] As a comparison, patients with recurrent GBM treated with lomustine and bevacizumab have a median overall survival of 9.1 months with a 40-60% incidence of serious adverse events.[21] No head-to-head comparison has been performed comparing LITT to chemotherapy for recurrent GBM, but these data suggest that LITT may present a favorable, alternative strategy for treatment of recurrent GBM.

LITT has also been used for treatment of brain metastases, particularly for lung, breast, and colon adenocarcinoma.[6,14,19] At present, standard treatment modalities for cerebral metastases include surgery, radiotherapy, and/or stereotactic radiosurgery. A recently published multicenter prospective study of 20 patients with recurrent metastatic brain lesions treated with LITT suggests that LITT may stabilize Karnofsky performance score (KPS), preserve quality of life and reduce steroid use in patients with few alternative options for salvage therapy.[13] The authors reported a 12% rate of immediate LITT-related complication, including 4 cases of worsening neurological deficit due to damage to adjacent eloquent tissue and 1 case of intracerebral hemorrhage that did not require additional surgery and did not result in neurological deficit. Other complications related to LITT included seizures, transient neurological symptoms, and asymptomatic increase in radiographic cerebral edema.[13] Given the limited data available, how LITT will fit into the treatment paradigm for brain metastases remains to be determined, but there is increasing enthusiasm for its use in treatment-refractory brain metastases.

Lastly, LITT has been used to treat patients with radiation necrosis. Radiation necrosis occurs in approximately 5-10% of patients treated with radiation therapy and 10-20% of patients treated with stereotactic radiosurgery.[5] Treatment for radiation necrosis is generally conservative, with observation and, when symptomatic, dexamethasone. However, in cases of medically refractory, symptomatic radiation necrosis, surgical resection may be necessary. As with recurrent glioblastoma, patients requiring a second surgery for resection of radiation necrosis are at elevated risk of surgical complications, with many patients unable to tolerate a craniotomy due to their general health and medical comorbidities. In their study of 19 patients with biopsy confirmed radiation necrosis treated with LITT, Ahluwalia and colleagues reported that LITT stabilized KPS, preserved quality of life, and reduced steroid. Furthermore, nearly 100% lesion control was achieved with LITT in patients with radiation necrosis.[13] It is of interest to note also that the thermal dose threshold (yellow TDT line) for effective treatment of radiation necrosis is thought to be lower than that for tumor.[5,13]

Epilepsy

Epilepsy has a lifetime prevalence of 3%, with significant medical, social, psychological, and economic implications for patients. The first

line of treatment for epilepsy generally relies on anticonvulsant drugs, but approximately one third of patients treated with anticonvulsants continue to have seizures that are medically refractory. Drug-resistant epilepsy, defined as lack of seizure freedom despite a two anti-epileptic drug regimen, is frequently associated with mesial temporal sclerosis. In these patients, and in many patients with seizures localizable to a defined epileptogenic focus, surgery has been proven to be highly effective in controlling or abolishing seizures.[22] Given the potential morbidity associated with many epilepsy surgeries such as selective amygdalohippocampectomy, hemispherotomy, corpus callosotomy, and resection of deep-seated hamartomas, significant efforts have been devoted to improving the safety profile of these surgeries.[9] Multiple authors have described the successful use of LITT to treat epilepsy, harnessing its minimally invasive nature to improve the safety of epilepsy surgery.[23-25]

In 2014, Willie and colleagues reported their success in performing LITT amygdalohippocampectomy. In 13 patients, 60% of the volume of the amygdalohippocampal complex was ablated, with a median hospitalization of 1 day, and 77% of patients achieved meaningful seizure reduction, with 54% being free of disabling seizures.[23] More recently, Lehner et al. described their success in treating 5 patients with medically refractory epilepsy with LITT ablation of the corpus callosum. Four of the 5 patients achieved greater than 80% seizure control after the procedure.[25] Selective amygdalohippocampectomy involves creation of a temporal scalp incision and craniotomy, and places structures such as the temporal lobe and optic radiations at risk. Open corpus callosotomy involves creation of a large scalp incision and craniotomy, and risks injury to neurovascular structures such as the sagittal sinus and cingulum. The minimally invasive nature of LITT significantly reduces risk to these structures and makes it a more attractive surgical option for intractable epilepsy patients who are often hesitant to undergo invasive brain procedures.[25] Furthermore, Drane and colleagues reported improved object recognition and naming outcomes after LITT amygdalohippocampectomy compared to matched patients undergoing open temporal lobe epilepsy surgery, suggesting that by sparing adjacent eloquent structures, LITT may have fewer neurocognitive side effects compared to open surgery.[24]

Emerging Uses of LITT

New case reports and series describing the use of LITT in intracranial lesions continue to be published, leading to the discovery of additional indications for the procedure. LITT is particularly well suited for treatment of difficult to access lesions, lesions in or adjacent to eloquent cortex, and/or scenarios in which standard therapies are not feasible. Although LITT has previously most often been used as an alternative to traditional treatments such as open craniotomy, in the future, it may be used as an adjunct to such procedures. For example, tumors near eloquent cortex greater than 3 cm in size that are not suitable for LITT may first be debulked with open surgical techniques, and the residual tumor then treated with LITT to achieve maximal treatment of the tumor.

Importantly, much of the underlying biological mechanism and effects of LITT in the brain remain poorly understood and is therefore an important area of ongoing investigation. In 2016, Leuthardt and colleagues analyzed post-LITT MRI scans and serum brain specific enolase levels in 20 patients with recurrent GBM. Interestingly, they found that peak brain permeability after LITT occurs 1-2 weeks after ablation and resulves by 4-6 weeks.[26] These findings suggest that LITT may create a window of time during which drugs may penetrate the blood-brain barrier, opening an interesting new area of investigation on combination therapies of LITT plus adjuvant chemotherapy. Other properties of the area of increased blood brain barrier permeability, such as the spatial distribution of permeability in relation to the area of ablation, have yet to be characterized. The finding of elevated brain specific enolase in the blood after LITT also implies that proteins normally confined to the immune-privileged central nervous system are being released into the systemic circulation. Thus, disruption of the blood-brain barrier after LITT may also have immune implications that are yet to be explored.

Conclusion

LITT is a minimally invasive, cytoreductive surgical technique that can be used to make targeted and conformal lesions in the brain. Several critical advances in probe design and the development of MR thermometry have made LITT a more practical surgical technique. This recent interest in LITT has spurred numerous reports describing efforts to treat

neurosurgical pathologies, including neoplasms and epileptogenic foci. The value of LITT for the treatment of certain pathologies such as recurrent GBM and epileptogenic foci has now become well established. Data on emerging uses of LITT are very promising, with the indications of the procedure continuing to grow.

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The Vaping Epidemic in Adolescents

by Kristen Jones, DO & Gary A. Salzman, MD



UMKC School of Medicine

It is time for physicians to ask their adolescent patients about vaping and to provide education to the child and parents on the dangers of vaping.





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Abstract

Electronic cigarette (e-cigarette) use has recently risen to the forefront of medical discussions across the country. A significant increase in e-cigarette use by adolescents has been observed over the last decade. This article discusses the targeting of adolescents by e-cigarette companies. It looks at how teenagers are uniquely affected by nicotine and at risk for progressing to using combustible cigarettes and marijuana. Lastly, it discusses the role of physicians in combating the spread of e-cigarettes.

Introduction

Every medical student is taught the three basic questions to ask for social history. "Do you drink any alcohol? Do you do any drugs? Do you smoke cigarettes?" While these are three very important questions to help us address potential health hazards with patients, they fail to identify some of the most significant factors in the lives of adolescent patients. Specifically, vaping in adolescents poses a grave risk to patients' health and is a topic that physicians have to confront.

Over the last 20 years, there has been a decrease in the number of teenagers smoking combustible cigarettes. The Youth Risk Behavior Survey demonstrated a decrease in the number of teens trying combustible cigarettes from 70% in 1991 down to 58.4% in 2003 and even further down to 28.9% in 2017.[1] The decrease is largely a response to exhaustive work done by physicians, advocacy groups and lawmakers. Physicians have worked diligently to improve education on the dangers of smoking and fought to pass new regulations to protect patients. The United States is seeing an explosive rise of adolescents' vaping and the renormalization of smoking (Table 1). Recent national surveys demonstrate a drastic increase in e-cigarette use among high schoolers. An article from the *New England Journal of Medicine* reported a 10% increase in adolescents using e-cigarettes between 2017 and 2018 alone, which is approximately 1.3 million teenagers.[2]

Electronic cigarettes are battery-operated devices that use an electric pulse to heat and aerosolize a flavored liquid that typically contains nicotine. They were first introduced to the U.S. in 2007, and they were advertised by the tobacco companies as an adjunct method to help patients quit smoking. This claim never had evidence to support it, as studies comparing the use of electronic cigarettes, placebos, and nicotine patches demonstrated no significant differences in abstinence rates.[3] But because e-cigarettes were seen as a treatment option, they were not subjected to the same regulations as combustible cigarettes. It wasn't until 2016 that the Congress passed the Child Nicotine Poisoning Prevention Act, giving the FDA the authority to regulate e-cigarette packaging.[1]

Advertising Directed to Teens

Advertising for e-cigarettes has been heavily aimed at adolescents. Everything from the billboards to the packaging to the product itself has been aimed at teens. Ads on social media were widely distributed. From 2014 to 2016, advertising for vaping exploded and one study found that 78% of middle and high school students had been exposed to at least one advertisement.[1] Pods come in fun packaging and the different pods are flavored to be attractive to adolescents, with everything from mint to gummi bear to frosted sugar cookie. This is especially concerning because studies have shown that flavor is one of the most important factors adolescents consider in trying e-cigarettes.[4] The devices to aerosolize the pods are designed to look like anything from USBs to pens to inhalers. They can be personalized much like a cell phone case and backpacks have special pockets for the mod devices.

Health Risks for Adolescents

This targeted marketing of e-cigarettes is particularly harmful given the significant health risks these products pose to teens. Many people know that nicotine causes lots of problems for the developing brain. However, it is not widely recognized that many e-cigarettes contain higher concentrations of nicotine than combustible cigarettes. JUUL is the most common e-cigarette brand used in the U.S.; it is so popular that teens use JUULing as a verb.[1] JUUL pods contain 5%, or 59mg/ml, of nicotine.[5] This is approximately equal to the nicotine contained in 20 combustible cigarettes.[6] To make this more concerning, one study demonstrated that 39% of adolescents did not consider JUULs to be e-cigarettes at all.[6] Another survey suggested that 63% of adolescents did not know that JUUL pods contained nicotine at all.[7]

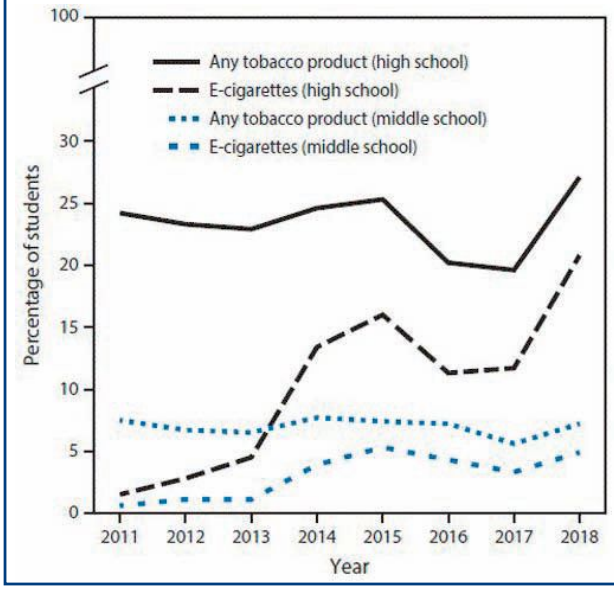
Many studies, primarily based on the use of combustible cigarettes, have demonstrated the adverse health effects of nicotine. Adolescent brains are still developing, and nicotine exposure has been linked with cognitive deficits and impairment in memory and executive function. Electronic cigarettes have been connected with increased impulsivity, with one animal study demonstrating that exposure to e-cigarette vapor during times of rapid brain growth (like during adolescence) can cause hyperactivity and impulsive behavior changes.[4] Another study looking specifically at the teen population found increased risks of physical fighting, attempted suicide, and alcohol/marijuana use when comparing non-users to teens who smoked or vaped.[8]

Nicotine Addiction in Teens

There has also been evidence that suggests e-cigarette use increases an individual's chance of using combustible cigarettes. Adolescents who use e-cigarettes are 3.6 times more likely to report using combustible cigarettes later in life.[9] Teens have also been shown to be more susceptible to addiction. We know that nicotine addiction often originates in adolescence with studies showing that close to 90% of adult daily smokers started before the age of 18.[10] Thus, e-cigarettes are effectively helping to create a new generation addicted to nicotine.

Table 1. The rise of adolescents' vaping and the renormalization of smoking.

Source: Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Products Among Middle and High School Students – United States, 2011-2018. MMWR Morb Mortal Wkly Rep 2018;67:1276-1277



Gateway to Marijuana Use

Many vaping devices can also be used to inhale cannabinoids. One study demonstrated that teens who use nicotine liquid in e-cigarettes were 3.6 to 4 times more likely to use marijuana in the next two years.[1] Another study demonstrated that 1 in 10 seniors in high school vape cannabis.[6] This should be extremely distressing to physicians and medical providers because it is known that marijuana is extremely harmful to the development of the adolescent brain and studies have actually shown changes in brain structure. As a result, deficits in attention, learning, and memory associated with cannabis use in adolescents has been reported.[11] One study demonstrated that high schoolers who use marijuana were four times more likely to have multiple sexual partners when compared to students who only use tobacco or alcohol.[12] A sizable portion of adolescents who use marijuana report symptoms of paranoia, anxiety and hallucinations.[13] Adverse effects from marijuana

use, including cannabis hyperemesis syndrome have become common among pediatric patients.[14]

Flavors and Additives

Beyond the nicotine, the flavoring chemicals and additives present their own danger. Currently there are no federal laws to ensure that the labels on e-cigarettes are accurate. Until August 2018 they did not even have to include the nicotine concentration on labels. Testing has demonstrated different carcinogens in e-cigarettes including aldehydes, metals, and polycyclic aromatic hydrocarbons.[6] One recent study looking at the different additives found that that vapes containing cinnamaldehyde for cinnamon flavor were associated with impaired mucociliary function in bronchial epithelial cells. Biopsies from chronic vapers demonstrate structural changes in lung tissue.[1]

Education

Physicians caring for adolescent patients are quickly realizing the health hazards associated with vaping and are looking for ways to combat the epidemic. First and foremost is education for both the teen and their parents. Teens obtain most of their knowledge on e-cigarettes from social media and their peers. One in three adolescents in the U.S. still consider electronic cigarettes to be less harmful than traditional combustible cigarettes.[4] It is imperative that teens are given accurate information on e-cigarettes.

Unfortunately, parents often face the same challenges in finding resources for vaping education as their children. They rely on schools to educate both the parent and their child on e-cigarettes, yet studies have shown that most parents receive little communication from their school on the topic.[15] This is an area where physicians can help fill the knowledge gap. One study found that while parents understood that nicotine exposure is detrimental for teens, most did not know that JUUL pods contain nicotine. Less than half of the middle school and high school parents could identify a JUUL mod in a picture.[15] Most parents were concerned about the use of e-cigarettes in teens but only two in five were concerned about use in their own child.[15] Parents who do not feel that their children are at risk are less likely to talk to their children about the risks associated with vaping. It is imperative that physicians encourage parents to discuss vaping with their teens and provide tools to facilitate that discussion.

Advocacy

The other way physicians can help address vaping in adolescents is by participating in advocacy at a local, state or national level. Currently in the state of Missouri, e-cigarettes are not included in the definition of "Tobacco Products" and thus are not subject to the same restrictions as combustible cigarettes. The sale of e-cigarettes to those under 18 years of age is prohibited, just as with tobacco. But the only regulation in place for e-cigarette packaging is that the liquid must be in child-resistant containers. The American Academy of Pediatrics is currently advocating for Missouri to include e-cigarettes in smoke-free laws and to increase the minimum age to purchase electronic cigarettes to 21 years.[16] Organizations like the American Academy of Pediatrics and the American College of Physicians have both released position papers on vaping and offer further ways to join the fight. It is time for physicians to ask their adolescent patients about vaping and to provide education to the child and parents on the dangers of vaping. Physicians have the responsibility to be advocates for their patients working with medical organizations, state and local governments to address the adolescent vaping epidemic.

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None reported. **MM**

Medications for Opioid Use Disorder: A Guide for Physicians

by Naazia Azhar, MD, Ravikumar Chockalingam, MD & Asad Azhar, MD



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Physicians should prescribe responsibly and hold their patients accountable. We should not enable addiction; we should promote recovery.



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Abstract

The opioid crisis has shaped the national public health dialogue for some time now. A "call to action" is a strong and resounding cry from multiple disciplines. This piece intends to detail the nuts and bolts of prescribing medications used for the treatment of opioid use disorder. The underlying message here is that opioid use disorder is a chronic, treatable illness and physicians of all specialties have a responsibility to not turn a blind eye.

Foreward

This article grows from the 1st Annual Larry Lewis Symposium held at Washington University School of Medicine in St. Louis, Missouri, in August 2017.[1] The symposium was a scientific forum addressing the current opioid epidemic. This is the fifth essay in this series.

Overview

Evidence clearly demonstrates that abstinence programs are not the standard of care for opioid use disorder (OUD),[2,3] and are an unacceptable recommendation from any medical professional. Abstinence-only, or no medications, when treating OUD has a higher rate of continued illicit opioid abuse and lower rate of retention in treatment. Patients on medications are less likely to die of an overdose death compared to those not taking medications.[4] Medication assisted therapy or medication for addiction treatment (MAT) uses pharmaceuticals to combat the underlying neurobiological changes that occur in opioid addiction.

An important first step is to identify a patient with OUD.[5] The DSM 5 describes OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress. There are 11 criteria (Figure 1), and a patient must meet two to three criteria to qualify for a mild disorder; more than six is a severe disorder. As you might imagine, a patient may not readily reveal this information to their doctor, especially if their doctor is the one prescribing the opioids. Further, the nature of addiction comes with some denial of the problem and it is commonplace to have several attempts at initiation of treatment before a patient accepts that they need help. Notably if the patient is taking an opioid as prescribed, tolerance and withdrawal are not criteria for an OUD.

If concerned for an OUD, a physician should utilize concepts of motivational interviewing to discuss substance use with their patient. Expressing empathy builds rapport and encourages a patient to be more forthcoming regarding their struggles. In clinical practice and experience, this translates to increased identification of OUD. When a patient has an OUD, there is a discrepancy between their values or goals and their actions or behavior, i.e., what they say they want compared to what is occurring in their life or what they are doing. The role of the physician is to develop this discrepancy with the patient. In motivational interviewing, recommendations are to avoid arguments

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12 month period		
1	Opioids are often taking in larger amounts or over a longer period of time than was intended	AMOUNT
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	CRAVING
3	A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects	TIME
4	Craving, or a strong desire or urge to use opioids	CRAVING
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	RELAPSE
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids	DYSFUNCTION
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	HARM
9	Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance	INSIGHT/ JUDGEMENT
10	A need for markedly increased amounts of opioids to achieve intoxication or desired effect / A markedly diminished effect with continued use of the amount of opioid	TOLERANCE
11	The characteristic opioid withdrawal syndrome / The same or a closely related substance is taken to relieve or avoid withdrawal symptoms	WITHDRAWAL

Figure 1. DSM 5 criteria for OUD[6]

or direct confrontation. Information from collateral sources is a useful tool in diagnosing OUD. Recognizing that time is limited especially for a primary care physician who has many other medical problems to address in a short appointment slot, there is certainly room for referral to addiction professionals or psychiatry for a more intense diagnostic evaluation. However, the scope of the opioid epidemic is vast; opioid overdose caused more deaths in 2016 than those caused by motor vehicle crashes.[7] As such, it is not possible for one specialty of medicine to handle this. It will require a multidisciplinary approach, and each physician needs to take ownership of their role here.[1]

After identifying and establishing a diagnosis of OUD, the next logical step is to facilitate treatment. There are currently three FDA approved medications for the treatment of OUD: methadone, buprenorphine and naltrexone. These medications are superior at reducing illicit opioid use over no medication in randomized clinical trials.[2,3,8] Buprenorphine and methadone are demonstrated to reduce mortality from opioids.[4,9–11]

With regards to each of the three medications, we shall review strategies, shall review prescribing information, and offer clinical wisdom. It should be noted that there is no "one-size-fits-all" approach to treatment, nor is there a "typical" patient. Addiction is a complex pathology with a multifactorial etiology, therefore its treatment must reflect that.

Methadone

Our "old faithful" in the treatment of OUD is methadone. Methadone is listed as a World Health Organization essential medication. It is the oldest of the three medications for OUD, and thus has the largest evidence-base, with large multi-site studies from all over the world describing its effectiveness in reduction of illicit drug use, retention in treatment, reduction of death by overdose, reduction of cellulitis, HIV and Hepatitis C infections, and reduced criminal and HIV high-risk behavior.[12]

Methadone as treatment for OUD is restricted to the setting of a federally-certified and -accredited opioid treatment program (OTP). There are approximately 1,500 OTPs in the United States.[12] It is dispensed in these settings in a liquid formulation. OTP admission criteria includes patients over age 18 and diagnosis of an OUD for at least one year. These can be waived for pregnant women and patients recently released from incarceration.

Initially, patients are required to go to the OTP daily. Importantly, methadone can be initiated in hospitalized inpatients even if the hospital is not an OTP.

Chemistry and Mechanism of Action

Methadone is a Schedule II controlled substance and is a full agonist at the mu-opioid receptor. Its bioavailability and half-life are highly variable between individuals. The average half-life is 24 hours (but can range from 8 to 59 hours).[13] Steady-state concentration is reached in about five days. The peak serum concentration is about two to four hours after the dose is administered, so it is necessary to monitor for sedation around that time. There is no ceiling effect, and it is metabolized by CYP450 3A4 enzyme. Initial dosing and dose increases are times when methadone causes respiratory depression and must be done with great caution and daily monitoring as rapid escalation can lead to respiratory depression. The goal of the first weeks of treatment is to relieve withdrawal but avoid oversedation and respiratory depression.

Risks and Adverse Effects

Of the three medications, methadone has the most potential for drug-drug interactions. 3A4 inhibitors will cause methadone accumulation. These include antacids (cimetidine), antibiotics, antifungals (erythromycin, ciprofloxacin, fluconazole) and antidepressants (fluvoxamine, sertraline, paroxetine). 3A4 inducers increase its metabolism potentially resulting in methadone withdrawal and cravings for opioids. Common side effects include constipation, nausea, sweating, sexual dysfunction, drowsiness, weight gain, and edema.

Potential contraindications include allergy, acute asthma, patients with buildup of CO_2 from lung disease, and paralytic ileus. The risk of respiratory depression is highest in patients who are older, cachectic, have COPD, or with concurrent use of benzodiazepines, alcohol, or other sedatives. In these situations, patients should be treated with lower doses and with even more caution. A black box warning for QTc prolongation and torsades de pointes was issued in 2006.[14] Intake assessment should include screening for risk factors including a family and personal cardiac history, current medications, current use of methamphetamines or cocaine (both can prolong QTc), labs (to evaluate for low potassium or magnesium) and an EKG. When the QTc is between 450-500, discuss risks and benefits with the patient. If it is over 500, do not initiate methadone. If the patient is already on methadone, consider decreasing the dose, switching to a different medication and eliminating other medications that prolong the QTc.[15]

There is a risk of misuse, diversion, and accidental overdose with methadone which is why patients are initially required to go to an OTP every day. Patients should be strongly counseled about the risks of diversion and misuse, and about safe storage to prevent accidental overdose by a child, pet, or an opioid-naïve person.

When a patient prescribed methadone through an OTP is admitted to the hospital, it is necessary to call the OTP clinic to verify that the patient is in treatment, their dose, when the last dose was administered, and whether the patient has any take-home medications. Patients should be continued on their methadone while hospitalized unless it is medically contraindicated. The OTP should also be notified upon discharge so that they are aware of the patient returning for treatment.

Buprenorphine

Buprenorphine was initially discovered in 1966 as a structurally similar compound to morphine without incorporating some of its less desirable addictive properties. However, it was not until 1978 when Janski et al. discussed the role of buprenorphine as a treatment for OUD. In his subsequent work, Janski described buprenorphine as a medication with "unique pharmacology in man" with very little risk of dependence following chronic administration.[16] He described the search for a medication to treat analgesia and addiction which culminated in the discovery of buprenorphine. Interestingly, the Food and Drug Administration did not approve buprenorphine for the treatment of OUD until 2000.[17] In order to prescribe Buprenorphine, a prescriber must undergo an eight-hour approved training followed by applying for an "X-waiver" from the Drug Enforcement Agency (DEA). However, it can be dispensed in the emergency department or hospital without a waiver.

Chemistry and Mechanism of Action

Naturally produced endorphins activate mu receptors resulting in analgesia and euphoria. Heroin and other exogenous opioids activate mu receptors resulting in similar effects in addition to respiratory and central nervous system depression. Buprenorphine is a partial agonist resulting in a submaximal ceiling effect, thereby offering a therapeutic opportunity with a safety net to mitigate the ill effects of full agonists such as heroin. This dose dependent ceiling also curtails risk

of overdose which can occur with full agonists such as methadone. Importantly, children and pets can still develop respiratory depression from buprenorphine.[18] Another important chemical property of buprenorphine is its high binding affinity to opioid receptors. This prevents the positive reinforcement and euphoria that often occurs if full agonists are used concomitantly following buprenorphine induction, i.e. the patient injects heroin while using buprenorphine. The high affinity also explains how buprenorphine can precipitate withdrawal in a patient on opioids. If the patient is still under the effects of opioids (not in withdrawal) buprenorphine will outcompete the other opioid to bind at the mu receptor. However, since it is only a partial agonist, it will activate the receptor to a lesser extent than a full agonist resulting in withdrawal. This is otherwise referred to as the antagonist effect as a full agonist is displaced by the partial agonist with stronger affinity.[12] Practice guidelines recommend that patients are in early withdrawal prior to induction to significantly reduce this risk. Buprenorphine is also a potent kappa receptor antagonist. Its effect on kappa receptors produces significant mood benefits with studies exploring the use of buprenorphine as an antidepressant.

Formulations

Sublingual formulation of buprenorphine, used in addiction comes in tablet form (Zubsolv® with naloxone and Subutex® as buprenorphine alone) and sublingual film (Suboxone® with naloxone). While Buccal films are also available, they are not currently deployed in the treatment of OUD. The choice of formulation in clinical practice is one of patient and provider preference, although the combination yields an additional benefit of protection from improper use due to the antagonistic properties of naloxone. When administered sublingually, 50% of buprenorphine is immediately absorbed while none of the naloxone is absorbed.[17] When crushed and injected or insufflated, the naloxone becomes bioavailable and can displace buprenorphine resulting in immediate withdrawal from its antagonistic effects. This effect of naloxone is the primary reason for providers to prefer the combination of the two. The exception is in pregnancy where buprenorphine alone (Subutex®) is recommended, although more recent data questions this approach.[19] While subdermal implants, transdermal and injectable formulations are available in the U.S., they are mainly used for its antinociceptive properties. However, they were recently approved for OUD.[20]

Dosing Guidelines

It is critical for patients to be in withdrawal prior to "induction" or initiation of buprenorphine in order to avoid precipitated withdrawal. The Clinical Opiate Withdrawal Scale (COWS)[21] can assist with this quantifying the patient's degree of withdrawal. A typical first dose once the COWS score is greater than 6 is 4 mg for monotherapy or 4/1mg (4 mgs of buprenorphine with 1 mg of naloxone) for combination.[12] During this period, the patient's vital signs are typically monitored and they remains under observation. One to two hours later, another 4 mg dose may be administered with a usual max dose on day 1 around 8-12 mg of buprenorphine. On day 2, the first dose is typically the maximum dose of day 1 followed by an additional 2-4 mg depending on residual withdrawal symptoms with a typical maximal dose for day 2 being around 12-16 mg. By day 3, providers typically get to a maintenance dose of 16 to 20 mg at which almost all the opioid receptors are saturated limiting need for further increasing the dose, as was the practice prior to dosing studies. Maximum daily dosing is between 24-32 mg. More recent sources may recommend a more aggressive induction strategy. Home induction is also safe in the correct patient population.[22] Patients may prefer their dose be split and administered twice a day as opposed to methadone which is generally administered once a day.

Detoxification/Maintenance

The best available evidence for long-term sobriety from opioids rest with using buprenorphine for prolonged maintenance without arbitrarily stopping therapy against the patient's wishes. Studies comparing two and four-week detoxification using buprenorphine suggest superior rates with four weeks of taper with duration of taper being the strongest predictor of success.[23] In some clinical practices it is common to use buprenorphine primarily for detoxification from opioids. In this case, the objective is to alleviate individuals from withdrawal symptoms and treatment usually lasts days if not weeks. Naltrexone is often deployed in the transition from buprenorphine with evidence suggesting that such a combination will aid in relapse prevention in the long-term.[24] However, such rapid detoxification strategies do place most patients at an elevated risk of relapse and overdose. With regards to maintenance, most studies suggest that patients are more likely to stay in treatment and reduce relapse if they are maintained on buprenorphine, long term. Here, the duration is often open ended with patient preference influencing the duration of maintenance.[25]

Naltrexone

Naltrexone works as a competitive mu opioid receptor antagonist with high affinity, blocking the effects of exogenously administered opioids. It was investigated in the 1970s before obtaining FDA approval in 1984. Randomized trials demonstrated that oral naltrexone was not superior to placebo or to no medication in the treatment of opioid use disorder.[26] This is mainly because patients are required to take the medication daily. The long-acting extended release naltrexone (XR-NTX) was approved by the FDA in 2010. The medication is encapsulated in polymer microspheres and delivers steady naltrexone concentrations for approximately a month. It is indicated for the treatment of alcohol and opioid use disorders, and was found to be superior to no medication[8] and placebo[27] in reducing return to opioid use. If a patient maintained on XR-NTX were to use opioids, naltrexone would block their effects. This theoretically could be overridden if enough opioids were used or from opioids with extremely high binding affinities such as some of the novel illicit opioids. Recent studies comparing naltrexone to buprenorphine[28,29] demonstrated that XR-NTX was not inferior to buprenorphine in rates of return to opioid use, but that there was a significant challenge in retention during naltrexone induction. In a large randomized multisite trial that took place in residential treatment programs in the United States,[28] a large portion of patients did not actually receive the naltrexone injection which was a major limitation. The major challenge is that patients require a period of abstinence from opioids prior to induction (approximately one week) which many are unable to achieve. Often this can be achieved in an inpatient or rehabilitation setting. Naltrexone will precipitate withdrawal in patients still using opioids. This is important to avoid, as it can deter patients from the medications in the future and lead them back to opioid use. Naltrexone has no abuse liability or specific regulations surrounding its prescribing.

Naltrexone undergoes renal and hepatic metabolism, but there is no CYP450 enzyme involvement and drug-drug interactions are limited compared to buprenorphine and methadone. Contraindications include allergy, current use of opioids, acute opioid withdrawal (as evidenced by urine drug screen, patient self-report or having withdrawal symptoms when given a naloxone challenge), or severe hepatic impairment. It is not recommended for patients who are pregnant. Common side effects include injection site pain, insomnia and elevated liver enzymes. Liver function tests should be monitored at baseline, six and 12 months during treatment.

Dosing Guidelines

When performing an induction of XR-NTX, physicians must ensure patients are abstinent for at least seven to 10 days (possibly longer for long-acting opioids) and can consider use of "naloxone challenge" where 0.8 mg naloxone is injected intranasal (IN), intramuscularly (IM), or IV and then the patient monitored for opioid withdrawal. Alternately, naltrexone 25mg is administered on day 1, 50mg on day 2, and if tolerated without symptoms of opioid withdrawal, patients receive XR-NTX dosed at 380mg IM q4weeks.

Patients are vulnerable to opioid overdose and death after taking XR-NTX, as their tolerance is significantly diminished. Patients should be counseled about this risk and given a naloxone kit. If a patient requires emergency pain treatment, regional anesthesia and non-opioid analgesics can be used as alternatives. If they require opioids, they will require a high dose and potentially continuous monitoring in a hospital ICU setting.[12]

Duration of Treatment

Patients can receive medications for OUD for varying periods of time. It is established that discontinuation of medication leads to relapse and short-term treatment is generally not recommended.[9] Rather, the preferred treatment approach is maintenance therapy, meaning that the patient stays on medication for as long as it provides a benefit. Medication for OUD allows patients to have time and ability to focus on their long-term recovery without experiencing withdrawal and minimizing cravings. Their lives can go from thinking short-term ("where and how can I get my next fix?") to thinking long-term (jobs, relationships, other responsibilities).

Medically supervised withdrawal (also known as detoxification) demonstrates poor results, with only 11% being retained in treatment at 14 weeks when on a detox regimen, and 66% retention with maintenance medication, in this case buprenorphine.[30] Detox patients are also at higher risk for overdose likely due to reduction in tolerance from a short period of sobriety. During a two-year follow up after discharge from a detoxification program, over a quarter of the patients reported a non-fatal overdose.[31] There should be no pre-determined duration of treatment with medications for OUD; rather we should approach OUD as a chronic disease with a chronic care model of treatment that we might use for diabetes or hypertension.

Conclusion

This article outlines key concepts for prescribers of MAT, with the intention of more and more physicians prescribing MAT in order to adequately combat the opioid epidemic. Opioid addiction is chronic and debilitating and can affect anybody including our fellow physicians. Most importantly, it is treatable and our available treatment options are effective and well-tolerated.

We end with a cautionary word that is the opinion of these writers. The need for expanding MAT in the treatment of OUD must be balanced with the need for holistic treatment for OUD. Addiction is complex and requires more than just writing a prescription. On the contrary, for many patients this problem started with a physician and a prescription pad, and we ought to be careful not to repeat that history. Physicians should prescribe responsibly and hold their patients accountable. We should take time to discuss psychosocial issues with our patients and utilize motivational interviewing. We should not enable addiction; we should promote recovery.

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The Benefits of Omega-3 Fats for Stabilizing and Remodeling Atherosclerosis

by James J. DiNicolantonio, PharmD & James H. O'Keefe, MD

Vulnerability of the plaque to rupture, rather than the degree of atherosclerosis, is the primary determinant of thrombosis-mediated acute cardiovascular events.[1]

-Cawood AL and colleagues 2010





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Abstract

The majority of acute coronary syndromes are caused by the rupture of plaques rendered vulnerable by oxidized lipids, inflammation, and a thin fibrous cap with reduced collagen and smooth muscle cell content.[2] Thus, stabilizing and reversing vulnerable atherosclerotic plaques can help to prevent cardiovascular events. In this regard, long-chain omega-3 fatty acids have a plethora of data for stabilizing vulnerable atherosclerotic plaques as well as reversing atherosclerosis. This review paper will summarize the observational data as well as animal and human studies supporting such a role and further discuss the current controversies around omega-3 supplementation.

Mechanistic Data

Dietary omega-3s, from fatty fish such as salmon, herring, and sardines, are not only building blocks of cellular membranes but are also precursors to eicosanoids or signaling molecules in the body. Whereas the metabolites from omega-6 are generally pro-inflammatory (such as thromboxanes, 2-series prostaglandins and 4-series leukotrienes), the metabolites from marine omega-3s are generally anti-inflammatory. Additionally, several benefits have been noted with marine omega-3 consumption, including reductions in triglycerides, lowered heart rate and blood pressure, improved left ventricular ejection fraction, reduced inflammatory cytokines, anti-thrombotic and anti-arrhythmic effects.[3]

Observational data

The observational data indicate that long-chain omega-3s play an important role in stabilizing atherosclerosis and reducing the risk of cardiovascular events. Indeed, patients with acute coronary syndrome have been documented to have significantly lower serum levels of eicosapentaenoic acid (EPA) and the elongated metabolite of EPA, docosapentaenoic acid (DPA), compared to those without.[4] Low levels of omega-3s in blood, including EPA, DPA, and docosahexaenoic acid (DHA), are also associated with lipid-rich, less fibrous plaques, which are at an increased risk of rupturing.

Low levels of DHA in heart tissue is associated with increased mortality in those who have died from both cardiac and non-cardiac causes.[5] Moreover, patents who have died from sudden cardiac death also have lower levels of omega-3 polyunsaturated fatty acids in their coronary arteries versus patients who have mainly died from traffic accidents.[6] This suggests that eating more long-chain omega-3s may reduce the risk of death from both cardiac and non-cardiac causes.

Table 1: Possible mechanisms for the atherosclerotic plaque stabilizing and remodeling effects of EPA/DHA[3, 25]

- A reduction in adhesion molecule expression on endothelial cells, monocytes, and macrophages
- A reduction in adhesion molecule expression on endothelial cells, monocytes, and macrophages
- A reduction in chemo-attractants (leukotriene B4, platelet-derived growth factor and monocyte chemoattractant protein-1) and matrix metalloproteinases (MMPs)
- A reduction in macrophage number in atherosclerotic plaques
- A reduction in small-dense LDL, triglycerides and inflammationt

Higher dietary intake, as well as increased blood levels of alpha-linolenic acid (ALA), EPA, and DHA are associated with a reduced carotid intimal-medial thickness (CIMT), a lower prevalence of atherosclerotic plaque, and less atherosclerotic plaque progression.[7-10] One study in 487 elderly men found that higher plasma phospholipid EPA was associated with less carotid and femoral intima-media thickness.[11] In a study of 1,920 Japanese patients, higher intakes of long-chain omega-3s (EPA, DHA, and DPA) were significantly and inversely related to CIMT.[8] Additionally, a randomized trial in patients with type 2 diabetes found that supplementation with 1,800 mg of EPA per day significantly decreased CIMT and improved brachial-ankle pulse wave velocity suggesting a reduction in atherosclerosis and improved endothelial function.[12]

Animal Studies

The fat-1 transgenic mouse model, which converts omega-6 to omega-3 producing an omega-6/3 ratio of around 1:1 in tissues and organs, reduces atherosclerotic lesions by inhibiting systemic and vascular inflammation.[13] This is one of the best ways to test the "omega-6/3 hypothesis" of heart disease whereby genetically lowering the omega-6/3 ratio reduces atherosclerosis. Moreover, supplementing mice with EPA reduces aortic atherosclerosis, macrophage infiltration, and matrix metalloproteinases-2 (MMP-2) and MMP-9 mRNA in aortic lesions and increases plaque stability via increased collagen and smooth muscle content.[14] However, the shortcomings of these studies include being in mice, being underpowered, and the genetic background of these mice (APOE-/-). DHA is also hypothesized to inhibit MMP-9 release from human macrophages partially explaining its plaque stabilizing benefits.[15] DHA also reduces NADPH oxidase activity and most, if not all, of the benefits of long-chain omega-3s for reduced inflammatory genes are a result of their inhibition of nuclear factor-kappa beta (NF-kB).[15]

In a mouse model of hyperlipidemia, compared to no EPA supplementation, a diet containing 5% EPA for 13 weeks significantly reduced atherosclerotic lesion formation.[14] Staining of the aorta revealed that EPA not only suppressed atherosclerotic lesion development but also stabilized atherosclerotic plaque by causing an increase in collagen and smooth muscle cells content with less macrophage infiltration. The authors concluded, "EPA may potentially reduce and stabilize atherosclerotic lesions through its anti-inflammatory effects...The atherosclerotic plaques of EPA-treated mice displayed a stabilized morphology that was characterized by less lipid deposition, decreased accumulation of macrophages, more smooth muscle cells, and increased collagen content. EPA also suppressed the expression of adhesion molecules and MCP-1 by endothelial cells and the production of MMPs by macrophages in a PPARalpha-dependent manner."[14]

The ability of fish oil to reduce the formation of atherosclerosis by reducing oxidative stress has also been confirmed by others.[16, 17] In fact, mice fed fish oil, as compared to corn oil, have a significant reduction in atherosclerotic plaque formation possibly due to an increase in antioxidant enzyme activity.[17] In summary, fish oil may reduce atherosclerosis by activating numerous nuclear receptors including PPAR-alpha and PPAR-gamma, by inhibiting the infiltration of macrophages and as the release of MMPs, and by preventing the weakening and rupturing of atherosclerotic plaque.[14,18]

Human Studies

In 30 untreated dyslipidemic patients, supplementation of EPA at 1.8 grams per day on top of rosuvastatin (titrated to achieve an LDL-C < 70 mg/dL) for nine months increased fibrous cap thickness and reduced macrophage accumulation in atherosclerotic plaques versus those on statin therapy alone.[19] The authors concluded, "The concomitant use of EPA and rosuvastatin may stabilize vulnerable plaques better than the statin alone, possibly by suppressing arterial inflammation."[19] In a randomized controlled trial in 193 coronary heart disease patients

who underwent percutaneous coronary intervention the combination of EPA plus high-dose pitavastatin lead to a greater reduction in total atheroma volume compared to pitavastatin alone.[20] Plaque stabilization was also reinforced with the addition of EPA to pitavastatin especially in those with stable angina. The authors concluded, "The addition of EPA is a promising option to reduce residual CHD risk under intensive statin therapy."[20]

In another randomized controlled trial this time in 121 patients awaiting carotid endarterectomy, those who received ~1.5 grams of EPA/DHA for a mean of 21 days prior to surgery had significantly fewer foam cells in their carotid plaque ($p=0.039$).[1] This was thought to be due to the incorporation of EPA into the atherosclerotic plaque phospholipids suppressing inflammation. Indeed, plaques with higher EPA incorporation had less plaque instability ($p=0.0209$), plaque inflammation ($p=0.0108$), number of T cells in plaque ($p=0.0097$) and an overall lower plaque score ($p=0.0425$). More importantly, plaques from patients who supplemented with fish oil had significantly less mRNA for matrix metalloproteinases (MMP)-7 ($p=0.0055$), MMP-9 ($p=0.0048$) and MMP-12 ($p=0.0044$), again which are thought to cause plaque rupture.[21-23] Interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1) were also significantly lower in plaques ($p=0.0395$ and $p=0.0142$, respectively) in those who supplemented with long-chain omega-3s suggesting reduced inflammation and increased plaque stability due to their incorporation into atherosclerotic plaques.[24-26] Thus, the more EPA in atherosclerotic plaques, the less inflamed and the more stable the plaques.

In a randomized, investigator-blinded trial, 7 grams of omega-3 fatty acids (EPA 41.4%, DHA 23.6%, providing a total of 4.55 grams of EPA/DHA) reduced platelet-derived growth factor (PDGF)-A and PDGF-B mRNA as well as monocyte chemo-attractant protein-1 (MCP-1) mRNA steady state levels in unstimulated and adherence-activated human mononuclear cells (MNCs).[27] These benefits were not found with omega-6 or omega-9 fatty acids. This demonstrates that omega-3 fatty acids can modulate inflammatory gene expression. MCP-1 induces monocyte activation and attraction and both MCP-1 and PDGF are thought to promote atherosclerosis. Omega-6 PUFA via corn oil (providing LA 50.1%, 12.9% saturated fats) tended to increase PDGF-A and MCP-1 (although not significantly).[27]

In one trial, 188 patients awaiting carotid endarterectomy were randomized to either sunflower oil (providing 3.6 grams of linoleic acid), fish oil or control until surgery with a median duration of treatment being 42 days. Compared to control and sunflower oil, EPA/DHA decreased the prevalence of thin fibrous caps, increased thick fibrous caps, reduced signs of inflammation and reduced the number of macrophages within plaques. The authors concluded, "Atherosclerotic plaques readily incorporate omega-3 PUFAs from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of omega-6 PUFAs does not affect carotid plaque fatty-acid composition or stability [...]"[25] Interestingly, there was numerically more thin fibrous cap atheroma (29.6% vs. 22.8%), less thick fibrous cap atheroma (53.7% vs. 56.1%) and a greater percentage of plaque rupture (5.6% vs. 3.5%) in the sunflower oil group vs. control, respectively. Although none of these differences were significant the numerical trend for worse plaque morphology with the intake of omega-6 PUFA is concerning. Additionally, what is generally considered stable plaque (calcified nodules and fibrocalcific plaque) tended to be lower in the sunflower group compared to the control group (1.9% vs. 10.5%, $p=0.06$). Some of the possible mechanisms for the ability of EPA/DHA to reduce and stabilize atherosclerotic plaque include are summarized in Table 1.

Clinical Studies Testing Hard Endpoints

Negative Trials

There have been several negative trials testing marine omega-3s, which has caused a recent controversy with omega-3 supplementation. Our group has published several papers discussing potential reasons why these trials have not been successful.[3, 28-30] Table 2 is a summary of those trials and reasons why they likely did not show benefit.

Positive Trials

In the REDUCE-IT study, which randomized 8,179 patients with established cardiovascular disease or diabetes with hypertriglyceridemia with other risk factors to 4 grams of Vascepa (icosapent ethyl) and followed them for 4.9 years.[31] There was a significant 25% reduction in the primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) in those who were supplemented with 4 grams or Vascepa. High dose marine omega-3s also reduced major adverse cardiovascular events (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) by 26%. Again, these benefits were noted on top of statin therapy (> 99% of participants were on statin therapy).[31]

Table 2. Recent Fish Oil Trial Failures and Reasons Explaining Their Failure[3, 28-30]

Study	Population	Potential reasons for failure
OMEGA	3,851 patients with a history of acute MI	Used a low dose of omega-3 (1 gram), short duration (1 year), inappropriate use of olive oil as a placebo, high baseline intake of fish, unexpected low rate of sudden cardiac death and use of aggressive background medical treatment and the study lacked power to show benefit.
Alpha Omega	4,837 patients with a history of MI	Patients were already receiving antihypertensive, anti-thrombotic, and lipid-modifying therapies.
SU.FOL.OM3 trial		Low dose of omega-3 used (380 mg of EPA/DHA). Small power to detect any positive effect of omega-3s, low major vascular cardiovascular disease events were 15% lower than initially expected, insufficient duration and follow-up. Average time to start omega-3s from cardiovascular event was 101 days compared to 16 days in GISSI-P. Higher use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers at baseline in the placebo vs. the omega-3 group. Higher number of patents with a history of myocardial infarction and current smoker status in the omega-3 group compared to placebo.
ORIGIN	11,119 patients with high risk of cardiovascular disease and impaired glucose tolerance or diabetes	Low dose of omega-3 (1 gram/day) used and high background intake of omega-3 fatty acids in study participants.

A prospective, open-label, blinded endpoint-randomized trial in 241 patients with acute coronary syndrome found that adding 1,800 mg of EPA to pitavastatin 2 mg/day cut the primary endpoint by more than half compared to those given pitavastatin alone (9.2% vs. 20.2%, p=0.02) with a significant reduction in cardiovascular death (0.8% vs. 4.2%, p=0.04).[32] Another prospective, open-label, blinded endpoint, randomized trial in 115 patients with acute myocardial infarction, EPA at 1.8 grams per day given within 24 hours after percutaneous coronary intervention (PCI) significantly reduced (by over 50%) the combined occurrence of cardiac death, stroke, reinfarction, ventricular arrhythmias, or paroxysmal atrial fibrillation at 1-month compared to those not receiving EPA (10.5% vs. 29.3%, p=0.01).[33] Thus, the atherosclerosis plaque stabilizing effects of marine omega-3s also translates into significant reductions in hard endpoints if given soon after an acute coronary syndrome.

Other studies that have found benefit with marine omega-3s include GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial) and JELIS (the Japan EPA Lipid Intervention Study). GISSI-P was likely successful for several reasons including providing omega-3s early after acute myocardial infarction (average 16 days) as well as being in an Italian population with a notoriously lower background intake of omega-6 compared to the United States.[34] JELIS was likely positive because it used a higher dose of omega-3s (1.8 grams of EPA) and again was in a population with a lower intake of omega-6 versus the United States.[34]

It is important to note that the composition of polyunsaturated fats in the body is not only determined by dietary intake but also metabolism which is controlled by genetic polymorphisms. For example, delta-5 and delta-6 desaturases, otherwise known as FADS1 and FADS2, respectively, influence blood and phospholipid concentrations of omega-6 and omega-3 as they affect the elongation of these fatty acids. Thus, genetics may also play a role in determining the effects of dietary omega-3 intake.[35]

In summary, it is plaque vulnerability, not the degree luminal stenosis, that is the major determinant of the risk of atherothrombotic events.[21] The overall evidence suggests that supplementation with long-chain omega-3s reduces, and can positively remodel, atherosclerotic plaque formation. The totality of evidence also suggests that supplementing high-risk patients with EPA/DHA, either early after an acute coronary syndrome, or using a high dose (4 grams of EPA), reduces the risk of coronary heart disease events and/or coronary heart disease mortality.[3]

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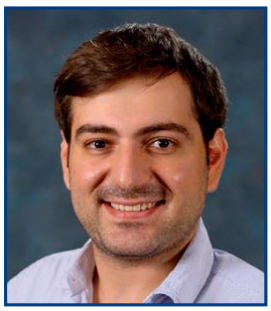
Disclosure

JJD is author of The Salt Fix, Superfuel, and The Longevity Solution. JHO is Chief Medical Officer and Founder of CardioTabs, a nutraceutical company, and has a major ownership interest in the company. The company, CardioTabs, sells products that contain Omega-3. **MM**

Spontaneous Coronary Artery Dissection in a Liver Transplantation Candidate

by Zachary Oman, DO, Nauman Khalid, MD, Ihab Hassanieh, MD, Michael Lim, MD & Tarek Helmy, MD

Spontaneous coronary artery dissection is becoming an increasingly well recognized etiology of myocardial infarction.



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Abstract

Spontaneous coronary artery dissection (SCAD) is an uncommon and potentially fatal cause of acute coronary syndrome, myocardial infarction, and sudden death primarily affecting women. While the exact cause of SCAD is unknown, associated risk factors are emotional or physical stress, female gender, pregnancy-related factors including hormonal changes, fibromuscular dysplasia, mixed connective tissue disorders, and inflammatory disorders. In this report, we present a middle-aged female with ulcerative colitis and cirrhosis secondary to primary sclerosing cholangitis who was found to have SCAD on cardiac evaluation for liver transplantation workup.

Introduction

Spontaneous coronary artery dissection (SCAD) is becoming an increasingly well recognized etiology of myocardial infarction. While SCAD is a heterogeneous disease, it primarily affects women ages 40-65 years-old presenting with acute coronary syndrome (ACS).[1] Currently there are no established guidelines for the management of SCAD; however, expert consensus is conservative therapy if there are no urgent indications for revascularization such as hemodynamic compromise or impending cardiovascular collapse.[2,3]

Case Presentation

A 64-year-old woman with cirrhosis, secondary to primary sclerosing cholangitis, and ulcerative colitis underwent dobutamine stress test for liver transplant evaluation which was positive for moderate hypokinesis of the left ventricular apex at rest and with peak dobutamine. She was referred for coronary angiography which revealed a spontaneous coronary artery dissection (SCAD) of the left anterior descending artery (LAD) (Image 1). A Fractional Flow Reserve (FFR) wire was successfully advanced past the true lumen of the LAD with a resting intracoronary pressure gradient of 0.69. Given her need for liver transplantation, the decision was made after discussion with the transplant team to perform percutaneous coronary intervention (PCI). A second wire was advanced down the large first diagonal branch (D1). After pre-dilation of the mid-LAD, she developed another dissection of the proximal-LAD extending down the D1 with distal occlusion of the flow (Image 2). 2.5 mm x 38 mm Synergy and 2.5 mm x 12 mm Synergy drug eluting stents (DES) were placed in the mid-LAD along with a 2.5 mm x 24 mm Synergy DES in distal D1 restoring flow. At the bifurcation of the mid-LAD and D1, double kissing stents were placed with a 3.0 mm x 20 mm Synergy DES in the proximal D1 abutting a 2.25 mm x 16 mm Synergy DES in mid-LAD (Image 3). Following this, there was a thrombotic occlusion of the distal D1 (Image 4) despite effective anticoagulation with

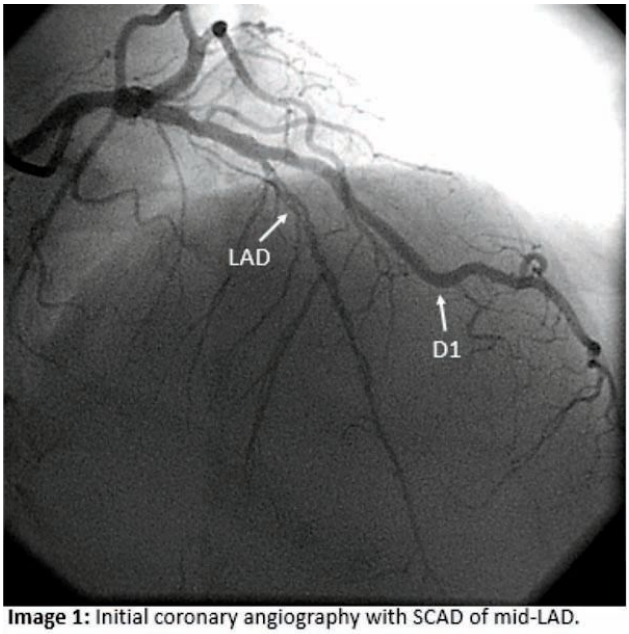


Image 1: Initial coronary angiography with SCAD of mid-LAD. SCAD: spontaneous coronary artery dissection, LAD: left anterior descending artery, D1: diagonal artery.

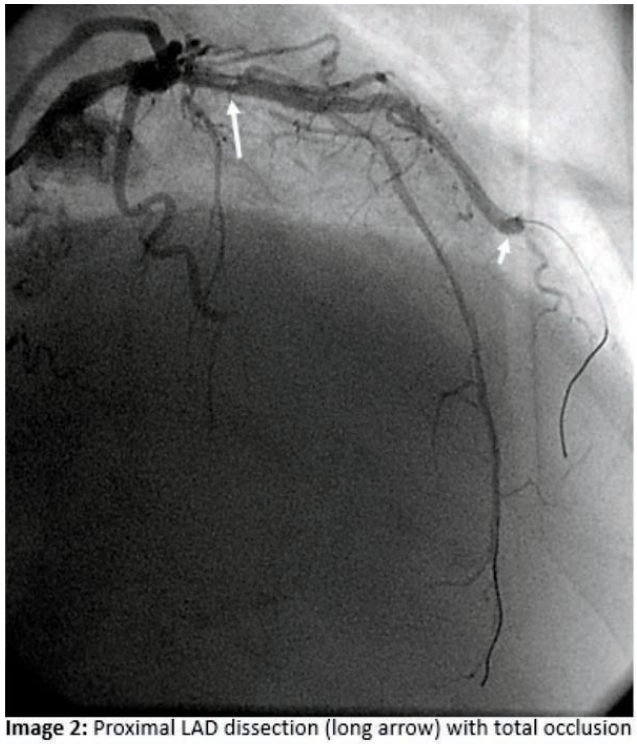


Image 2: Proximal LAD dissection (long arrow) with total occlusion of D1 (short arrow) after pre-dilation of mid-LAD. LAD: left anterior descending artery.

an activated clotting time of greater than 250-seconds. Intracoronary abciximab was given; however, she quickly lost contractile blood pressure requiring hemodynamic support with vasopressors and percutaneous left ventricular assist device (Impella CP). She was transferred to the cardiac intensive care unit where the hemodynamic support was weaned off after four days and she was eventually discharged home.

Discussion

SCAD is a rare entity which is becoming more recognized with growing awareness. The pathophysiology of SCAD has been described as the development of intramural hematoma (IMH) within the tunica media of the coronary artery with or without intimal disruption creating a false lumen and external compression of the true lumen leading to distal cardiac ischemia.[2,3] Currently there are three varying types of SCAD lesions; type 1 lesions appear to have contrast staining of the arterial wall with multiple radiolucent lumens, type 2 lesions are longer with more diffuse stenosis (usually >20 mm) of varying severity and are often missed angiographically secondary to subtle changes in arterial caliber, and type 3 lesions mimic atherosclerotic lesions with focal or tubular stenosis.[2,3,4]

In patients who present with SCAD, the diagnosis of ACS is often missed as most patients have no or only a few traditional cardiovascular risk factors.[1] While SCAD affects both men and women, up to 90-94% of SCAD presentations have been described in women[1] and has often been associated with pregnancy or postpartum state.[5,6] Current literature supports multiple risk factors including fibromuscular dysplasia, mixed connective tissue disorders (Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome) and systemic inflammatory disorders (systemic lupus erythematosus, inflammatory bowel disease, polyarteritis nodosa, sarcoidosis, celiac disease, cryoglobulinemia in setting of hepatitis C infection) albeit the correlation between systemic inflammatory conditions and SCAD is not well understood.[1,2,3]

Our patient was a 64-year-old asymptomatic postmenopausal female who underwent elective coronary angiography for further liver transplant candidacy evaluation which revealed SCAD of her mid-LAD. Consider the asymptomatic presentation of this chronic SCAD, conservative management and repeat angiography would have yielded similar results. Additionally, because our patient was in need of liver transplantation, the decision was made with the transplant team to perform PCI. We suspect that her SCAD was related to her gender, possibly to her ulcerative colitis, and to increased levels of estradiol secondary to her cirrhosis.[7] The thrombotic occlusion of her distal D1 stent despite effective anticoagulation was largely due to her prothrombotic milieu from her underlying liver disease.

While there are no exact treatment guidelines, the consensus has been conservative therapy unless there is hemodynamically instability or high risk of developing cardiovascular collapse with prolonged inpatient

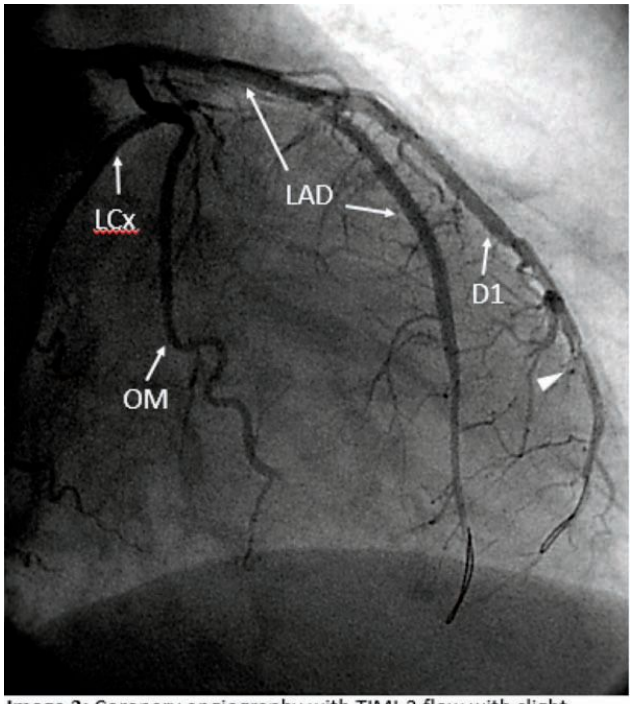


Image 3: Coronary angiography with TIMI-3 flow with slight thrombus formation (triangle) in distal-D1 after DES placement in LAD and D1. LAD: left anterior descending artery, D1: diagonal artery, LCx: left circumflex artery, OM: obtuse marginal artery.

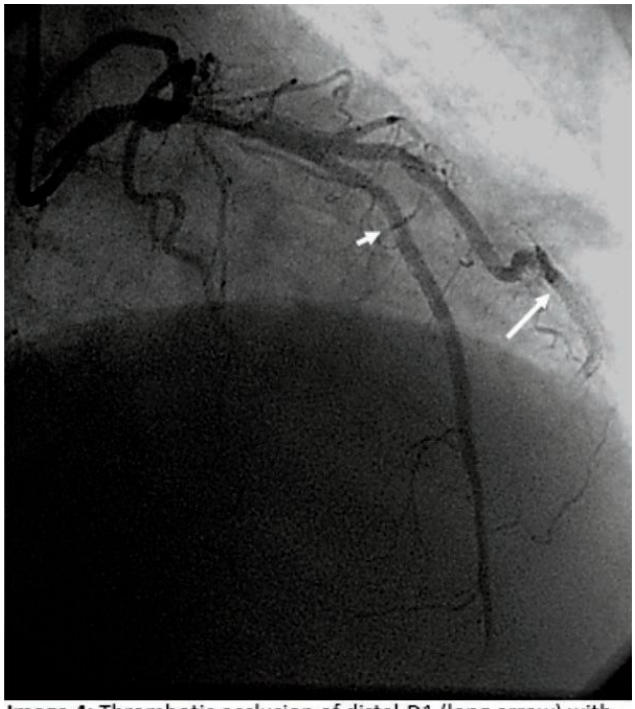


Image 4: Thrombotic occlusion of distal-D1 (long arrow) with patent LAD (short arrow). D1: diagonal artery, LAD: left anterior descending artery.

hospitalization and follow up angiography.[2,3,8] The use of anticoagulant and antiplatelet medication is controversial as the underlying pathophysiology of SCAD is intramural hematoma. Available data suggest that anticoagulation should be limited to the acute setting, dual antiplatelet therapy should be used if PCI is performed in accordance with the current ACS guidelines, and thrombolytic therapy is contraindicated as it has been associated with propagation of dissection and coronary perforation leading to cardiac tamponade[2]. There is no data to support the use of glycoprotein IIb/IIIa inhibitors.[3] Long-term cardiovascular outcome data has found a reduced risk of recurrent SCAD with effective blood pressure control and beta-blocker therapy.[9]

When PCI is considered, data has shown that the femoral, when compared to radial, approach is associated with fewer complications and that a variety of PCI strategies have been utilized with no single technique superior than the other.[2,3] Coronary artery bypass grafting (CABG) have also shown poor outcomes with high rates of both venous and arterial conduit failure.[2,3]

Conclusion

This case highlights the challenging management of SCAD in a patient with advanced liver disease. Given her need for liver transplantation, PCI was performed which unfortunately led to propagation of dissection requiring treatment with DES complicated by acute stent thrombosis (despite therapeutic anticoagulation) and cardiovascular collapse necessitating mechanical circulatory support.

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Disclosure

None reported.

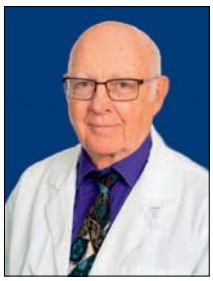
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Atropine Eye Drops Inappropriately Used for Diplopia Following Cosmetic Botulinum A Toxin Injections

by John C. Hagan III, MD

FIRST LITERATURE REPORT

The use of atropine eye drops for treating double vision caused by lateral rectus palsy subsequent to botulinum A toxin injections as described in this case report is inappropriate and puzzling.



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Abstract

This is a first case report of atropine eye drops used inappropriately to treat diplopia that followed botulinum A toxin injections for a cosmetic indication. Also presented is a review of precautions on use of atropine eye drops by non-ophthalmic physicians.

Introduction

Botulinum A toxin (onabotulinumtoxinA) injection is the most common cosmetic procedure performed on U.S. adults.[1] Botulinum A toxin has an expanding number of promising therapeutic applications, especially migraine management.[2] Atropine eye drops, usually 1% or 0.5%, (Figure 1) is a potent drug used since the 1800s, mostly by ophthalmologists, for ocular diagnosis and therapy. Recent uses include dilute 0.01% atropine for slowing myopia progression.[3]

This is a first case report of atropine eye drops used inappropriately to treat diplopia that followed botulinum A toxin injections for a cosmetic indication. Also presented is a review of precautions on use of atropine eye drops by non-ophthalmic physicians.

Case Report

In June 2019, a 46-year-old self-referred female consulted the author for complaints of recent double vision, inability to read and fixed dilated pupils. She stated she had received bilateral botulinum A toxin injections for mild radiating aging skin lines at the lateral canthus ('crow's feet'). The spa-type clinic where she was treated is physician-directed but she was injected by a nurse. The physicians there are not ophthalmologists, ENT, dermatologists, or plastic surgeons, specialties usually trained in these types of injections. Four to five days after the first set of injections, she noted double vision. The diplopia was worse at distance than at near; worse in lateral gaze. She returned to the treating clinic. After telling them of her diplopia and having an examination, atropine eye drops were instilled in both eyes. The purpose of the drops was not explained to her. Within an hour after receiving the drops she noted her pupils were nonreactive, large and she could not read. At this point she made an urgent same day appointment with the author.

On examination her corrected distance vision was 20/20 with glasses, but her near vision was 20/80 near equivalent. Abnormal findings included underaction of both lateral recti, no ptosis, nonreactive 5 millimeter pupils in both eyes. The remainder of the eye examination was normal. During the exam, phone calls were placed to the treating clinic. The author's staff was told that a physician

there had directed atropine eye drops be instilled in both eyes after the patient returned with complaints of diplopia. With this additional confirmatory history, diagnoses of botulinum A toxin injection caused paresis of both lateral recti and subsequent iatrogenic mydriasis and paralysis of accommodation due to inappropriate atropine eye drop instillation were made. The patient was told that the double vision might take several months to clear. The dilated pupil and trouble reading might require weeks to over a month to wear off. The patient was given a time limited work excuse and warned about driving. She was told to return if her symptoms did not clear in the time outlined or other complications developed.

Subsequent calls were made by the author to the treating clinic office manager and the clinic's physician medical director. Both refused to identify the physician ordering the atropine eye drops, or the reason for their installation or even why atropine eye drops were kept in their office. The patient's double vision and dilated pupil gradually cleared over the following two months and she made a complete recovery.



Figure 1. Atropine eye drops have a red top and can keep a pupil dilated for over a month.
Source: Alcon

Discussion

Since the days of ancient Greece and Rome it has been known that plants containing atropine (Atropa belladonna 'deadly nightshade,' jimson weed, mandrake) were toxic poisons[4] (Figure 2). Pure atropine was synthesized in the 1830s. Once widely available, atropine caused a large number of deaths by accident, suicide, and homicide.[5] Publication of iatrogenic morbidity or mortality from instillation of atropine eye drops were reported in medical journals as early as 1903[6] and continue to the present day.[7]



Figure 2. Attractive but deadly! Atropa belladonna extracts have been used for deadly poisons, medications, and highly diluted to cosmetically enlarge the pupil. *Source: Wikipedia*

Atropine is an anti-cholinergic drug and, in eye drop form, a powerful, long acting pupil dilator (mydriatic) and paralyses the ability of the ciliary body to focus (cycloplegic) (Figure 3). Atropine eye drop effects may last several weeks in a dark brown iris and over a month in a light-colored blue iris. There are no eye drops, including pupil constrictors (miotic), that neutralize atropine in the eye. Intravenous physostigmine is used to reverse systemic overdose, usually from atropine taken by mouth to reduce oral secretions or by accident or intention.[8] Eye drops that dilate the pupil by convention have bottles with red caps to help prevent accidental installation.

Atropine eye drops are not normally stocked in non-ophthalmic physicians' offices. In the author's ophthalmology office, atropine is kept apart from other short acting mydriatics and black tape applied to the red lid. Installation of atropine eye drops should ideally only be done after an ophthalmologist has examined the eyes to determine an indication for use and/or identify a contraindication. Atropine eye drops can cause potentially blinding acute angle closure glaucoma especially in hyperopes and Asians. A biomicroscope examination, plus in some cases gonioscopy, is needed



Figure 3. In eyes with narrow angles atropine can cause acute angle closure and loss of eye. Physicians should consult an ophthalmologist before using or prescribing atropine or other mydriatics to the eye. *Source: Wikipedia.com by Nutschig*

to determine if the cornea-iris filtration angle is occludable.

Diplopia due to lateral rectus palsy from botulinum A toxin injection was first described in 2007 in a patient with facial spasms. [9] She recovered completely a month after injection. Diplopia due to botulinum toxin injection of the lower lids causing inferior oblique palsy has also been reported.[10] Ptosis of the upper eyelids following botulinum toxin injection is reported and sometimes improved by the use of apraclonidine eyedrops.[11] Neither apraclonidine or any other eye drops have been reported to be useful for botulinum A toxin caused diplopia. Ocular muscle paresis or eyelid ptosis can be due to improper injection technique, excessive volume of injectant, unusual anatomy or idiosyncratic hypersensitivity to injectant. The incidence of these complications decreases with increased skill and experience of the person doing the botulinum A toxin injections. Given the frequency of botulinum A toxin injections, diplopia is an uncommonly observed complication of cosmetic treatment.

The use of atropine eye drops for treating double vision caused by lateral rectus palsy subsequent to botulinum A toxin injections as described in this case report is inappropriate and puzzling. There are no physiological mechanisms or scientific literature to support atropine use. Perhaps the physicians treating this case confused atropine with apraclonidine and the appropriate indication of ptosis with the inappropriate indication of diplopia.[6] The treating physicians refused to discuss their rationale so this remains speculative.

Conclusion

Atropine eye drops have no role in the treatment of botulinum A toxin complications. Physicians considering using atropine eye drops to the eye should seek ophthalmological consultation before using or prescribing.

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Disclosure

None reported.

MM

“Fascinating.

That’s how Samantha Lund, describes her education at Washington University School of Medicine in St. Louis.

“Medical school is never boring,” says the third-year student, an MSMA member since 2017, “and I’m always excited to see what comes next.”

Lund, a native of the St. Louis area, attended Tufts University in Boston, Mass., where she was a double major, earning bachelor’s degrees in International Relations with an emphasis on global health and in Community Health.



Her path to medical school took an unconventional turn – a three-year detour, actually – as she debated how to best utilize her degree and passion for helping others.

“I came to the conclusion that, to have the most impact on individuals, (I needed) go to medical school to become a doctor,” Lund says.

She’s enjoyed the educational opportunities that each of her first two years of medical school provided. As an M3, she’s excited about more clinical time and patient contact.

“I’m really enjoying getting to interact with patients and to see what medicine is actually like,” Lund says.

It was important for her to become a member of the AMA and MSMA because, through those organizations, physicians can have a significant impact on public health. That was something her father, Herluf Lund, MD, a cosmetic surgeon and MSMA member since 1991, modeled for her.

“With my public health background and interest, (I wanted to know) how physicians can have an impact on the health of their patients,” adds Lund, MSMA’s student alternate delegate to the AMA. “A lot of that is in the individual rooms, when you’re talking with folks, but a lot of it is in these big policy decisions.

“One of the best ways to address these problems is to be active, go to Jefferson City or show up in Washington, D.C. Organized medicine … whether it’s SLMMS, MSMA or the AMA, that’s how we can have an impact.”

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