Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine November/December 2022



A NEW PARADIGM IN KILLING

America is Losing Its Most Deadly War The Carnage of Poisoned Pills



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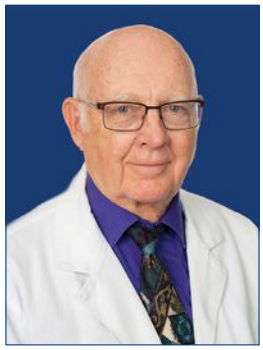
A NEW PARADIGM IN KILLING

America is Losing Its Most Deadly War: The Carnage of Poisoned Pills

by John C. Hagan, III, MD

Without effective abatement, a million total fentanyl deaths loom ahead.

In 2021, more Americans were killed by fentanyl–laced pills and other addictive drugs than in all the wars the United States has fought since the end of World War II. In 2021, there were 108,000 fake–drug deaths, more than twice as many as automobile, gunshot, or suicide deaths (Figure 1). Ultra–lethal, easily formulated fentanyl accounted for 80% of the deaths. The remainder of these tragic demises came from abuse or misdirection of pharma/non–pharma products e.g., opioids, methamphetamines (meth), and cocaine. The year 2022 will assuredly surpass this grim harvest of death. There are no local, state, or national government strategies to abate the carnage. For the most part this federal governmental failure is 'off message' and ignored by the media.



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

Most poison pills are non–pharma produced but intentionally fabricated to look like the real thing. Most of these highly addicting faux medications are admixed with deadly fentanyl. Recently and terrifyingly, fentanyl pills are colored to appeal to younger users (Headline image). Children have been killed believing the fentanyl tablets were candy.

Other common addictives also include pharma/illegal drug lab–produced heroin, meth, cocaine, methadone, and others. These drugs are sold illicitly, but blatantly, on the streets and in 'trap houses.' Addicting drugs are readily available on the internet and dark web. Sometimes, the deadly product is conveniently delivered to the user's residence. Much of so called 'gun violence' and most of homelessness is related to drug trafficking.

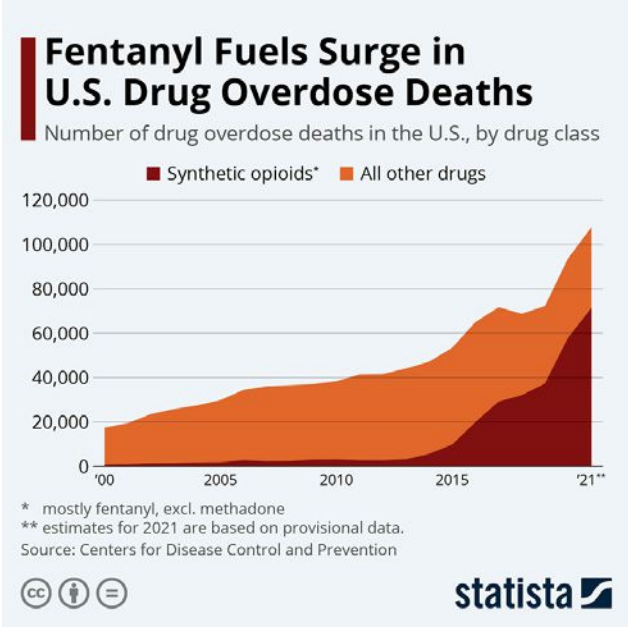


Figure 1. Fentanyl U.S. Drug Overdose Deaths

Three tsunamis of overdose deaths have swept across America[1,2,3,4] (Figure 2). In the late 90s, the first opioid death wave was iatrogenic, perpetrated by segments of pharma and shilling by their highly remunerated 'pain experts; foremost among many, Russell Portenoy, MD.[5] A decade later, as deceived physicians belatedly stopped blithely prescribing opioids, their addicted patients frequently turned to illegal, but widely available, heroin. This was the second death wave.

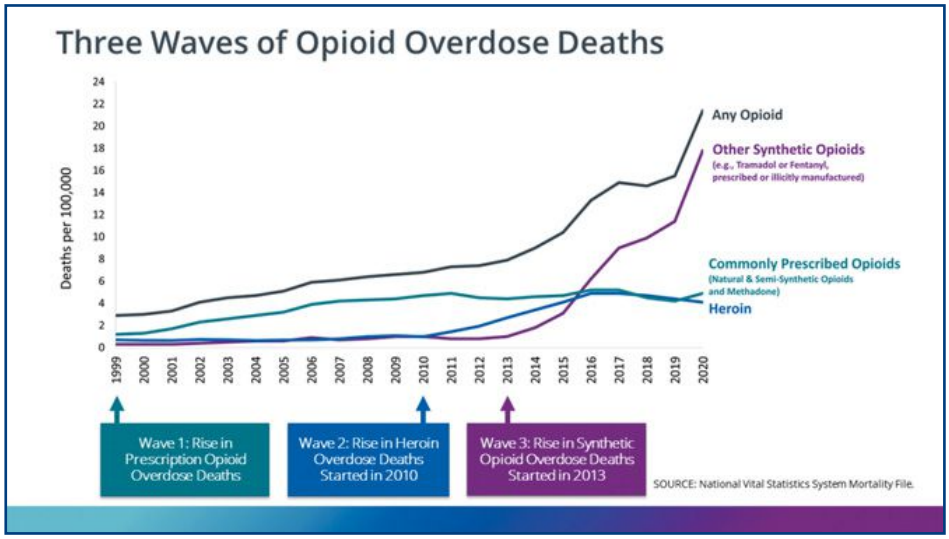


Figure 2. Three Waves of Opioid Overdose Deaths

Heroin production, transportation, and distribution of plant–based, mostly Afghan poppy resin, is lengthy, burdensome, and expensive. Circa 2013, in search of a heroin substitute easy to produce, highly addictive, and profitable, the Mexican crime cartels happened on synthetic fentanyl. We are presently awash in the third and deadliest wave. It is a new paradigm in killing.

With the best of intentions, Paul Janssen, MD, PhD, founder of Jansen Pharmaceutica, created fentanyl in 1959. He was lauded and honored for use of fentanyl as a level IV surgical analgesic 50–100 times more potent than morphine. Fentanyl's highly addictive properties gradually made it a favorite of illegal drug dealers to foist on the burgeoning number of addicts. Cartel fentanyl is often sold as heroin. The first celebrity death of note was Prince in 2016. Scores of celebrities and hundreds of thousands of other unfortunate user deaths followed.

Street fentanyl, made from chemicals manufactured by some 160,000 companies in China, is formulated by innumerable small

and large makeshift laboratories in cartel–controlled areas of Mexico. In a *Wall Street Journal* article on Mexican cartels that rule fentanyl smuggling (August 31, 2022 page 1A), a 25–year–old fentanyl 'cook' started in his home lab, he has made up to one million pills and earned up to $2,500 USD per week! This fentanyl is so abundant and inexpensive it is used as a diluent and high enhancer for many addicting drugs. This is known as 'cutting' and increases the profit along the chain of distribution. Believing it is heroin or a pharma–produced product, users get an unknown and often fatal amount of fentanyl.



Figure 3. Enough fentanyl to kill every person in the United States is smuggled in monthly. Prosecutors and courts consistently fail to prosecute drug dealers whose products kill more than100,000 people per year. Above 2022 example: 'low risk' traffickers no–shows in court after being released by Tulare County judge without bail, found with 150,000 fentanyl pills. (Fresno, California, July 2022)

After nicotine and alcohol, marijuana is the most prevalent addicting substance.[6] With more states like Missouri permitting gateway drugs like sham medical marijuana and high THC recreational marijuana, the fear and stigma of using addicting products is rapidly waning.[7] Deleterious changes in funding law enforcement and wanton failure to criminally prosecute felons greatly compound the already out of control situation[8] (Figure 3). Without effective abatement, a million total fentanyl deaths loom on an ominous horizon.

This issue of *Missouri Medicine* presents superb articles by knowledgeable authors on the two most common addictives in the United States: fentanyl and methamphetamines. In an all–too–common story, Ed and Mary Ternan recount the tragic poison pill death of their son, Charlie. Additionally, they discuss the organization they founded and direct (www.songforcharlie.org) to reduce poison pill deaths of others, especially the gullible, uninformed young.

Know that in a single month enough fentanyl is smuggled into the U.S. to kill every person in our country. Recall the Tylenol poisoning deaths.[9] A terror organization or hostile nation–state could undoubtedly devastate the United States with organized, innovative, surreptitious fentanyl poisoning. An unprecedented, coordinated national effort needs to be quickly implemented to avert apocalypse.

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Just Say KNOW
Fentanyl, Fakery & the New Drug Talk

by Ed & Mary Ternan

When Charlie, my healthy 22–year–old son, died in May 2020, I had heard of fentanyl; I didn't know it was common in street drugs. I soon learned that a bootleg formulation of the potent, deadly opioid was the main ingredient in the fake Percocet that killed my son. Of the 108,000 poison pill deaths in 2021, 80% were due to these realistic looking "fentapills," which are intentionally designed to look like familiar medications, such as Oxycodone and Xanax.



Charlie Ternan (center) died in May 2020 at age 22 after taking one "fentapill," a counterfeit pill made to look like Percocet but containing deadly fentanyl. His parents, authors Ed and Mary Ternan (left and right), established the nonprofit foundation A Song for Charlie to help make parents aware of the dangers posed by counterfeit prescription drugs. Visit www.songforcharlie.org.

When I recount Charlie's death, a common reaction is "Wait. What? Fake pills with fentanyl?" I then explain drug traffickers are intentionally making counterfeit prescription pills and selling them as legitimate medications, often to unsuspecting young people who are seeking to relive stress or otherwise self–medicate. This is no fluke. This is their new business model. Regrettably, it is here to stay.

Since Charlie's death, my wife Mary and I have devoted our time and energy to warning youth and parents about this deadly new risk. We have taken a deep dive into the fentanyl epidemic and related issues, speaking at length to experts in all relevant fields. This is the first time we have published our experience in a peer–reviewed medical journal. We hope physicians and other healthcare professionals will join the effort to flatten the fentanyl poisoning curve.

Essentials of the Fake Pill Death Pandemic

- The drug landscape has changed forever with the emergence of fentanyl, deceptive marketing and social media.
- Counterfeit pills put a new demographic at risk—teens and young adults who are often experimenting or self–medicating.
- Updating our national response takes time. We desperately need to alert kids and parents right now.
- Medical professionals (doctors) are well positioned to educate families.

Seismic Shift: From the Farm to the Lab

The drug landscape has shifted. Back in the day, when drugs were plant–based, we were warned about "getting off on the wrong track" and possibly becoming addicted to booze or coke or, God forbid, heroin. Today, in the age of fentanyl and fakery, the world of street drugs is like a minefield; your next step (or perhaps your first) may be fatal.

The seismic shift started with the migration of drug production from the farm to the lab. For eons, we humans have cultivated and processed plants for their nutritional, medicinal, and euphoric effects. Ultimately, the supply of our intoxicants was subject to the same limitations as our food, like geography, weather, and yield. Not anymore. Synthetic opioids like fentanyl are a mixture of freely available chemical precursors that can easily be produced anywhere, in unimaginable quantity. This is going on 24 hours per day. No sophisticated equipment is required. And what happens when supply of any commodity can rise almost effortlessly to meet demand at any level? The price plummets.

Illicit, street/internet level fentanyl and its many chemical analogues are up to 100 time stronger than morphine and 50 times more potent than heroin. Fentanyl is cheap and potent. The properties equate to enormous profits for drug dealers. Fentanyl is the 'Mother Lode' of drugs and dealers at every level are working it into their product lines.

Synthetic fentanyl is the proverbial better mousetrap. Regrettably, there are new substances in the pipeline, like nitazines, another opioid yet more potent than fentanyl. Of course, this new generation of street drug makers are not PhDs. They are amateurs; keyboard chemists researching compounds online and devising formulations by trial and error. And American drug consumers, many young and unsuspecting, are their lab rats.



Fakery—What You Don't Know Might Kill You

The earthquake of fentanyl was soon followed by a powerful aftershock—fakery. About 2014, profit–driven drug dealers began cutting fentanyl into heroin without telling their customers. Overdose deaths spiked. Since then, thousands of people have died after taking ecstasy, methamphetamine, or cocaine cut or contaminated with fentanyl.

The most despicable use of illicit fentanyl is when drug traffickers use it as the active ingredient in counterfeit prescription pills. The buyers of these products are usually younger, less savvy kids who are experimenting or self–medicating. They go online seeking legitimate medications, which they expect to be consistent, regulated, and safe. They are offered pills that look and feel like those commercial products. But they are fake. Fentanyl and filler—unevenly dosed and often fatal.

The combination of fentanyl and fakery has permanently upended the drug landscape—from a path with warning signs to an unmarked minefield. And we are seeing the deadly results. Previously unaffected groups—experimenting teens, self–medicators, occasional partiers—have been pulled into the danger zone by the deceptive practice of selling drugs laced with fentanyl without the buyer's knowledge or consent. Consequently 77% of drug related deaths among teens ages 14–17 involve fentanyl.

The New Drug Talk—Just Say 'Know'

Mary and I decided early in our journey to take our warning message directly to youths and parents. We partnered with all major social media platforms to target our content to ages 13 to 24 and their caregivers. We have reached over 60 million unique viewers since our campaigns launched in July 2021.

Our online messaging needs a louder voice. We recently commissioned a survey to determine what Gen Z knows about fentanyl. The results hold some promise and present some challenges. Although general awareness of fentanyl is up since 2021 (from 31% to 40%), only 48% have heard about fentanyl in fake prescription pills. We have more work to do.

Physicians and medical workers, this is where you can help. When asked who they trust to provide reliable information about fentanyl, 76% of young Americans ranked healthcare professionals first. You have a unique opportunity to turn the tide of this unprecedented crisis; one–on–one, up close and personal.

COVID serves as an equalizer. As we slowly emerge from the pandemic, mental health issues have become mainstream, less stigmatized. This helps to facilitate conversations about the dangers of self–medication in the age of deadly fentanyl. It makes sense to have the "drug talk" in the context of a public health warning for youth. Acknowledge and honor their stress and anxiety. Tell them they are not alone with these problems. Coach them that relieving stress by self–medicating is no longer an option. As we say, "You can't solve real problems with fake pills."

Our strategy is to engage young people and empower them to protect themselves and their friends. This means taking a "Just Say Know" approach—give them the facts they need to make informed decisions and spread the word among their peers. We have designed the website: www.songforcharlie.org as a resource for "real talk about fake pills." We hope you will join us by amplifying our message in your practice and in your community. **MM**

Part I

Missouri's Fentanyl Poisonings Rise to Record Levels

by William V. Stoecker, MD, Colin L. Smith, BS & Elizabeth Connors, MSW

Abstract

Missourians are dying of fentanyl poisoning at an unprecedented rate. We identified growth areas in Missouri for fatal fentanyl encounters in rural and western counties. Though the deaths occur for a multitude of reasons, a growing trend adds to the surge in fentanyl fatalities: poisonings from counterfeit pills. The tablets are often labeled with brand names for alprazolam or oxycodone, but may contain only fentanyl at a dangerous level. Teenagers find counterfeit pills all too easily via social media. Believing they have found an easy way to obtain a quick high or relief of minor pain and anxiety, they take the pill alone in their bedroom, with no possibility of reversing a fatal fentanyl dose. There is a wide range of respiratory depression from illicit drugs containing fentanyl. We reviewed the physiologic respiratory response to drugs containing fentanyl that varies with genetics and the unpredictable amount of fentanyl contained in illicit drugs.



William V. Stoecker, MD, MS, (left), is at S&A Technologies and The Dermatology Center, Rolla, Missouri and in the Department of Dermatology, University of Missouri Health Sciences Center, Columbia, Missouri. **Colin L. Smith, BS**, is at the Kirksville College of Osteopathic Medicine, A.T. Still University, Kirksville, Missouri. Elizabeth Connors, LCSW, MSW, CRADC, is at the Missouri Institute of Mental Health, University of Missouri-St. Louis, St. Louis Missouri.

Several Trends Drive Increase in Fentanyl–Related Deaths

In this article, we document the increase in fentanyl–related deaths in Missouri with new statistics. This report updates a previous report on fentanyl in Missouri.[1] The most important trend accounting for fentanyl–related deaths is the increased fentanyl content in illicit drugs. We spoke with Tom Van De Berg, MD, Medical Examiner for Greene County, about the increase in opioid–related deaths there from 62 in 2020 to 101 in 2021.[2] He stated: "Last year it really shot up for us. There is so much of it on the street."

This persistent rise of fentanyl–related deaths in America began in 2014.[3] Ben Westhoff, author of *Fentanyl Inc.*, stated of fentanyl: "It's so cheap to produce and it's so powerful, that drug dealers began realizing it was a way to increase their profits."[4]

Part I of this update on illicit fentanyl reports a record–breaking total of fentanyl fatalities in Missouri and a new pattern for those deaths. Dealers now deliver fentanyl to virtually any town in Missouri. A recent fatal case due to ingestion of just one–half of a counterfeit pill typifies a growing trend. Part I concludes with new research findings pinpointing the location of the lethal effect of fentanyl on respiration in the brainstem and explaining the variation in susceptibility to fentanyl toxicity.

Part II will document the critical change in fentanyl manufacturing—from a finished Chinese product to a Mexican product made from basic Chinese chemicals. Missouri statistics on narcotic prescriptions and significant harm reduction efforts will complete this two–part update on fentanyl in Missouri.

Missouri Opioid Fatalities in 2021: Rural Rates Rise; St. Louis City and County Decline

The result of the heavy influx of fentanyl–contaminated drugs from Mexican cartels, manufactured from basic Chinese chemicals, is apparent in recent statistics for opioid–related fatalities in Missouri. Provisional data from the Bureau of Health Care Analysis and Data Dissemination, Missouri Department of Health and Senior Services (MO DHSS), give a total of 1,581 opioid overdose deaths for Missouri residents in 2021.[5] This represents a significant increase from the 1,375 fatalities recorded in 2020.[6]

Figure 1 shows the opioid death rate per 100,000 for counties that recorded five or more deaths from provisional data available May 20, 2022.[7] Counties not reporting data or with four or fewer deaths are shown in gray. St. Louis City still leads the state in opioid death rates at 86 per 100,000 population, followed closely by Dent County, which had 83 per 100,000 population (12 opioid deaths in Dent County, population 14,421). In descending order, the six counties that follow the top two counties, with opioid fatality rates between 45–69 deaths per 100,000 population, are Crawford, Washington, Phelps, St. Francois, Jefferson, and Warren. This data from 2021 demonstrates a rise in fatalities for many counties outside the urban fringes, especially along the Interstate–44 corridor.

St. Louis City and County demonstrated a fall in opioid death rates from 2020 to 2021—the first decline observed in these areas in years. The growth rates were high in some western counties such as Jackson and Greene counties, although both have a far lower opioid fatality rate than St. Louis City and even lower than many rural counties. Overall, the Interstate–44 corridor is the predominant pattern observed in counties with the highest opioid death rates and the highest percentage increases in Missouri opioid fatalities.

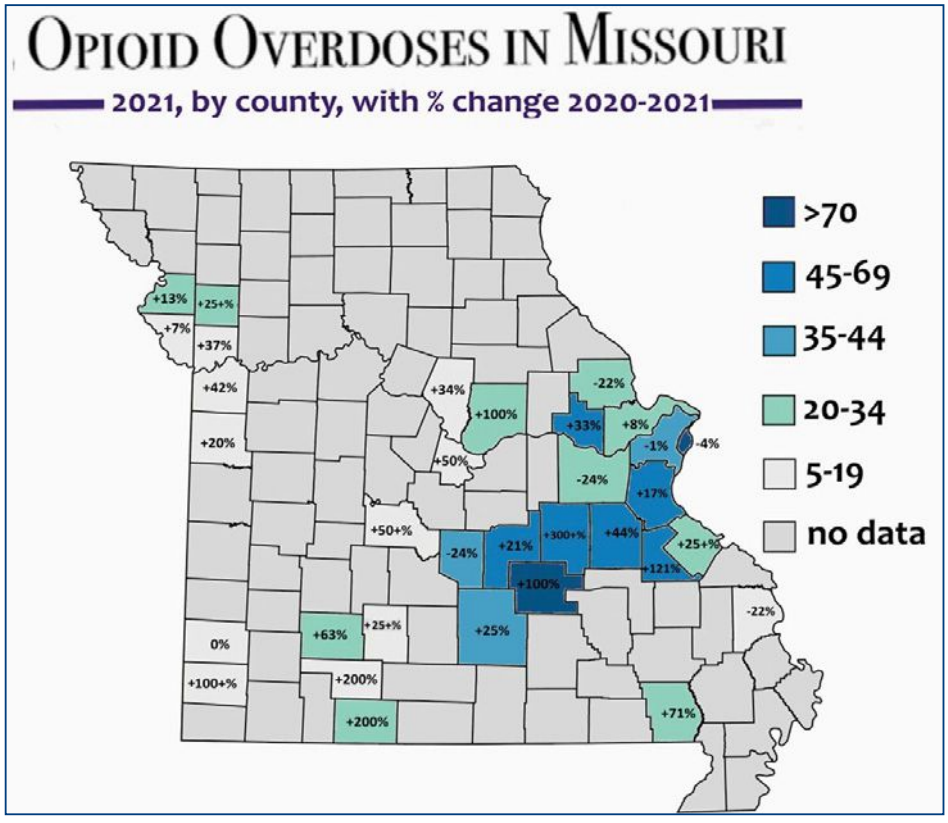


Figure 1. Lethal opioid overdoses in Missouri, rate per 100,000, statistics from MO DHHS. Percent changes from 2020 to 2021 are noted in + or – percent. Gray areas: statistics not available. For counties with a "+%" notation, statistics are incomplete; the minimum percentage increase is noted. [7]

Fatal drug overdose statistics presented here represent all fatalities from opioids and are taken from ICD–10 coding for drug overdose deaths on death certificates and combined with available toxicology data.[8] The opioid drug category includes both natural and synthetic opioids. The latter category includes fentanyl, fentanyl analogs, and other synthetic narcotics such as U–47700. This drug is known as "pink," "pinky," or "U4" and is associated with an increasing number of fatal opioid overdoses.[9, 10]

These fatal overdose totals are preliminary and subject to death–certificate reporting error. A combination of drugs (e.g., opioids and methamphetamines) sometimes contributed

to fatal outcomes. Nora Volkow, MD, of the National Institute on Drug Abuse (NIDA) stated: "Unfortunately, comprehensive toxicological testing is not performed in many cases, or the results are not recorded on death certificates, so the reported numbers of fatal opioid overdoses and overdoses due to fentanyl might not capture the full scope of the epidemic."[11]

Poisonings From Lethal Counterfeit Pills

Libby Davis of Shawnee, Kansas, the mother of sixteen–year–old Cooper Davis, told us how her son died. Cooper and three friends bought two light–blue pills with the label "Perc 30," indicating that the pills contained 30 mg of oxycodone. Cooper and his friends traveled from Shawnee, Kansas to Missouri to meet a drug dealer through a contact they found on Snapchat.[12] Each of the friends agreed to take one–half pill. Mrs. Davis and her husband, Randy, knew nothing of this until they received a phone call from the police about Cooper. Libby Davis told us: "About six p.m., we got the call that every parent fears. The officer said: 'Cooper is having a medical emergency. You need to get to this address as soon as you can.' "

Cooper's parents stood in the driveway waiting for the EMTs to give an update. The team had been attempting to resuscitate Cooper for 40 minutes. After a change in his EKG reading that gave the EMTs hope, they brought him out of the house to transfer him to the hospital. Cooper's parents were alarmed to see Cooper under a mechanical compressor pumping his chest, part of an intense effort to revive their son. Following a prolonged resuscitation effort, his lungs began hemorrhaging, and the Davis couple agreed to suspend efforts to revive their son. The three teenagers who shared the pills with Cooper walked away unharmed.

Cooper's death was front–page news. His parents told the *Kansas City Star* that as far as they knew, Cooper did not have any addiction or drug use other than marijuana. He took half a counterfeit pill and died.[12]

Libby and Randy Davis decided to begin an educational effort to counteract the rise in fatal fentanyl encounters. She told us that the word "overdose" carries the wrong message. Since the person is not seeking any amount of fentanyl, the event cannot be described as an overdose, but should instead be called a poisoning. She explained: "Teenagers with anxiety and depression are turning to self–medication. Pills have been normalized and these teenagers are trying to fix themselves. Curious teenagers decide to self–medicate and not bother their parents." She added: "There is a stigma when we say 'overdose,' and the public thinks, not my family, not my kid. People aren't listening if we call it an overdose. Let's call it a poisoning. If they poisoned our milk supply, everyone would know." She further stated: "This happens so suddenly, there is no time to learn from mistakes. How do you cure a kid's curiosity?"

Fentanyl poisonings in Missouri from counterfeit pills rose sharply in 2021. Another sixteen–year–old, Ethan Everley, also from the Kansas City area, died of fentanyl poisoning from a counterfeit pill.[13] "Social media is almost exclusively the way they get the pills," said Morgan Gire, district attorney for Placer County, California, who filed murder charges against a dealer accused of killing 20–year–old Kade Webb.[14] These recent reports continue a trend going back to at least 2015, when eight overdoses from counterfeit Xanax (alprazolam) pills were reported.[15] The number of counterfeit pills seized by federal agents has soared—from 42,202 in the first quarter of 2018 to 2,089,186 in the fourth quarter of 2021.[16] Reports vary, but according to one Drug Enforcement Agency (DEA) analysis, about 42 percent of these fake pills contain a lethal dose of fentanyl.[17]

The DEA released a public safety alert about the dangers of fake pills on September 27, 2021, their first public safety alert in six years. According to Andree Swanson of the DEA, the organization seized as many counterfeit pills in 12 months as they had in the previous 24.[18] In their "One Pill Can Kill" campaign, the DEA cites the hazards of counterfeit pills.[19] Drugs sold by counterfeiters, labeled as Xanax, Percocet, and Oxycontin knowingly contain fentanyl.[19] An increasing number of deaths occur in opioid–naïve teenagers who use social media to find and take just one pill or part of a pill.

A 17–year–old girl from Cameron, Missouri, Faith Richardson, died after taking illicit pills obtained in Chillicothe, Missouri.[20] A 34–year–old woman also from Chillicothe died in similar circumstances.[21]

Cooper Davis Died, and His Three Friends Were Unharmed: Variation in Response to Opioids

Fentanyl is a potent narcotic: 80–100 times as strong as morphine.[22, 23, 24] Although the DEA gives 2 mg as a lethal dose of fentanyl, one toxicologist states, "Giving someone 500 mcg (0.5mg) would be seen as

irresponsible if ordered in the hospital…The fatal dose of fentanyl in an opioid–naïve adult is likely less than 2000 mcg." [25]

Fentanyl's potency and low–price boosts profits for dealers who do not have to purchase more expensive drugs. The trouble ensues when cartels and drug dealers use crude methods to mix fentanyl, e.g. with a spoon.[26] As a result, The amount of fentanyl in illegal drugs as well as counterfeit pills is completely random—even from the same supply or supplier—which increases the probability of someone being poisoned or overdosing. One portion or pill may not contain fentanyl, while others from the same supply may.[27] Toxicology reports from counterfeit pills, when available, may show only fentanyl as the active opioid ingredient, though many limited tests may not detect fentanyl analogs. Cooper Davis's toxicology report, for example, showed only fentanyl, caffeine, and naloxone; the opioid antagonist employed too late to save him.[28]

In addition to the unpredictability of fentanyl exposure, variability in genetics, and therefore, varying kinetics of drug metabolism, heighten the risk of an overdose.[29, 30, 31] The variation in effective analgesic opioid dose has been found in multiple clinical studies.[29, 31] This effective clinical dose for analgesia depends on the variation in response to a given dose of opioids as well as the variation in individual response to painful stimuli.

Opioid effects are mediated by multiple opioid receptors including the μ–opioid receptor, coded by the Oprm1 gene.[32] The activity of the μ–opioid receptor can differ significantly depending on the Oprm1 gene variant. The Oprm1 polymorphism A118A>G has been studied in a mouse model and in possible relation to opiate addictions in humans.[33, 34, 35] The implication of these studies is that persons with this polymorphism have less of a response to opioids.

The most critical adverse effect of fentanyl, as well as all opioids, is respiratory depression mediated via the same μ–opioid receptor on a tiny cluster of neurons in the brainstem.[32, 36, 37] These neuron clusters include the pre–Bötzinger complex, the parabrachial nucleus, and the Kolliker–Fuse nucleus.[37, 38, 39] In–vivo work in the mouse model implicates the Kolliker–Fuse nucleus in apneic events at high opioid doses.[39] Experimental work by Bachmutsky et al. utilized mice with Oprm1 gene deletion from selected respiratory sites.[40] The researchers demonstrated contributions from all of these brainstem respiratory centers in opioid–induced respiratory depression.[40] Just 70–140 neurons in the brainstem were found to govern respiratory toxicity from opioids.[40]

Oertel et al. demonstrated 118A>G carriers received less analgesia from alfentanil and that homozygous 118A>G carriers were protected from respiratory depression.[41] The ARUP reference laboratory[42] for the 118A>G allele test notes a wide variation among populations in the presence of a single 118A>G allele: African Americans 1.5–4%, Whites 11–14%, Hispanics 14–24%, and Asians 49–60%.[33, 34, 35]

Fentanyl is metabolized by the CYP3A4/5 enzyme, rather than the combined CYP2D6 and CYP3A4/5 pathways used in metabolizing hydrocodone, oxycodone, and methadone.[43] The CYP3A5*3/*3 allele reduces the metabolism of fentanyl. Takashina et al. found a two–fold increase in fentanyl plasma concentration and a greater number of CNS adverse effects in patients homozygous for CYP3A5*3/*3 in comparison to CYP3A5 patients.[44] Barratt et al. analyzed CYP3A4 and CYP3A5 polymorphisms in cancer pain patients receiving transdermal fentanyl using stepwise linear regression.[45] Only 14% of the variability in serum fentanyl levels were accounted for by CYP3A4*22 and CYP3A5*3 variants, CYP3A inhibitors (i.e. drug–drug interactions), and variables relating to liver and kidney function implying other genetic differences may be important.[45] For example, the P–glycoprotein adenosine triphosphate (ATP)–binding cassette transporter, encoded by the ABCB1 gene, regulates transportation across the blood–brain barrier, controlling entry of drugs into the brain. Two studies showed that, because of effect on the P–glycoprotein transporter, patients with ABCB1 transport gene alleles had different fentanyl requirements for pain relief.[44, 46]

We have reviewed new data showing that Missouri has record numbers of fentanyl poisonings. We discussed the growing instances of poisonings from counterfeit fentanyl pills. We also reviewed new basic science findings on the effects of opioids on the brainstem and how those effects vary significantly in the population. This concludes Part I of our two–part series: *Missouri's Fentanyl Poisonings Rise to Record Levels.*

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Caring for Patients Using Methamphetamines: An Interprofessional Collaborative Approach

by Erinne N. Kennedy, DMD, Sarah Getch, PhD, Benjamin Grin, MD, Russell D. Campillo, CPS & Linda C. Niessen, DMD

National data show that individuals who use methamphetamine are more likely to use or misuse other substances including cannabis, prescription opioids, cocaine, prescription sedatives, tranquilizers or stimulants, and/or heroin.

Abstract

Methamphetamine use is increasing in the U.S. and in Missouri, as are the number of deaths associated with its use. Many systemic and mental health issues are associated with methamphetamine use or methamphetamine use disorder (MUD). Given the range of health issues associated with methamphetamine use or MUD, a collaborative approach to the care of patients can improve outcomes. This article provides an overview of a collaborative approach to caring for patients using or have used methamphetamine, from the perspective of the primary care, behavioral and dental clinician.

Introduction

Methamphetamine is a highly addictive stimulant that affects the central nervous system. National data from 2015–2018 estimated that 1.6 million U.S. adults over age 18 years reported past–year methamphetamine use; 52.9% had a methamphetamine use disorder (MUD) and 22.3% reported injecting methamphetamine within the past year.[1] Although the population use rates have remained relatively stable, mortality associated with methamphetamine use has increased in the U.S.[2] These increased death rates for methamphetamine are thought to be related to opioids being laced with methamphetamine.[3]

Missouri is not immune from this drug epidemic. In 2013, the Missouri Highway Patrol Report ranked Missouri third by state in methamphetamine seizures.[4] A 2020 report from Millennial Health ranked Missouri ninth in the U.S. with 10.2% of the population testing positive for methamphetamine use, with Arkansas ranking first.[5]

National data show that individuals who use methamphetamine are more likely to use or misuse other substances including cannabis, prescription opioids, cocaine, prescription sedatives, tranquilizers, or stimulants, and/or heroin.[1] Methamphetamine use in Missouri continues to cause significant health problems for the population. In addition to increasing death rates, from 2012–2018, the number of Missourians receiving treatment for MUD increased 76%.[6] (See sidebar for an example of an individual who has used and recovered from MUD.)

Since the implementation of federal and state regulations restricting the sale of pseudoephedrine used in the manufacturing of methamphetamine, production in Missouri has decreased considerably. Meth lab incidents have decreased 96% between 2006 and 2018. Today, methamphetamine is thought to be



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transported from Mexico to U.S. cities. In Missouri, St. Louis appears to be a transportation hub for methamphetamine and accounts for the majority of methamphetamine incidents in the state.[6]

Methamphetamine use is associated with a variety of health issues, including cardiovascular and renal disease, oral diseases, infectious disease transmission, psychosis and other mental health illness, and overdose.[1] Primary care and behavioral health clinicians will see patients with health and mental health disorders related to methamphetamine, or patients with chronic diseases who are using methamphetamine. Dentists will see individuals in which methamphetamine has destroyed their dentition. This article describes the physical, behavioral, and oral health issues associated with methamphetamine use and an approach to treatment planning using a collaborative approach to care.

Prevalent Health Issues

Given the prevalence of methamphetamine use in Missouri, primary care clinicians should be familiar with the health effects that stem from chronic methamphetamine use. Primary care considerations of long–term methamphetamine use include cardiovascular complications; a higher incidence rate of risky sexual behavior; an increased chance of contracting and/or transmitting HIV; and potential concomitant misuse of other substances, including prescription medications. The primary care provider should also be familiar with opportunities for treatment and harm reduction.

The physical sequelae of chronic methamphetamine use are numerous and may affect several organ systems. Cardiovascular and cerebrovascular events most often contribute to morbidity and mortality associated with methamphetamine use. These effects are mediated by methamphetamine's effect on the sympathetic nervous system. Cardiovascular complications of chronic methamphetamine use are among the leading causes of death in chronic methamphetamine users; these complications include malignant hypertension, myocardial infarction, stroke, aortic dissection, and methamphetamine–associated cardiomyopathy.[7]

Chronic usage of methamphetamine can lead to hypertension and predispose the user to methamphetamine–associated cardiomyopathy, a condition characterized by left ventricular dilation and left ventricular dysfunction. Importantly, methamphetamine–associated cardiomyopathy may be reversible with cessation of methamphetamine usage. Methamphetamine use is associated with about a five–fold increased risk of stroke, which are often hemorrhagic.[7] Chronic methamphetamine use is increasingly being recognized as a cause of pulmonary arterial hypertension (PAH), causing progressive dyspnea and hypoxemia, right ventricular failure, and eventual death.[8]

One important consideration related to chronic methamphetamine use that may be overlooked is its association with risky sexual behavior and risk for HIV and other sexually transmitted infections. In the U.S., methamphetamine is used more frequently among men who have sex with men (MSM) than among other men. Use of methamphetamine and other substances to enhance sex has often been referred to as "chemsex." Chemsex is a practice often seen among methamphetamine users in the MSM community.

Methamphetamine usage has been associated with a greater number of sexual partners, reductions in condom use, and poor adherence to antiretroviral pre–exposure prophylaxis and antiretroviral treatment and has been clearly established as a factor contributing to HIV transmission in the U.S.[9] The route of administration must also be considered when linking methamphetamine use with an increased risk for communicable diseases as methamphetamine may be smoked, snorted, inserted rectally, or injected. Injected methamphetamine may increase risk for transmission of HIV and Hepatitis C.[10]

When caring for patients with methamphetamine use disorder, one should consider concomitant use of other substances. Co–use of methamphetamine and opioids has been linked to an emerging epidemic of opioid–related mortality. It is thought that rising rates of stimulant–related death may be related to co–use with opioids, particularly high–potency synthetic opioids like fentanyl. The reasons for increasing co–use of these substances requires further study.[10]

Prevalent Mental Health Issues

Primary mental health issues associated with regular methamphetamine use include depression, anxiety, and psychosis. Often, it is difficult to ascertain whether the mental health condition preceded the methamphetamine, however, it is safe to say that regular methamphetamine use would most certainly exacerbate any underlying biological bases related to mental health issues.[11] Methamphetamine intoxication can

result in hallucinations, paranoia, and psychosis.[12] Methamphetamine use can be conceptualized as activating, resulting in major changes in impulse regulation and mood.[13] Symptoms associated with impulse regulation can include agitation, irritability, suicidality, and even aggression. Other symptoms associated with activation include panic and anxiety.[14] Methamphetamine withdrawal symptoms can result in a sharp decline in mood resembling depression. A majority of methamphetamine users report experiencing depression with symptoms of low mood and anhedonia.[15]

Methamphetamine use sets itself apart from other drug use because of the increased risk of psychosis. Individuals experiencing psychosis do not recognize that they are suffering from mental illness.[16] The experience of psychosis, or a psychotic episode, is a defined by losing touch with reality and the experience of hallucinations, delusions, disorganized thinking, and disorganized movement or motor behaviors. Delusions are fixed false beliefs and often revolve around themes of persecution, hidden meanings in every day occurrences, physical experiences, religion, and grandiosity. Hallucinations are unreal sensory perceptions that occur without an external stimulus. Despite the lack of an external stimulus, it is important to remember that those experiencing hallucinations sense them as very real and will respond as such. Disorganized thinking will present itself as speech that is disjointed, incoherent, or even randomly spoken words. Disorganized behavior can present as behavior that includes purposeless movements, talking to oneself, or even being childlike and silly.[16]

Specific to methamphetamine users, psychotic symptoms can be short–lived and resolve once the bloodstream is free of the drug.[17] The psychotic symptom profile of methamphetamine users often includes auditory and visual hallucinations as well as delusions revolving around persecution (e.g., being followed, being spied on, being lied to).[18]

The activating nature of methamphetamines can result in agitation, and there is evidence that methamphetamine use is related to irrational, violent behavior. Large population studies and some longitudinal studies have provided strong evidence for a causal relationship between violent behavior and methamphetamine use, but more research is needed in this area.[19,20]

Significant evidence indicates that increased usage of methamphetamines is related to increased rates of depression and anxiety.[21] Methamphetamine users report high rates of a lifetime prevalence of depression and a third of users report having been diagnosed with depression or anxiety at some point in their lives.[22] Drawing a distinction between independent mood and anxiety disorders, and symptoms of methamphetamine use and withdrawal is easier said than done.

The hyperarousal associated with use can mimic symptoms of unease and panic, while the withdrawal period after use can result in feelings of fatigue, lethargy, and apathy. Clinicians, when given the time, can work to make accurate diagnoses of mood, anxiety and substance use disorders by paying close attention to onset of episodes as it relates to lifetime usage.[23]

More frequent use of methamphetamines is associated with higher levels of suicidality.[13] In addition to understanding patient mood, anxiety, and substance use profiles; particular attention should be paid to the assessment of suicide in patients using methamphetamines. The rates of suicide attempts and completions remain higher than the general population among methamphetamine users with a history of self–harm or attempts and current mental illness serving as the best predictors of attempted or completed suicides.[23]

The relationships between psychotic, mood, and anxiety disorders and methamphetamine use are complex and demand comprehensive assessment and diagnosis. Fragmented screening and assessment methods can lead to poorer health outcomes for methamphetamine users.[24] Understanding these complex relationships, assessment, and treatment methods, and by using a strong interprofessional referral network, the physician or dentist can contribute to better outcomes for their patients.

Prevalent Oral Health Conditions

Sam Quinones in his book, *The Least of Us*, described the ravaged teeth and tooth destruction caused by methamphetamine use.[25] Methamphetamine use is associated with changes in the saliva, exposure to noxious chemicals, and changes in behavior that result in a pattern of oral diseases seen primarily among methamphetamine substance users called "meth mouth" (See Figure 1).[26]

Methamphetamine causes the body to release a wave of dopamine that stimulates the sympathetic nervous system (SNS), constricting smooth muscle. In the oral



Figure 1. Example of oral destruction that can result from methamphetamine use.
Source: American Dental Association. Mouthhealthy.org. accessed 3/30/22

cavity, salivary glands constrict and salivary flow is reduced.[26] As the saliva decreases, the acidity of the saliva increases and buffer capacity diminishes, creating an environment that is hyper–susceptible to oral disease. One study found that 95% of participants experienced dry mouth or xerostomia.[27] This hypersusceptible oral cavity when exposed to methamphetamine's acidic and noxious chemicals favors pathogenic bacteria and tooth decay.

The tooth destruction seen in methamphetamine use occurs in an unusual pattern. Dental caries usually occurs in the pits and fissures of the chewing surfaces of the teeth. Dental caries on smooth surfaces of the enamel occurs between the teeth where plaque accumulates, and is difficult to remove. With methamphetamine use disorder, dentists see tooth decay presenting as black holes on the buccal or facial surfaces (smooth surfaces) of the teeth, in addition to the usual locations for dental caries.

Users of methamphetamine are increasingly likely to use sugar sweetened beverages such as carbonated soft drinks (soda pop).[28] This use of sugar increases the risk for tooth decay by providing a substrate for pathogenic bacteria known to cause tooth decay. While this substrate could be mitigated with increased oral hygiene, patients who are experiencing a dopamine high may be unable to complete oral health practices and/or unable to remember to do so.

High levels of dopamine can trigger bruxism or the clenching of teeth together. Pathogenic bruxism (grinding) on teeth that are fragile and brittle due to tooth decay and exposure to chemicals can result in tooth fracture.[29]

Treatment Planning – Primary Care Clinician

Management of patients with methamphetamine use disorder in the primary care setting is challenging and requires an interdisciplinary approach that includes linkage to behavioral health services.[30] There are no FDA–approved medications for methamphetamine use disorder, and no medications that have shown consistent efficacy for treating this condition across multiple clinical trials. Behavioral treatments remain the standard of care. Medications that have been studied in treating methamphetamine use disorders include bupropion, naltrexone, and mirtazapine.

One promising recent randomized controlled trial studied 12 weeks of combination pharmacotherapy with injectable extended–release naltrexone with oral daily bupropion compared with placebo, and did show a statistically significant decrease in methamphetamine use with naltrexone/bupropion combination therapy.[31] Overall response rate to this treatment was low overall and prescribers may face other logistical challenges including cost, but may be a treatment option for selected patients. Pharmacotherapy currently has a limited role in treating methamphetamine use disorder and is an area requiring further study.

Harm reduction is an important consideration for primary care physicians. Even in patients who are not yet ready to reduce or stop using methamphetamine, PCPs can engage in treatment planning to reduce certain risks of chronic methamphetamine use. For patients who inject methamphetamine, PCPs can provide education on safer injection practices and linkage to syringe service programs to reduce risk of contracting HIV, Hepatitis B and Hepatitis C. For patients who use methamphetamine with sex, PCPs should counsel on safer sex practices including condom use, offer HIV pre–exposure prophylaxis (PrEP), and provide regular screening for sexually transmitted infections. Maintaining a therapeutic alliance and non–judgmental approach can strengthen efforts at harm reduction and open opportunities for behavior change when patients are ready to consider change.

Treatment Planning – Behavioral Health

The primary care clinician should be comfortable assessing the level of anxiety, depression, suicidality, and substance abuse in a patient. Being able to distinguish between a true psychotic disorder and substance–induced psychosis will be critical to the successful treatment of patients. When patients present with acute methamphetamine intoxication, the provider's first response is to use de–escalation techniques to build a rapid rapport and sense of connectedness with the patient. These techniques include the use of collaborative language, providing the patient with your full attention, empathy, and reflective listening. If a patient presents in an acute psychotic episode, referral to a behavioral specialist is indicated.

While clinical trials have explored the use of antipsychotics, antidepressants, and anticonvulsants as tools to decrease cravings, usage, and withdrawal symptoms, the results of these trials do not provide evidence for their usage.[32] Long–term treatment of patients with methamphetamine addiction will likely focus on evidence–based behavioral therapies, such as cognitive behavioral therapy, motivational interviewing (MI) and contingency management interventions provided by a mental health professional.[33]

Cognitive behavioral therapy (CBT) is a psychotherapeutic approach designed to identify and modify the dysfunctional or maladaptive behaviors and thinking patterns that cause and maintain addiction. Mental health providers will focus specifically on the behavioral component of CBT and use contingency management strategies to shape behavior.[17] Contingency management strategies reinforce positive behaviors, such as treatment adherence and abstinence, by providing tangible incentives.[34] Motivational interviewing techniques have proven to be effective in the treatment of addictions through the exploration of any ambivalence towards change.

Due to the interaction of thoughts, behaviors, and the environment in which one operates, clinicians created a Matrix Model treatment approach aimed at integrating behavioral therapy, family education, individual counseling, 12–step support, drug testing, and encouragement for non–drug–related activities. This model has been shown to be effective in reducing methamphetamine misuse.[35,36]

Understanding current evidence–based behavioral health treatment approaches allows clinicians to collaborate in the interprofessional treatment planning process. It provides a common language between the patient in recovery and their providers. Because these treatments target the development and maintenance of addiction and addiction behaviors, a thorough understanding of these treatment approaches allow providers the tools to gain greater insight into their patients' history and relationship to addiction.

Treatment Planning – Dental Clinician

To assist in coordinating care for patients with SUD, the National Council for Mental Wellbeing developed a toolkit to facilitate the coordination and integration of oral, mental, and substance use treatment.[37] This toolkit provides examples of how mental health and oral health clinicians have worked together and improved patient outcomes.

Lack of access to needed dental care for methamphetamine users often results in their arriving in emergency departments for toothaches, which are a leading cause of avoidable emergency department visits, providing evidence of lack of access to regular oral health care.

When treatment planning patients who use methamphetamines, referring these patients to a dental home is an essential first step. The dentist will evaluate the patient for inflammatory periodontal disease, severity of tooth decay, tooth infections and the risk for oral cancer or other oral lesions.[29] The patient will be treated initially for any acute infection by removing infected teeth or those that are unable to be saved and receiving therapy for the inflammatory periodontal (gum) disease.

After the acute phase of treatment is complete, the oral health care team will address the patient's xerostomia, educate them on oral health behaviors, and provide in–office preventive treatments to improve their quality of life. Patients often require frequent preventive treatments including fluoride in the form of a varnish and/or silver diamine fluoride that can be provided in a physician or dental office.

The dental team can provide a patient with severe tooth destruction from methamphetamine use with a plan for restoring his/her smile. This plan can include a combination of fillings (restorations), crowns (caps), implants, and/or removable dentures. For patients who are currently using methamphetamine, the dentist should provide treatment 24 hours after their last dose of meth.[38] However, restoring the patient's smile is typically most effective when the patient is undergoing or has completed rehabilitation. Continued use of methamphetamine after dental replacements is likely to break down any new restorations that were placed.

Summary

With methamphetamine use increasing in Missouri, primary care physicians, behavioral health professionals, and dentists should be aware of the signs and symptoms of this disorder, the diagnosis of methamphetamine use disorder and approaches to care for these patients. Given the range of symptoms in which patients can present, these patients can benefit from a collaborative approach to their management, as outlined in this article.

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My Experience and Recovery from Meth Addiction

by Russell Campillo, CHW, CPS, MARS
Peer Educator, KC Care Health Center

For most of us, meth is an energy that you've never had. Your eyes widen, your heart races, your senses are amplified, and goosebumps run across your skin. You become hyper–aware and sensitive to noises, smells, even your vision. I was able to read a book for the very first time. I was creating stories and art pieces one after another. I felt more productive than I had ever been.

Things slowly began to crumble, loss of a job, odd jobs working for people. Payment for drugs is not always monetary, but you always pay in one form or another. As the crumbling continues, so do the tooth aches, dry mouth, eyes, skin, twitching, and restlessness; homelessness, lack of self–care, including medical care; visual, auditory, even physical hallucinations, teeth grinding, cramps, no sleep. You begin to forget hunger and thirst.

Some surveys show only one out of two crystal meth users will stay sober for the first three months after they try to get sober. Without formal treatment however, only one in nine users will make it through the first three months. The success rate of crystal meth users to continue sobriety after three years without any rehabilitation or treatment is ONLY 5%. When all relapse incidents are grouped together, it is estimated that 92% of crystal meth users will relapse at least once in their recovery efforts.

Referring to my own experience, familial, friend, and counseling supports are the most integral part of my recovery. I also was able to find work in HIV services which is not where I ever expected to be. This position is fulfilling and challenging. I became an HIV Peer Educator in 2019, obtained my CHW (Community Health Worker) in 2019 and my CPS (Certified Peer Specialist) for mental health and substance use shortly after. I was also certified MARS (Medication Awareness Recovery Services) a bit later.

The work I do allows me to stay focused in my recovery. Today I am successful through these experiences and have been given opportunities to share my story on HIV and substance use disorder to medical students, to others who are challenged with substances, and other professionals.

I have always been capable, but today I am grateful and fortunate to be one of the 5%.

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MSMA: Building Consensus & Advocating for Patients and Physicians *Shape Your Future & Get Involved!*

by Albert L Hsu, MD

Who is the best person to speak about medicine to your legislature? Your neighbor or you?

The practice of medicine is under siege. We physicians spend much of our clinical day struggling with insurance companies, worrying about liability, and drowning under ever–increasing clerical duties. Ethically, we cannot abandon our patients to go on strike, while anti–trust law hamstrings our ability to effectively negotiate with payors. Recent events highlight the worrisome and increasingly intrusive nature of governmental interference in our practices.

Despite the ongoing and exciting revolutions in biology and medicine today, we are also in a time of great financial pressures. As health systems continue to consolidate and private equity and corporate medicine increasingly encroach on medicine, most of us are fighting just to preserve funding for quality clinical care, for medical education and research, and for public health initiatives. As we emerge from the COVID–19 pandemic, physicians are increasingly burned–out, short–staffed, and wondering what all that personal sacrifice was for. For a brief and shining moment, early in the pandemic, physicians were heroes; now, the sentiment of the general public has apparently turned against us yet again, especially in our state legislatures.



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In this era of prickly and rancorous national discourse, where everything seems overly politicized, MSMA and your local and national medical societies (organized medicine) are opportunities for all of us to collaborate on shared interests and advocacy. In organized medicine, we do not have permanent "friends" – just permanent interests. We work closely with both Republicans and Democrats to advance solutions to issues that are important to us, such as with Republicans on liability reform and with Democrats on preventing abuses by insurers. Medicine has "friends" in both parties, but we also have politicians of all stripes who view us as the problem, and not as part of the solution. When protecting our patients, our profession, and our colleagues, we are most effective when we speak with a unified voice.

But achieving consensus is not easy. From gun control to climate change, from abortion to cannabis legalization, we live in a highly polarized society in which many of us are reluctant to be too vocal. Medical societies can struggle if they establish policies and advocacy platforms based on razor–thin majorities, which may alienate a significant portion of their membership. While we physicians will likely never agree on certain contentious moral issues like abortion or gun control, we have much in common: we all oppose intrusions in the physician–patient relationship, we are aghast at the criminalization of medical care, and here in Missouri, many of us are deeply concerned about the epidemic of maternal mortality in our state.

As a young physician member of the American Medical Association (AMA) a few years ago, I raised concern about cannabis legalization and became embroiled in a very contentious discussion over



MSMA congratulates "graduates" of our 2023 Advocacy Training held in Jefferson City along with the October Council Meeting. Speakers included **Jon Patterson, MD**, State Representative, Lee's Summit; **David Barbe, MD**, WMA, AMA, MSMA Past President; Pat Thomas, Chief of Staff to Sen. Lincoln Hough; Sen. Caleb Rowden, Senate Majority Leader, Columbia; and Trent Watson, Watson Governmental Consulting. Topics included Physician Perception in the Current Legislative Environment; Engaging with Your Legislators; How to Testify; Legislative Leadership; and Preparing for the 2023 Session.

libertarian concerns and social justice issues. Upon further reflection, I returned with a proposal to establish "marketing guardrails" to oppose marketing of cannabis products to pregnant women, children, and other vulnerable populations. My colleagues and I persuasively argued that taking a neuroactive drug like cannabis during pregnancy, while the fetal brain is undergoing rapid growth and development, is simply not a good idea for future success. By defining a narrow policy that could elicit broad support, we were able to establish a new AMA policy[1] on this issue in 2022.

Here in Missouri, Columbia and Boone County are viewed by some as "liberal bastions," but our Boone County Medical Society (BCMS) includes all political stripes: we have progressive viewpoints espoused by some Columbia physicians, balanced by conservative advocates from Jefferson City and the Lake Ozark region. Early in the pandemic, several of our BCMS leaders wanted to make a strong statement about the need for mask mandates (before vaccines were available, and before we truly understood the virus as we do now). While several of us wanted BCMS to make a very strong statement, important voices pointed out that as physicians in private practice, they simply could not afford to alienate their patients, and that the science was continuing to evolve. Rather than issuing a statement supported by a slim majority of our leadership, we spent the time to craft a consensus opinion[2] that emphasized the scientific consensus about mask–wearing at the time, and that all of us could agree on.

As a leader of our BCMS, I have found that diversity of opinion has made us stronger. As economist Larry Summers recently stated: "I go out of my way to find people that I disagree with because I always learn something that way." Some physicians consider the AMA to be too conservative, others consider it to be too liberal. In my experience, I have seen the AMA tackle some very controversial issues, including gun safety, climate change, and abortion policy, with some very spirited discussions before achieving consensus.

Organized medicine is also a "force multiplier." For example, Calli Morris, one of our medical students at the University of Missouri, who is now a pediatrics resident in Ohio, introduced a 2019 MSMA resolution[3] on the important issue of "Addressing healthcare needs of children of incarcerated parents." Less than three years later, our Missouri state legislature has passed a bill to enact a Correctional Center Nursery Program in our state

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MSMA - The Champion for Every Physician, Every Day

Thanks to the support of MSMA members, we achieved major victories for medicine in the 2022 legislative session.

Defeated: Collaborative Practice Repeal
- Would have removed the familiarity rule, the 10 percent chart review requirement, and the geographic proximity requirement
- Would have gutted the provisions that ensure patients receive physician-led care

Passed: APRN/PA Home Health Orders
- Creates compromise language to ensure that home health patients, who often require complicated services, get the healthcare services they need while maintaining physician involvement in their care

Passed: Naltrexone Statewide Order
- If the Director of the Department of Health and Senior Services is a physician, a statewide standing order could be issued to allow pharmacists to sell or dispense naltrexone under that physician's protocol

Passed: School Epipens
- While schools have been allowed to stock epinephrine auto-injectors, this expands on the law by allowing school-contracted employees (e.g. bus drivers) to be trained to administer an Epipen on a student experiencing a life-threatening anaphylactic reaction
- Creates a Good Samaritan-style law by removing liability for a contracted employee acting in good faith

Passed: Preceptorship Tax Credit
- Creates a tax credit for physicians who serve as preceptors for medical students in rural areas
- Increases better access to health care services in the most remote corners of the state

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Defeated: Vaccines
- Would have removed childhood immunization requirements from private and parochial schools and added "conscientious belief" to Missouri's current religious and medical childhood immunization exemptions
- Would have allowed dentists and pharmacists to administer vaccines
- Would have made it more difficult for employers to decide for themselves regarding requirement of COVID vaccines

women's prison, which has been shown in other states to reduce recidivism and be beneficial for mother–baby bonding. This bill, HB 1897, passed the Missouri state legislature by an overwhelming margin (127–1 in the House, unanimous in the state Senate), and would allow children born to incarcerated women to stay with their mothers for up to 18 months.[4]

Recent Supreme Court decisions have shown that it is now more important than ever for us to speak for ourselves. Very few physicians serve in our local and state governments, and well–meaning politicians, economists, and businesspeople in our legislatures will often establish policies that affect the practice of medicine. Term–limits are also creating a significant "churn" in our state legislatures, so we need to constantly educate and re–educate our representatives on medical and public health issues, as well as unintended consequences. Communicating our work and our successes is also important, and there will likely be an ever–increasing role for social media outreach to inform and expand our membership. As a leader in my national specialty society recently pointed out: "Who is the best person to speak about medicine to your legislature? Your neighbor or you?" It's time for all of us to vote, to get involved in campaigns, and if you're not already a member, time to join and becoming active in your local and state medical societies.

If you are a MSMA member, renew your dues and help recruit new members. If you are not a MSMA member, on behalf of our president and leadership council, please accept my invitation to join in 2023. To learn more about MSMA, renew your membership, or join as a new member, you can call 573–691–4510, email cwilliams@msma.org or visit: msma.org/membership.

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Who Do You Call? The Champion in Our Exam Room

by George P. Hubbell, MD

"If you do not take an interest in the affairs of your government, then you are doomed to live under the rule of fools." — *Plato*

As I reflect on my travels this year throughout the state, I'm amazed at how resilient we've been as a profession in the past year. Despite many major affronts, we have undeservingly taken a lot of the blame through misinformation. In lieu of our evidence–based recommendations, we continue to confront false claims such as physician profiteering from the pandemic.

Missouri physicians simply aren't to blame. As a result, greater than 6 of 10 physicians are experiencing burnout, and 20% intend or have expressed a desire to retire in the next year. If our current time doesn't cry "crisis," tell me anytime in the past two centuries when physicians in Missouri and our profession have been more at risk.

The only consistent stalwart support through it all has been the MSMA, unending even after 172 years, yet still relevant for us and our patients. While we can't fix the all the upheaval alone and look to our big fortresses of industry, don't expect handholding from the insurance industry, the pharmaceutical companies, or even our network of hospitals in which we work.

MSMA embraces the diversity in each of us whether it be by our indicated specialty disciplines, the side of the aisle on which we vote, our ethnic and gender identities, geographic locale, and regardless of who directly employs us. This diversity has truly produced unity and a cause for justice. It's never been clearer how to best face our target audience at the Capitol but through our advocates at MSMA. Aligning the profession provides the positive interaction of emotion with a team as opposed to the personal degradation of isolation. If we don't look after ourselves as a group of professionals, we can't reclaim the support and collegiality that sets us apart from an assembly line worker. We need to restore the public reputation of who we are: compassionate, of great intellect, and exuding goodwill.

As physicians imbuing our basic altruistic nature and placing others before ourselves, we never seem to have the time to face all the growing obstacles. The multitude of pertinent scope–of–practice details, needed med–mal insurance reforms, legislative intrusions into our exam rooms, prior authorization battles, and the burden of EHRs cannot be addressed simply or individually but only by our MSMA organization, (and often while we sleep).

MSMA communication comes in five different ways throughout the year, this journal, *Missouri Medicine*, is the second most rewarded state society journal, only superseded by the *New England Journal of Medicine*. Weekly e–mail blasts keep us up to date in the house of medicine and *Progress Notes* keeps us aware of MSMA news, CMS updates, and changes for compliance on a regular basis. Only a minority of Missouri physicians currently utilize our impeccable, doctor–led insurance company, the MSMA Insurance Agency, which offers independent counsel and expertise specific to medical malpractice. This not found in any other broker in the state; truly working for us and not themselves.

In June, the *Dobbs* Supreme Court decision enacted



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a trigger law that introduced both civil and criminal liabilities for medical management of essential health care for Missouri women. Legislator's actions are now in all our exam rooms, not just OB/GYNs but oncologists, surgeons, cardiologists, et al. Such a decision is "reckless and dangerous," according to AMA President Jack Resnick, MD, in his recent AMA Interim Meeting address. Our patients and their care suddenly don't fit directly into a new state statute, hampering emergent and essential care, which is far more complex now that the courts and state Attorneys General are tasked with discerning whether something that had been well established and essential healthcare in the recent past is now appropriate. Corrective legislative action is needed to fix such a political intrusion into our practices and patients, and the only immediate approach is action through our MSMA advocates.

Burnout that currently affects most of us isn't addressed by a simple hospital CEO invite to go to lunch just to talk or mindfulness classes, both of which are ineffective ovations for frustrating conditions that exist, not by our own doing. MSMA, in conjunction with the Missouri Association of Osteopathic Physicians and Surgeons, and Missouri Academy of Family Physicians is sponsoring a weekend retreat in 2023. MSMA also encourages physicians to utilize the Missouri Physician Health Program, which helps struggling medical professionals return to healthy lives, and is available to all Missouri physicians, physicians–in–training, and medical students.

Additionally, a member physician doesn't have to be without support for grievances, contract disputes, and malpractice claims. Who will you call? Answer: MSMA, who is a physician liaison and has direct relationships with the state's Board of Healing Arts and the Missouri Department of Health and Senior services.

In sum, MSMA makes us one with each other and addresses our real political issues that are close to home. As is said: "all politics is local," and to that something our specialty boards and the AMA miss for lack of local involvement. It is only with MSMA that we can get politics out of Missouri physicians exam rooms, amend prior authorization hassles we all face, confront the myriad of Missouri scope–of–practice challenges, help define and control the pharmacy benefit managers, directly address our burdensome EHRs and their vendors, and have someone have our backs daily in the state Capitol.

Corporate pharmaceutical, medical insurers, and hospitals don't always have your best interest, but MSMA continues to be your champion. Please join me in recruiting a new member, and renewing your pledge today to have an effective voice in Jefferson City. Together we are a choir and will be heard even louder and more resonant in solidarity. **MM**

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Report of the American Medical Association Special Meeting

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

The 2022 Special Meeting of the American Medical Association (AMA) House of Delegates (HOD) was at the Hawai'i Convention Center, Honolulu. As the second HOD meeting, and the first Special (formerly "Interim") Meeting to be held in person for three years, it was especially pleasant to have it in Hawaii. Tropical paradise aside, it is good to be back to meeting in person. Interpersonal interaction is really the point of AMA meetings. Keen observers will note that the AMA has renamed the meeting. It is now the Special Meeting, not the Interim Meeting.

The HOD sessions were better attended than previous virtual meetings, drawing 96% of delegates. The Special (Interim) Meeting focuses on advocacy, particularly on current and pending legislation, other urgent issues, and ethics. Some of the resolutions offered were not considered at the meeting. The Resolutions Committee has been responsible for screening. This process was started with the virtual meetings, and will no doubt become a permanent part of the process. Quite frankly, too many resolutions are submitted to permit adequate consideration of all of them. There was considerable discussion of this process at the meeting, and on whether to include such a screening process for the Annual Meeting.

Jack Resneck Jr., MD, AMA president, addressed the meeting. Physicians have had tough times for the past three years. Physician burnout has grown from 36% to 68% over the period 2019–2021. Some 20% of us plan to retire within two years. We need relief. It's not the doctors who are broken, it's the system. But frustrated doctors just give up, which is burnout, or simply retire. We need to fix our health systems, and take better care of our physicians.

The Physicians Recovery Plan is a series of goals which are designed to promote physician recovery after the stresses of the last two years. Specifically, we must prevent the scheduled 8% Medicare payment cuts. We strongly support the prior authorization reform which is presently working through Congress. Inclusion of a cost–of–living allowance for physician payments is a crucial goal. We will work towards more comprehensive reform of Medicare physician payment. Finally, the AMA will continue to work for health system reform to promote health equity.

James Madara, MD, Executive Vice President, explained the strategic long–term goals of the AMA. He noted that the long–range strategic plan was begun 10 years ago. The plan is dynamic, yearly refining a five–year projection. There will always be unanticipated short–term needs, as well as new initiatives from the HOD. The strategic arcs are removing obstacles that interfere with patient care, confronting chronic disease, eliminating health inequities, and reimagining medical education, and lifelong learning. These are driven by three accelerators: equity, advocacy, and innovation.

We really don't know what the health care system will look like in 10 or 20 years. But we know that it is essential to educate new physicians, to support practicing physicians, and to improve public health. In medical education, a consortium of medical schools will enhance and transform medical education. There is a new consortium of 11 large health systems to improve resident training. Removing obstacles is exemplified by the Physician Recovery Plan. There are physician–controlled companies working to deliver better care and better clinical research. Confronting



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Above, Alternate Delegate Kayce Morton, DO, in the AMA House of Delegates.

Left: The Missouri Delegation to the AMA, L–R standing: Drs. Ravi Johar, Charlie Van Way, and Ed Cabbabe; L–R sitting: Drs. Peggy Barjenbruch, Joe Corrado, Elie Azrak, and George Hubbell.

chronic disease is exemplified by working toward the control of hypertension in cooperation with physicians and with other organizations.

Moving to the main business of the HOD, well over 100 resolutions and reports were considered. Certain themes emerged. The Physician Recovery Plan is strongly being supported. Several resolutions dealt with various aspects of Medicare reimbursement. Health equity was a major theme. There were two open forums on the subject, several reports and resolutions. As expected, speakers generally deplored inequities in the health care system. There are millions of people still uninsured in the U.S. The AMA will continue to work for universal health care. There was debate over whether this will be best done using a single payer system or improvements to our present mixed system. At present, the AMA favors a mixed system.

There was much agitation over abortion. The *Dobbs* Supreme Court decision, which returned abortion regulation to the states, has produced a lot of fallout as states continue to go in multiple directions. Board of Trustees (BOT) Report #2 stated that abortion is a human right and should not be limited by legislation. Abortion is a medical procedure and should be performed by or supervised by a licensed physician. The Council on Ethical and Judicial Affairs (CEJA) Report #1 restated that physicians may ethically perform abortions and that the decision to terminate must be made within the patient–physician relationship. Resolution #8 asked AMA and state societies to support physicians actively defying state law. Resolution #223 changed AMA policy to hold that physicians should not be liable for civil or criminal penalties for abortion a result of medically necessary care or in other circumstances.

Climate change continues to concern many physicians. The Council on Science and Public Health (CSPH) Report #2 calls climate change a "public health crisis," supporting a commitment for the AMA to cut carbon emissions by 50% by 2030 and to be carbon neutral in 2050. It rescinded AMA policy supporting the use of nuclear power to achieve carbon neutrality, although it did not commit the AMA to oppose nuclear power. The question of just how to achieve carbon neutrality without nuclear power was not brought up in discussion.

The HOD continues to deplore gun violence. BOT Report #3 summarized current efforts. It called for a task force on gun violence with yearly reports. Several resolutions addressed such issues as illegally possessed guns, gun safety, safe storage, "smart" guns, suicide prevention, and increased federal funding for firearms research (#907, #908, #909, #922, #923). There is increasing attention being paid to preventing suicide. About 25,000 of the 45,000 firearm deaths in 2020 were suicides.

There continues to be interest in how best to address issues important to employed physicians, who have now become the majority in the AMA. BOT #2 suggested expanding the role of Organized Medical Staff Section (OMSS) and using it to incorporate these concerns into the AMA. This important concern was referred back to the BOT for further study and recommendations.

Resolutions #204 (from Missouri) and #210 (from the Young Physicians Section) called for the AMA to support a change to year–around standard time. Legislation in Congress ("Sunshine Act") favors keeping year–round daylight savings time (Sunshine Act). It passed the Senate in 2022 but stalled in the House. While it is the time change which produces the most harm, sleep specialists pointed out that standard time is better adapted to the human diurnal cycle. Supporting year–around standard time is now AMA policy.

Another Missouri resolution, #205, called for eliminating so–called "waiver of due process" clauses in physician contracts, because they greatly limit the rights of employed physicians. Resolution #203 advocated reducing the administrative burden of hiring International Medical Graduates.

Vaccinations were addressed. Resolution #913 emphasized that there are many HPV–related cancers, not just cervical cancer. The resolution advocated HPV vaccinations but not mandatory vaccination. However, resolution #906 supported mandatory COVID vaccination at all levels of education if the vaccine is fully approved by the FDA.

Obesity management has changed greatly, with better drugs, more reliable surgical options, and extension into the teen–age years or younger. Resolutions #917 and #937 advocated in favor of comprehensive obesity care for children, including bariatric surgery and reimbursement under federal programs for children.

Resolution #911 called for establishing systems of Emergency Cardiac Care (ECC) Centers in each state. There is strong evidence that such care can improve survival for myocardial infarction and cardiac arrests. This may be a good idea, but it was referred for further studies. While this system seems to work well in one or two states, it isn't clear that it would work everywhere.

Medical education is always a concern. The Council on Medical Education (CME) Report #2 addressed inequities in both undergraduate and graduate medical education. Specific concerns were the over–emphasis of medical honor society membership in the Electronic Residency Application Service (ERAS) and the increasing use of online assessments. Resolution #312 asked for demographic reporting and data collection. Resolutions #302, #303, #308, and #309 dealt with medical and parental leave policies for students, residents, and physicians. Resolution #317 dealt with access to abortion training for programs in states prohibiting the practice.

As usual, the HOD dealt with a mixture of physician–specific issues, such as Medicare, and societal issues, such as the public health impact of climate change. There was a lot of very specific action on specific issues. There was also a lot of virtue signaling on issues like climate change and gun violence. We may view this in a couple of ways. On the one hand, the AMA should stay "in its lane," advocating for policies that affect physicians. On the other, the AMA has a legitimate interest in public health, and a large number of societal issues have great effects on public health. In summary, the AMA sees itself as having an additional role beyond simple physician advocacy, which remains important to all of us.

Several Missouri physicians continue to serve in leadership roles. Edmond Cabbabe, MD, serves as chair of the Council for Long Range Planning and Development. Elie Azrak, MD, serves on the board of AMPAC, the AMA Political Action Committee. Jerry Kennett, MD, is on the AMA Foundation board. Kelly Schmidt, MD, is the Chair of the Resident and Fellows Section. David Fleming, MD, serves on the Council on Ethical and Judicial Affairs. Sue Ann Greco is a past president of the AMA Alliance. Charles Van Way III, MD, is on the steering committee of OSMAP, the Organization of State Medical Association Presidents.

Your AMA delegation would very much like to hear from AMA members throughout Missouri about all of the issues discussed at the meeting. The business of the meeting is available on the AMA website. Highlights and all of the reports and details are at https://www.ama–assn.org/house–delegates/interim–meeting The Annual Meeting of the HOD is scheduled for Chicago, June 12–16, 2023. We expect that it will take place as planned, in person. Meanwhile, the AMA continues to advocate for physicians and their patients at the national level. **MM**



MSMA: 173 Years as YOUR Advocate

The 2023 legislative session will begin on January 4, 2023. This marks MSMA's 173rd year of advocating for Missouri physicians. With a new basket of rookie legislators, and new leadership in both chambers, we are hoping for a productive session. As a result of term limits, the Senate will not include a physician for the first time since 2011. On the other hand, the House republicans have elected a physician as their new floor leader.

MSMA's Lobbying Team

MSMA is bringing three new lobbyists on board this session.



This will be Rich AuBuchon's 18th session in Jefferson City. Rich is a graduate of Westminster College and the University of Tulsa Law School. He is a successful litigator and has served in several roles in state government, including working as senior staff for Governors and Lieutenant Governors. Rich is one of the state's most knowledgeable tort reform lobbyists.

Trent Watson has been working the Capitol halls as a registered lobbyist since 2006, and is well–regarded for his effective advocacy. He worked in the Senate for a number of years prior to lobbying. Trent has been named a top lobbyist by *The Missouri Times* on multiple occasions. Trent's professionalism is beyond reproach, and he has a contact list that stretches from Jefferson City to Cape Girardeau and back.



Deanna Hemphill will begin her 16th session as a Missouri lobbyist in 2023. She has represented a number of diverse interests over the years, and brings a valuable set advocacy skills with her to MSMA. Deanna is well–respected by her colleagues and legislators, and has been involved with a wide array of legislative issues over the years. She is a natural leader.





MSMA Executive Vice President Jeff Howell will be spending a bit more time at the Capitol this session. This will be his 16th session as a registered lobbyist. This year's advocacy team will have nearly 80 years of cumulative advocacy experience in Jefferson City.

MSMA Keeps You Informed

Between January and May, MSMA increases the amount of advocacy content it produces. Each week (with the exception of the legislative spring break), MSMA members will receive our *5 Things You Need to Know* every Monday morning. As usual, the world famous *MSMA Legislative Report* is distributed to

the membership each Thursday afternoon during the session. Look for the year–end *Legislative Review* in late June.

MSMA will once again be producing a "Lunch with a Legislator" videoconference series. This year, we plan to have six videoconferences with a wide variety of legislators and issues. We are joining forces with the Missouri Association of Physicians and Surgeons (MAOPS) this year in sponsoring a single Physician Advocacy Day, instead of having one for each organization. It is scheduled for February 7 this year. Physicians and medical students can register for these events at msma.org/PAD.

What To Expect

We expect more than 2,000 pieces of legislation to be introduced this year. In a normal year, about a fourth of those have some impact on healthcare. Following are a few issues that we expect to deal with in 2023.

Advanced Practice Registered Nurses (APRNs)

The APRNs have been very consistent in their desires to repeal Missouri's collaborative practice laws. Although they have not been successful in riding themselves of it entirely, they have nibbled around the edges over the years to loosen supervision requirements. We're not quite sure what the APRNs have in store for us this year, but we're pretty sure they will be active. As noted above, there is no longer a physician in the Senate to serve as a backstop, so they likely will feel emboldened to further weaken—or try to repeal—collaborative practice.

12–month Postpartum MO HealthNet Expansion

MSMA will be part of a broad coalition attempting to extend MO HealthNet postpartum benefits from 60 days to one year. This issue fell victim to a few Senators who threatened a filibuster over it. In addition to the relationship this issue has with the Dobbs ruling, providing these benefits reduces healthcare expenditures in the long term. Besides, extending these benefits to moms and babies is the right thing to do, and the state has plenty of money to do it.

Trigger Law

Speaking of women's health, MSMA will join a coalition of like–minded organizations in an attempt to make adjustments to the state's Trigger Law, which went into effect shortly after the *Dobbs* decision. MSMA is opposed to the criminalization of the practice of medicine, and is in favor of kicking the government out of the exam room. This is be a difficult issue to tackle, but we hope to make some headway this session.

Prior Authorization

MSMA will be working with a few other provider groups to enact a "gold card" prior authorization law. This would allow physicians (and other providers) to have their requests deemed approved if they have a history of greater than 90% approval. The language of this bill will be complicated, and the insurance carriers are sure to think it's the end of the world, so we expect significant resistance.

State–Funded Residency Slots

There are still far too many medical students to fill available GME slots. Many states have begun to fund new slots on their own, and this is something we hope to have Missouri decision–makers do during the legislative session. There will likely be restrictions if something were to pass and this would require a multi–year commitment from the state. This might be the year to tap into the state's expected surplus.

Pharmacist Prescribing

The COVID pandemic required the suspension of various administrative rules. Some were necessary; some weren't. Many removed patient safety guardrails and expanded scope–of–practice for non–physicians. This gave the pharmacists the idea that statewide standing orders for the dispensation of drugs was a good idea, no matter what the public's best interest might be. Taking individual physicians out of the loop when it comes to the treatments afforded their patients is a non–starter.

These are just a few of the issues we expect in 2023. Every year, new things are introduced and old issues that have run their course fade away. Once the calendar turns, keep an eye on your email inbox for MSMA advocacy publications. That is the best way to stay informed on the issues that affect you, your patients, and your profession.

Your lobbyists are honored to carry the MSMA banner this year. If you would like to get more involved in physician advocacy, send MSMA EVP, Jeff Howell an email at jhowell@msma.org. **MM**

Contribute at msma.org/mmpac

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Risky Business: Violence in Healthcare

by Alison L. Huckenpahler, MD, PhD & Jessica A. Gold, MD

Verbal and physical workplace violence contributes to burnout and high turnover rates in medicine.

On June 2, 2022, a disgruntled patient entered St. Francis hospital in Tulsa with a pistol and a semi–automatic rifle. The gunman had previously had back surgery by a physician, Preston Phillips, MD, and, per reports, blamed him for his post–surgical pain and wanted revenge.[1]



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He ultimately ended up murdering his intended target, Dr. Phillips, as well as another physician and two others who got in his way. Though Dr. Phillips' story got more attention in the press and physician murders are more sensationalized, his story is unfortunately not unique; less than two weeks after the Tulsa shooting, a nurse, and a paramedic were stabbed and critically injured by a patient in a St. Louis hospital.[2]

Overall, there is not a lot of data on the murders of healthcare workers, but the Bureau of Labor statistics reported 64 on–the–job fatalities for healthcare workers in 2020.[3] Non–fatal assaults, on the other hand, are far more prevalent, with close to half a million in 2020,[4] and with healthcare accounting for nearly as many serious violent injuries as all other industries combined.[5,6] The data are limited by the sheer lack of reporting on workplace violence. Even the American

Medical Association (AMA) Taskforce on Workplace Violence acknowledges that "available data indicate that health care workers experience high rates of workplace violence [but] such events are widely underreported."[5–7] This is typically due to a lack of faith that reporting would lead to meaningful change, not having time to report, lack of a formal reporting system, and fear of retaliation.[5,7] In this review, we discuss the scope and magnitude of workplace violence in healthcare, the subgroups most affected, how the COVID–19 pandemic has impacted rates of violence against healthcare workers, and strategies for reducing risk.

Workplace Violence by Subgroups

Patients are responsible for the majority of violence towards healthcare workers, thus trends in violence can be best understood by examining which patients pose the highest risk for violence. The risk of workplace violence is not distributed evenly across specialty. Data shows that those who work in the emergency department, in geriatrics, or in psychiatry are substantially more likely to experience violence.[8] This may be partly explained by the fact that these patient populations are more likely to be intoxicated, exhibiting psychosis, delirious, or have dementia, which are known risk factors for violence.[5,6,9–13]

Beyond specialty, practice setting also impacts the risk of violence. Rates of workplace violence in hospitals are over double the risk of ambulatory care settings.[4] Unsurprisingly, psychiatric workers have the highest incidence rate of non–fatal injuries at more than 10 times the rate of other hospitals.[4,5] Long–term nursing and residential care facilities are also at increased rates of violence, about 75% higher than the rate of violence in the hospital.

Job position contributes to a worker's vulnerability to violence. Nurses, who typically have more day–to–day interactions with patients,[14,15] are far more susceptible to workplace violence than physicians.[3,4] It is worth noting that position and specialty have an intersectional effect and nurses who work in nursing homes or psychiatric facilities experience 3.5 times as many violent incidents as registered nurses[5] because of the additive effects of their position and their specialty. The cumulative burden of violence faced by psychiatric and nursing home nurses has contributed to a staggering shortfall of nurses in these areas.[16,17] In Missouri, the Department of Mental Health reports that "35% of registered nurse positions are vacant, 57% of licensed practical nurses are vacant, [and] 32% of entry–level psychiatric tech positions are vacant" and are unable to be filled.[17]

Despite the overall elevated rates of violence in United States (U.S.),[18] American healthcare workers experience comparable rates of violence as workers in other countries.[19] Studies show that healthcare workers who were born and educated in another country, but currently practice in the U.S. are more susceptible to workplace violence.[20] This is likely due to both xenophobic attitudes towards foreign physicians,[21] as well as potential language barriers.[20,21]

The Impact of COVID–19

In the context of the ongoing Covid–19 pandemic, violence against healthcare workers has worsened; the baseline environment is tenser, 'fuses' are substantially shorter, and it is far easier for violence to materialize. A meta–analysis performed in 2019 found that 69% (95% CI 58% to 78%) of healthcare workers experience workplace violence,[19] while a comparable meta–analysis performed in 2021 showed a sharp increase to 77% (95% CI 72% to 82%).[19] These statistics have become such a concern that the AMA adopted a new health policy to address the astounding rise in violence towards physicians. In their resolution, the AMA acknowledged the increase in violence "including physical violence, intimidating actions of word or deed, and cyber–attacks, ...particularly those [violent incidents] which appear motivated simply by [the victim's] identification as health care workers."[22] A study categorizing the increased violence towards healthcare workers during the pandemic found that the majority were related to disputes over masks, but in 22% of cases, the perpetrator intentionally coughed or spit on the healthcare worker while threatening to infect them.[23]

In the high–intensity setting of a hospital during the pandemic, increased violence compounds the burnout experienced by healthcare workers and contributes to healthcare's increasing resignations. It is well–established that workplace violence, both verbal and physical, contribute to burnout and drive high turnover rates in medicine.[24–28] In the face of violence and burnout, healthcare is experiencing an exodus of skilled healthcare employees. The number of physicians leaving medicine has quadrupled since 2019, increasing from 0.39% of physicians each year in 2019 to 1.3% of physicians in 2021,[29] resulting in an additional 10,000 doctors per year are leaving medicine.[30] Nurses have also been quitting in droves.[31] Surveys and interviews

overwhelmingly report that their decision was driven by the violence and burnout they've experience during the pandemic.[32–34]

Strategies to Protect Healthcare Workers

While violence towards healthcare workers is an evident problem, and one necessary to improve for workplace sustainability, there is wide disagreement on how to address the problem. Although the Occupational Safety and Health Administration (OSHA) has created sets of recommendations on how to limit violence towards healthcare workers, there is no specific enforceable standard.[6] Without a national enforceable standard, the decision is left up to the states and at the time OSHA published their report, only 10 states had passed legislation requiring programs on workplace violence prevention.[6] Concerningly, hospitals with these programs are seen to be the models to aspire to, rather than the standard.

Ultimately, there is no simple solution. An international report breaks the problem down into three phases: prevention measures to reduce violence, protection measures to handle violent incidents in the moment, and treatment measures to prevent the long–term consequences to healthcare workers.[35] When examining how to address violence towards healthcare workers, interventions must include a mixture of these three things to target prevention, protection, and treatment.

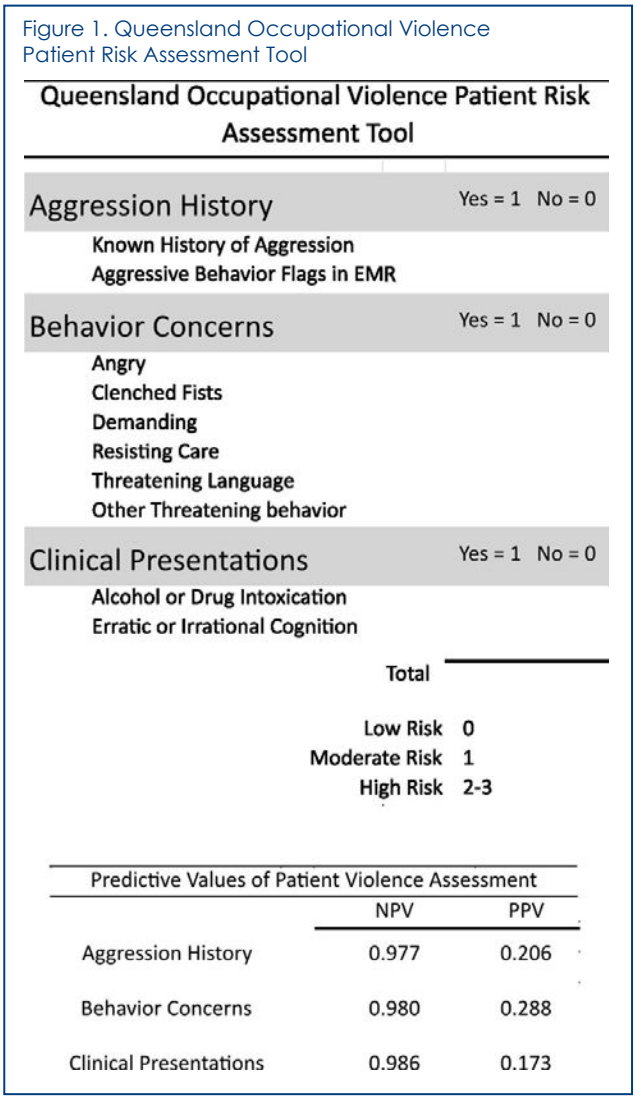
Starting first with prevention, hospital prevention strategies look at ways to prevent violence altogether and encompass a wide–range of strategies including de–escalation training for staff, electronic medical record flags and risk assessments for previously violent patients, and appropriate staffing ratios. A qualitative study investigating effective de–escalation techniques found that the most effective de–escalators apply rules thoughtfully, actively demonstrate equality and break down social barriers with patients, demonstrate shared humanity (through humor or self–disclosure), and show authenticity.[36] Studies have found that de–escalation training programs which teach healthcare workers these strategies to reduce tensions with patients are effective in preventing violence. The joint commission discusses several such programs, all of which focus on identifying the triggers and strategies for defusing tension.[37] One such program, Safewards, focuses on how staff may impact the environment, as well as how they can identify and react to flashpoints, which may spark conflict with patients. This program, which has a wide array of resources online, includes interventions such as clear mutual expectations, bad news mitigation, mutual help meeting, and calming down methods. Data suggests that the benefits gained from de–escalation training extinguishes at about six months, underlining the need for continuous education.[38]

Studies of risk assessment in psychiatric wards found a significant reduction in patient aggression after implementing a risk assessment on violent patients.[39,40] Several patient risk assessments tools exist, ranging in length from three to sixteen metrics.[41–44] The most effective assessments, like the Queensland Occupational Violence Patient Risk Assessment Tool, are quick, reliable, and allow healthcare workers to effectively evaluate potential risk (Figure 1). Finally, appropriate patient ratios are linked to a decreased risk of violence.[5] Providers who worked evening shifts, where patient ratios are less favorable, were up to 5.5 times more likely to be assaulted by patients;[45,46] though more investigation is needed to determine the size of effect. There has been substantial efforts by nursing organizations to pass legally mandated patient ratios, but so far only two states (California and Massachusetts) have laws codifying safe nurse to patient ratios or standards.[47] Nursing organizations have proposed fixed nursing ratios, ranging from 1:1 in the operating room and trauma bay to 1:6 in a well–baby nursery.[48] The ratios suggested for the ED and psychiatric units, areas at high risk for violence, were 1:3 and 1:4 respectively.[48]

Protection strategies focus on how to mitigate the risk in the moment and include interventions like panic buttons, metal detectors, and self–defense courses aimed at protecting staff. Unlike prevention strategies, which aim to prevent violence completely, protection strategies aim to minimize the severity of violence once it has erupted. After COVID–19 tripled the number of assaults of staff, a hospital in Branson, Missouri, issued panic buttons to staff. Reports from other hospitals using panic buttons indicate that it has decreased security response time.[49] Similarly, studies have demonstrated that while metal detectors effectively remove weapons in the hospital,[50,51] they do not decrease the number of assaults overall.[50] Although these mitigation strategies seem to be common sense approaches, little data has been published on their efficacy, making it difficult to fully assess their role in decreasing violence against healthcare workers.

Finally, if violence actually reaches the healthcare

Figure 1. Queensland Occupational Violence Patient Risk Assessment Tool



Queensland Occupational Violence Patient Risk Assessment Tool

Aggression History	Yes = 1 No = 0
Known History of Aggression	
Aggressive Behavior Flags in EMR	
Behavior Concerns	Yes = 1 No = 0
Angry	
Clenched Fists	
Demanding	
Resisting Care	
Threatening Language	
Other Threatening behavior	
Clinical Presentations	Yes = 1 No = 0
Alcohol or Drug Intoxication	
Erratic or Irrational Cognition	
Total	
Low Risk	0
Moderate Risk	1
High Risk	2-3

Predictive Values of Patient Violence Assessment		
	NPV	PPV
Aggression History	0.977	0.206
Behavior Concerns	0.980	0.288
Clinical Presentations	0.986	0.173

Figure 1. The Queensland Occupational Violence Patient Risk Assessment Tool (QOVPRAO, pronounced kvow–pro) provides a quick and effective method for evaluating patient's potential for violence in the hospital without relying on a patient's cooperation or putting the provider at any unknown risk in simply asking questions. It looks a history of aggression (as either noted in their chart or legal history), behavioral cues of the patient, and clinical presentation to assist providers in evaluating risk and provides a validated mechanism for quantifying risk during notes (low, moderate, high). Most importantly, each metric has a high negative predictive value (97.7–98.7%), meaning that a patient with a score of zero is highly unlikely to pose a threat to healthcare providers. This figure, as well as the positive and negative predictive values were adapted from Cabilan et al.[41]

worker, the hospital should have safe, easy, and confidential reporting combined with treatment for the victims. One of the primary difficulties in violence reduction is the lack of standardization in how data is collected. A 2022 study examined the compliance of California hospitals with workplace violence reporting regulations and found huge variation in reporting practices. Even within the same state, following the same legislation, some hospitals required reports to be made to security or management and some hospitals only reported incidents in physical harm to the employee.[52] A system which requires healthcare workers to report to a manager or limits reporting only to incidents in which the victim was physically harmed exacerbates the problem, since fear of retribution and lack of confidentiality is a major driver of under–reporting.[5] The reporting system needs to acknowledge that physical and verbal assaults impact healthcare workers equally [28] and need to be addressed equally. Given the potential for assaults to contribute to worsened mental health outcomes,[53] it is important that employees have quick, affordable, and easy access to confidential care, if or when they need it.

Conclusion

Violence impacts all healthcare workers and unfortunately, the rise of incivility means that assaults on healthcare workers will continue to be a problem for the foreseeable future. There is the pragmatic argument that reducing violence in the hospitals brings ensuing benefits (increased patient metrics, decreased staff turnover, and increased productivity), which ultimately benefit the hospital and patients. There are also more compelling moral arguments to ensuring the safety of healthcare workers. Every worker is entitled to a safe workplace, no matter where they work, in what role, or in what specialty. Evidence shows that certain employees will be at increased risk due to non–modifiable factors (e.g., country of origin), so addressing violence in the healthcare setting is not just an issue of safety, but one of equity. Healthcare workers, who often make huge sacrifices for their professions, and often put their patients before themselves, should not be put at risk in their jobs, period. Making investments in staff training and infrastructure now is the most effective way to ensure staff safety and create a healthcare system that is more humane for both its employees and its patients.

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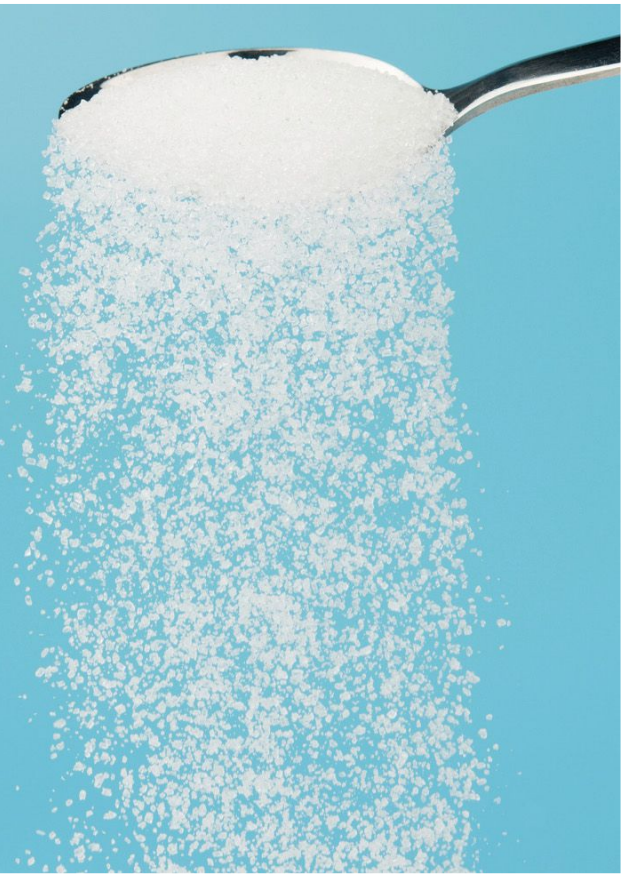
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Added Sugars Drive Insulin Resistance, Hyperinsulinemia, Hypertension, Type 2 Diabetes and Coronary Heart Disease

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



> **"The evidence incriminating insulin and carbohydrate in atherogenesis is strong, and that this scheme would link atherosclerosis with diabetes, obesity, hyperlipemia, lack of physical exercise, and, possibly, hypertension."**
>
> ***– Stout and Vallance–Owen 1969[1]***

It has been known for over 50 years that abnormal carbohydrate metabolism and elevated insulin levels drive high blood lipids.[2] This is because insulin increases the endogenous synthesis of fatty acids (lipogenesis).[3] Elevated levels of insulin are found in many diseases states, such as obesity, type 2 diabetes (T2D), hypertension, peripheral vascular disease, and coronary artery disease.[4] In individuals who have normal blood pressure, the higher the insulin level the higher the blood pressure.[5–7] Elevated insulin drives salt–sensitive blood pressure and precedes hypertension in many instances.[8] For example, insulin resistant individuals have an impaired excretion of sodium in the urine when put on higher sodium intakes.[9]





James J. DiNicolantonio, PharmD, (left), and **James H. O'Keefe, MD**, (right), are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri.

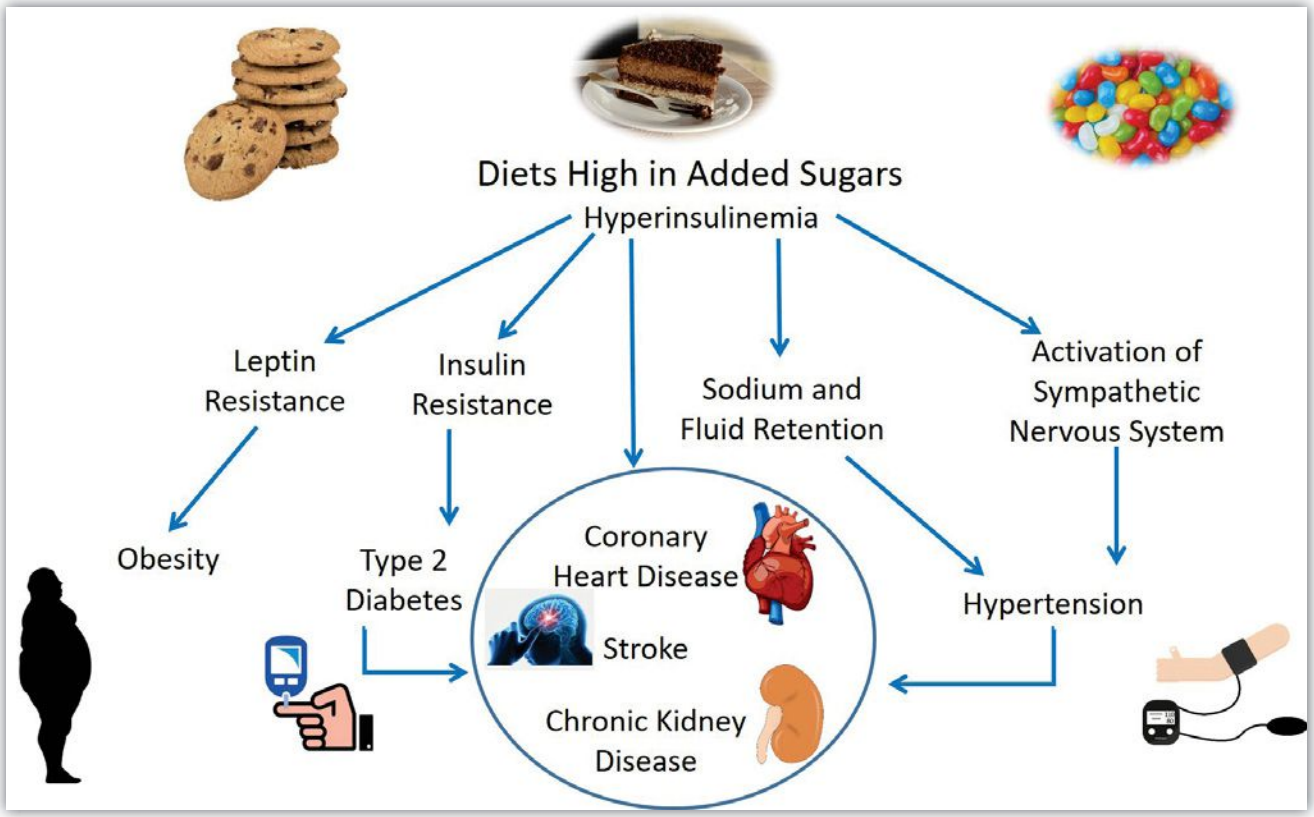


Figure 1. Approximately 13% of the U.S. population consumes at least 25% of their total caloric intake as added sugars.[68]

Elevated insulin results in sodium and fluid retention.[10, 11] Hyperinsulinemia also enhances sympathetic activity and increases plasma noradrenaline levels.[12–16] This enhanced sympathetic activity also stimulates the renin angiotensin system,[13, 17, 18] thereby promoting further sodium retention.

Salt–sensitive hypertensive patients are more insulin resistant.[19] Several studies have shown that people with normal blood pressure or high blood pressure who are salt–sensitive are hyperinsulinemic, insulin resistant or both compared to those who are salt–resistant.[8, 20–28] A large portion of salt–sensitive hypertensives are insulin resistant.[25, 29] However, individuals who are insulin resistant still retain their sensitivity to insulin's ability to promote urinary salt and fluid retention.[30] Thus, hyperinsulinemia drives sodium and fluid retention.[10, 11, 14, 30–34] Improvements in insulin sensitivity via weight loss and exercise decrease salt sensitivity.[35] Whatever dietary substance causes hyperinsulinemia leads to sodium and fluid retention and elevated blood pressure. It turns out that the chief dietary culprit driving hypertension may not be salt, but the other white crystal, sugar.[16, 36–41] Lowering the intake of refined sugars may be an effective strategy for reducing the incidence of hypertension.

Added Sugars Drive T2D and Coronary Heart Disease

The isocaloric replacement of starch, glucose, or a combination of both, with added sugars (sucrose or fructose), increases fasting insulin levels,[42, 43] reduces insulin sensitivity,[36, 38, 44] increases fasting glucose levels,[45] increases glucose and insulin responses to a sucrose load,[42, 43] and reduces cellular insulin binding.[36] In other words, calorie for calorie, consuming added sugar is more harmful than starch or glucose in regards to worsening hyperinsulinemia, insulin sensitivity

and glucose tolerance all of which are risk factors for cardiovascular disease.[46–49]

Individuals who consume 10–24.9% of their calories from added sugars, have a 30% higher risk of mortality from cardiovascular disease compared to those who consume less than 10% of their calories from added sugars.[50] A systematic review of 12 studies encompassing over 400,000 people found that the consumption of sugar–sweetened beverages was significantly associated with higher blood pressure and an increased incidence of hypertension.[51] Globally, sugar–sweetened beverage consumption is implicated in causing approximately 180,000 deaths per year.[52]

A diet high in added sugars also increases the prevalence of T2D; in contrast, when sugar intake is restricted the risk of T2D is reduced.[53–55] In humans, when added sugar is restricted to < 5% of total caloric intake there is an approximate 50% reduction in the prevalence of prediabetes/T2D.[53] Overconsuming sugar leads to fat cells that are less sensitive to the effects of insulin, which drives visceral adiposity.[56, 57] Consuming a diet high in added sugars for just a few weeks increases triglycerides, uric acid, lowers high–density lipoprotein cholesterol, and alters platelet function,[58–61] abnormalities that are found in patients with coronary heart disease or with risk factors for coronary heart disease.[62–65] Conversely, lowering the amount of added sugar in the diet will improve all of these cardiovascular risk factors.[42, 61] This suggests that overconsuming added sugars is a major contributor to hypertension, T2D and heart disease. Figure 1 shows the sequence of events for how the overconsumption of added sugars leads to hyperinsulinemia, hypertension, T2D, and heart disease. Figure 1 also depicts how a diet high in added sugars drives hypertension, T2D and heart disease.

Over the past 200 years, the average intake of added sugars went from 4 to 120 pounds per person per year.[66] In the United States, around 75% of all packaged food items or beverages contains added sugar.[67] Approximately 13% of the U.S. population consumes at least 25% of their total caloric intake as added sugars[68] (Figure 1). These current levels of sugar intake are fueling an epidemic of T2D, obesity, and coronary heart disease. Limiting the consumption of foods and beverages that contain added sugar would be a simple and effective strategy for improving the health of the population. One strategy that has already been implemented in the United Kingdom is a tax on sugar–sweetened beverages that contain high levels of added sugar, which has been shown to be effective among people in poorer socioeconomic circumstances.[69]

When it comes to health, there is nothing sweet about added sugar. Added sugars are used in approximately 75% of packaged foods in the United States.[67] The average American consumes a quarter to a half pound of sugar per day.[66, 70] What was once a sweet treat in the form of an apple, or a bit of wild honey, now takes a white crystalline form, and it has become a dietary staple that's hurting the health of the population.

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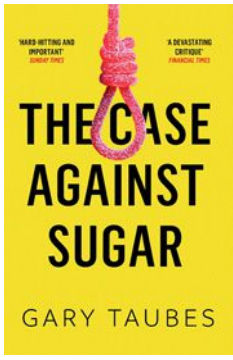
Disclosure

JHO is an owner of a nutraceutical company. **MM**

BOOK REVIEW

The Case Against Sugar

by Gary Taubes



Among Americans, diabetes is more prevalent today than ever; obesity is at epidemic proportions; nearly 10% of children are thought to have nonalcoholic fatty liver disease. And sugar is at the root of these, and other, critical society–wide, health–related problems. The author delves into Americans' history with sugar: its uses as a preservative, as an additive in cigarettes, the contemporary overuse of high–fructose corn syrup. He explains what research has shown about our addiction to sweets. He clarifies the arguments against sugar, corrects misconceptions about the relationship between sugar and weight loss; and provides the perspective necessary to make informed decisions about sugar as individuals and as a society.

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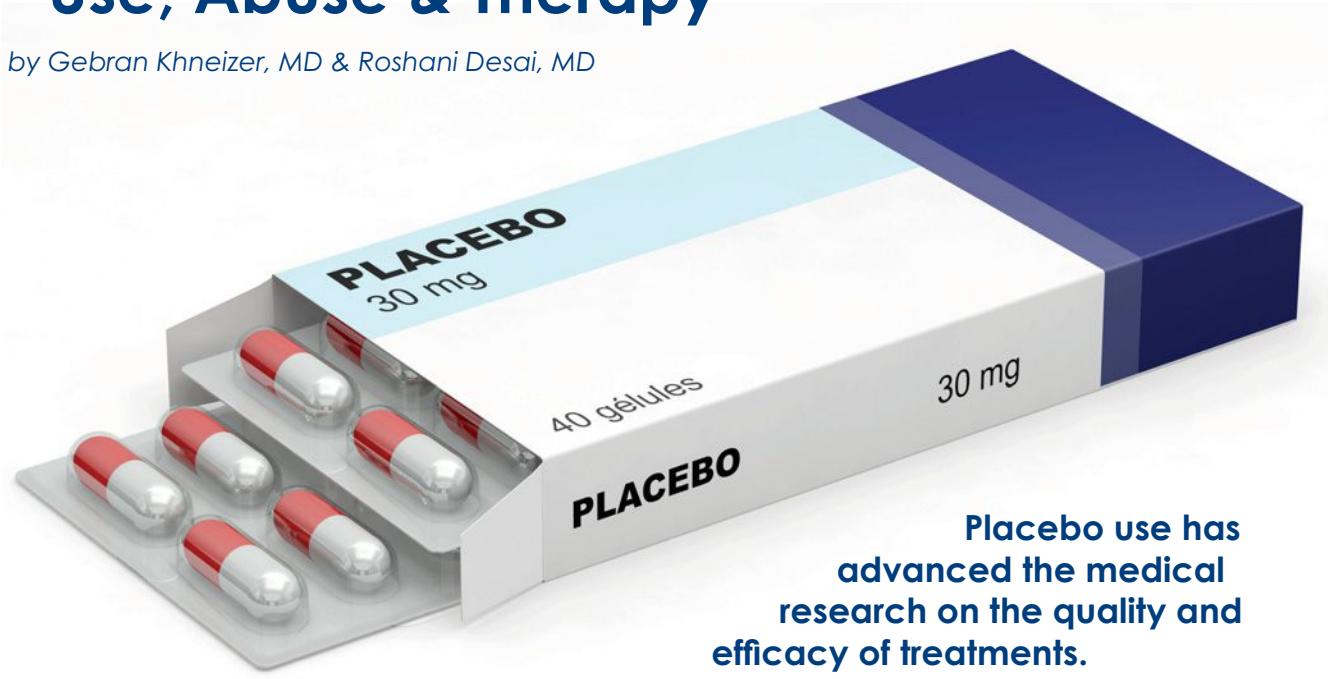
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50 Years Ago, Sugar Industry Quietly Paid Scientists to Point Blame at Fat

Source: NPR.org September 2016

Placebo Use in Medicine: Use, Abuse & Therapy

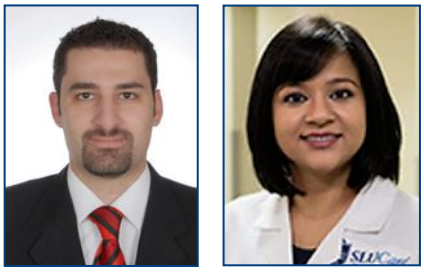
by Gebran Khneizer, MD & Roshani Desai, MD



Placebo use has advanced the medical research on the quality and efficacy of treatments.

Background and Definition of Placebo

A placebo is defined as a substance or procedure which is void of therapeutic value and can be used in multiple forms including tablet, physical, psychological, or surgical. While placebo has been a known notion since ancient times, the concept of placebo was initially introduced to the medical field in the late 18th century and currently has a designated role in the medical research. Examples of placebo include the use of oral or sublingual tablets of inert substances. They are considered placebo as they are without known intrinsic therapeutic properties. Other examples of procedural placebos are the use of intra–articular injections of inert substances or the use of sham surgeries. While at times considered controversial, placebo use has been instrumental in advancing the medical and healthcare knowledge as well as the quality and efficacy of treatments.



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History of Placebo and the Placebo Effect

The early mention of placebo in the medical literature dates to the late 1700s when English physician, Dr. Alexander Sutherland, coined the term to describe a physician with great bedside manners.[1] The term placebo was later used by William Cullen, a Scottish pharmacologist, to annotate the practice of prescribing a drug that was perceived to be ineffective according to the medical knowledge at that time.[1] This was done to

satisfy a patient's request for a remedy and meet their expectations rather than aiming to cure the underlying illness. At that time, placebo meant any substance regarded as a weak or ineffective medicine for a particular ailment. The use of placebo in this context was widely prevalent during this period. However, the approach to placebo uses progressively changed with the introduction of the concept of utilizing an inert substance without any pharmacological effect. Some materials that were commonly used include sugar and breadcrumbs. One example of this practice was described in the treatment of syphilis. In the 1800s, before the use of penicillin, patients were prescribed pills that were made of breadcrumbs in the treatment syphilis.[2]

More recently, placebo has been employed in clinical trials to test the effectiveness of a new treatment. Scientists compare the characteristics of a group of participants who received the study drug to those who received the placebo drug. Based on this, a conclusion is derived about the study drug's efficacy in achieving preset clinical parameters and end points. Typically, both study groups, intervention group and placebo group, as well as the investigators and study staff are blinded to the nature of the treatment that they receive. If no difference is seen between those two groups, the study drug is thought to be no different in efficacy than placebo. However, a new paradigm emerged noting that the lack of difference between the study drug and placebo groups can be indicative of other factors, including a component of patients' psychology and other non–pharmacological mechanisms at play rather than a treatment's lack of efficacy. The "placebo effect" was further defined as an improvement of a clinical condition through use of a sham treatment secondary to the patient's perception of that intervention. The examined disease and perceived outcome also impact the effect of placebo. For example, in the context of the treatment of pain, placebo has been shown to have a small beneficial effect based on the patient's perception, even though that there was no evidence of a powerful clinical effect.[3] The placebo effect is now regarded as a complex interplay of a patient's specific underlying psychological factors and neural pathways. The anticipation of an improvement with the prescribed treatment and a belief of its efficacy are fundamental to the concept of placebo effect.

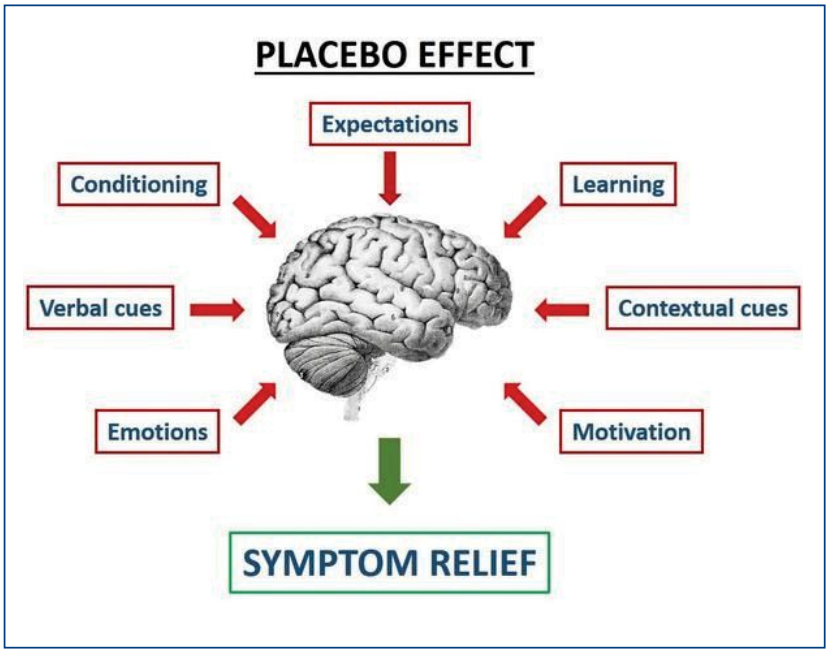
Placebo controlled trials were first conducted in the 1940s, soon followed by the landmark paper "The Powerful Placebo" which called attention to the placebo effect and underscored the importance of considering this concept to accurately determine a treatment's efficacy.[4] In that meta–analysis of 15 studies, placebo was used to alleviate multiple symptoms, including pain, cough, and anxiety. Placebo showed an improvement, on average of 35% of symptoms. Following this study, the interest in examining the placebo effect has progressively grown in the medical literature. Today, research data that is based on randomized double–blind placebo–controlled trials remains the highest quality of evidence available to test the efficacy of a specific treatment.

Uses of Placebo in the Clinical Practice and Research Field

Placebo has ubiquitous uses in clinical practice and research. For instance, in chronic pain conditions, clinical improvement is seen with a placebo response but is further strengthened by patient–centered care.[5] To help further differentiate the different roles of placebo, a distinction between pure and 'impure' placebo nomenclature was created. Impure placebo is identified as a substance with pharmacologic effect that is suspected or recognized to have no effect on clinical disease but is given for a potential psychological benefit.[5] On the other hand, pure placebo is an inactive substance without direct physiologic effect. Examples of impure placebo include the use of antibiotics in viral infections or vitamin infusions in the treatment of cancer, while examples of a pure placebo would include saline injection or the use of sugar–filled capsules. It is important to note that there remains a lack of consensus on the definition of 'impure' placebo.

Placebo has also been used in the form of a placebo surgery, or sham surgery, which involves replicating the surgical procedure setting with anesthesia use and an incision but without an intervention otherwise. In a study by Moseley

et al., participants with knee osteoarthritis were randomized under double–blind conditions to three groups of arthroscopic debridement, lavage or placebo surgery.[6] Both patients and the study personal who performed the assessment of the outcome were blinded to the patient's assignment to treatment and placebo groups. The surgeon who performed the procedure did not participate in the outcome analysis. Placebo surgery involved a skin incision with a simulated debridement without inserting the arthroscope, while the interventions included either debridement or lavage. The aim was to evaluate the efficacy of arthroscopic surgery of the knee in pain relief at two years. Remarkably, the placebo surgery group described a pain relief that is similar to the group who underwent the lavage or debridement surgical interventions over a two–year period.[6]



In contrast to prior practices, the current use of pure placebo as a deceptive form of treatment is rare and more importantly, is considered unethical. Prescribing supplements or drugs as 'impure' placebos is a widespread practice, particularly in chronic pain conditions.[7,8] In 2008, a national survey of 1200 practicing internists and rheumatologists reported that approximately 50% of physicians used such prescribing practices, and 62% of those physicians believed the practice to be ethically permissive.[7] In particular, the most commonly used placebo treatments in this U.S. study were over the counter analgesics at approximately 41% of prescriptions, followed by antibiotics and sedatives. Alarmingly, even use of saline and sugar pills was reported, albeit to a lesser degree, of around 2% of surveyed physicians.[7] Interestingly, the physician's description and presentation of the actual placebo is an important factor. Most physicians label placebo as a potentially beneficial medicine or treatment, but only 9% refer to them as a placebo.[7]

The frequency of prescribing pure placebo substances and impure placebo therapies differs.[9] In a European study, of 500 patient contacts per month in the United Kingdom (UK) and 1,000 in Germany, it was estimated that around 2% of UK general practitioners (GPs) prescribed pure placebo compared to 9–14% of German counterparts. On the other hand, prescribing non–specific therapies was much higher in both groups and approximated at 89% of GPs in the UK as opposed to around 57–69% of their German counterparts. The estimated use of 'impure' placebo was variable. Use of vitamins was reported by 23%–75% of GPs, use of antibiotics by 17%–69% of GPs, and use of supplements by 35%–59% of GPs. This study showed that while impure placebo use is not as prevalent as pure placebo use, both remain in the toolkits of practitioners.

Similar trends were also seen in another German study.[10] In 2014, a German survey regarding the use of pure and impure placebo use was sent to GPs, internists, and orthopedic specialists. This study found that the use of placebos, both pure and impure, were more commonly utilized by GPs and least used by orthopedists. It was also found that impure placebos were more commonly used

than pure placebos. Finally, it was found that the physician's attitude and belief in the use of alternative and complementary medicine impacted the behavior of prescribing such substances.[10] Such prescription practices pose significant ethical challenges, as the perspective and attitude towards placebo use can differ substantially between health care providers and patients. Within the healthcare provider group itself, opinions on placebo use remain divergent. Healthcare providers often have different reasons for prescribing placebo, some of which include satisfying patients' demands for treatment, offering a treatment option to patients with an incurable disease, or providing treatment for nonspecific symptoms.[11] Maintaining the patient–doctor relationship is a prominent motive for placebo use, primarily to avoid conflicts, limit drug addiction, and to shy away from telling patient that treatment options are limited.[11] Such complex interactions between patients and their health care provider create an ethical dilemma that is compounded by insufficient data and lack of evidence.[8]

Another role of placebo is to help differentiate functional etiologies of disease from organic causes.[8] While the use of placebo in this capacity is rare, there is an increased interest in pursuing open label placebo randomized trials whereby participants are aware that a placebo is given. One example is a study of patients with irritable bowel syndrome who were randomized in an open label fashion to either a no–treatment group or a placebo pill group.[12] Patients met with a health care provider prior to the randomization and were informed that the placebo was an inert and inactive pill without any medication in it with "self–healing properties" and the placebo effect was described to the participants. Patients in the open–label placebo group had higher reduction in symptoms as measured by standardized scales as compared to those in the no–treatment group. This study evidenced that an openly described inert placebo can be used and produce a symptomatic improvement without need for blinding or even deception.[12] Limitations of report bias and selection bias of motivated participants were noted in this study and could have impacted the results due to the open label study format.

Ethical Considerations of Use of Placebo

Placebo use in clinical trials, a robust debate is ongoing related to its ethical implications and whether such placebo use should be halted. The purpose of introducing placebo into clinical trials is to separate the effect of the drug in question from the presumed lack of effect of placebo.[13] Arguments against the use of placebo in clinical trials focus on the thought that patients may be deprived of potential effective treatments.[14] Critics has also raised the concern that placebo use can potentially lead to delays of the proper diagnosis and timely treatment of diseases with the current standard of care therapy. Some argue placebo use is noncontributory to the daily clinical questions that physicians face, which revolves around the choice of one treatment among two possible treatment modalities rather than choice between one treatment or a placebo.[15] Placebo use can also potentially interfere with the proper effect size estimation of the specific treatments at question.[15] Some argue that the aim of both the physicians and the patients is to clarify and measure the total effect of an intervention, rather than the consequences and course of the disease if that intervention was not used. When there is a large psychological component of the placebo used in trials, the effect size of the intervention is perceived as small but the total effect including placebo might carry a significant clinical interest. In that context, placebo–controlled trials measure the treatment effect only. With respect to the use of placebo surgery in clinical trials, some find it unethical since it subjects patients to an invasive procedure with potential risks, without gaining any of the potential benefits of the effective surgery.

Proponents of placebo use argue that this practice is ethically justified by the informed consent in circumstances where potential harm of delaying effective therapy is minimal. Along the same lines, advocates also reason that the vital need for scientifically valid clinical data that measures the true effect of a treatment justifies the methodology of using placebo while

considering the aforementioned risks which are minimized to the lowest degree possible.

Worries exist about the possible lack of transparency and accuracy of the information provided to the participants regarding the explanation of the benefits and harms of placebo which were detected in prior trials.[16,17] Such an issue places the informed consent at risk of being considered invalid. Another widespread critique of placebo use is that a valid assessment of the benefit of treatment requires concealment of placebo use. Open label placebo treatment trials offer a potential ethical solution to the problem of blinding of placebo use that some critics describe as deceptive. Open label placebo treatment was shown to conform with ethical standards of transparency, informed consent and respect for an individual choice and autonomy.[18] It is promising that patients are also open to trying such open label placebo studies.[19] Studies have shown that patients value the physician's transparency and honesty about the use of placebo with an emphasis on the physician's level of confidence in the benefits, safety and purpose of that treatment.[20] Physicians also viewed honest and transparent communication with the patient regarding the outcome as critical.[21] A shared decision–making model should involve a physician–patient conversation about the role of placebo effect in clinical care.[22]

Conclusion

Placebo use has become widespread in the medical field in multiple forms with varied applications. Since placebo use for prescriptions and for clinical trials carries problematic issues, numerous ethical considerations remain important in this discussion of their use. Transparency in informed consent as well as honest and clear communication remain key in maintaining patient–physician relationship. Despite the rising research interest in this field, there remains a paucity of data, and further research in this field is necessary to explore multiple unanswered questions.

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War, Medicine & Death

by Charles W. Van Way, III, MD

**You can't say that we don't progress.
In every war, they kill you in a new way.**

—Will Rogers, ca 1929

War is as old as human culture. But modern war is very different from warfare even two centuries ago. Technological advances have made weapons far more lethal. Yet medical progress in the care of casualties has partly offset the increased lethality of wounds in war.

Consider Table 1, which simply adds up the numbers of battle casualties (non–fatal casualties plus deaths) and compares that with the number of deaths for U.S. wars.[1,2,3] U.S. history goes back only to the late 18th Century. Trauma care at that time was far better than in medieval or ancient times. Yet over the 250 years of U.S. wars, the ratio of deaths to wounds decreased from 42% to 10%.

There are a number of reasons for this. Medical care of wounded soldiers has evolved from having a few poorly–trained doctors tagging along behind the army to a military health care system fully integrated with the military force. Entire systems of triage, evacuation, and surgical care are now in place, on the battlefield. Trauma care and surgical care in general has vastly improved. Antibiotics, blood transfusions, immunizations, and other non–surgical advances have contributed greatly. Public health in the military setting has greatly improved. Military medicine has developed into a true specialty over the last century and a half.



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

But there has been a much broader effect of military medicine on war itself. Consider medieval and early modern warfare. Armies were small. Weapons were either face–to–face or short–range projectiles. Everyone fought. Supply and services were non–existent. Battles were violent, but limited to a small area, and lasted only a day or two. Disease was endemic in armies, and in fact killed more fighters than did the enemy. Disease imposed a serious limitation on the size of armies, and on the length of time they could be kept in the field. Casualty care was primitive. Organized casualty care only began in the 19th Century, becoming effective only in the 20th.

Yet by the 20th Century, battles took place over large areas, involved millions of men, and lasted for months. Here, we encounter a paradox. Better casualty care has been a great benefit, despite the ever–increasing deadliness of our weapons. But by putting more soldiers back in the field, it has also reduced the impact of wounds on the overall force. Greatly improved public health in armies has lowered the toll of disease to a fraction of what it was in earlier centuries. Modern military medicine has thus allowed larger and larger armies. In short, military medicine, while greatly improving the care of the individual soldier, has enabled us to have bigger armies and wars.

The common image of war is the brave soldier charging towards the enemy with his comrades, dying heroically with the name of his loved ones on his lips. Like most other images of war, this image is nonsense. Soldiers die in many ways, most of which are not at all heroic. Let us consider just how soldiers die during

Table 1. War Wound Lethality over US History

War	Non-fatal wounds plus deaths	Deaths	Percent lethality	U.S. Population
Revolutionary	10,633	4,435	42	2,500,000
War of 1812	6,665	2,260	33	7,000,000
Mexican War	5,885	1,733	29	20,000,000
Civil War (Union)	422,295	140,414	33	31,000,000
Spanish American War	2,047	385	19	76,000,000
World War I	257,404	53,402	21	98,000,000
World War II	963,403	291,557	30	132,000,000
Korea	137,023	33,741	25	151,000,000
Vietnam	200,737	47,434	24	218,000,000
Persian Gulf (1990-91)	615	148	24	248,000,000
Iraq/Afghanistan	10,369	1,004	10	300,000,000

war. Broadly speaking, these are death from disease, from accidents, from battle, and from wounds.

Consider the pathways towards and away from that battlefield. Before he or she can charge across no man's land, the soldier goes to a camp in the U.S., then travels to the theater of operations and to the battlefield. This has its unique hazards. Up until a century ago, the greatest hazard was disease. Many more soldiers died from disease than from enemy action. As a classic example, Napoleon took his Grande Armee, 600,000 strong, across Russia to the outskirts of Moscow. Six months later, 100,000 returned, an 80% casualty rate. The Russian defenders shot more than a few. But most of the deaths were from cold, frostbite, typhus, typhoid fever, pneumonia, and epidemic diarrhea.

In the American Civil War, twice as many soldiers died of disease as from hostile action. In the Spanish–American War, nine times as many, largely from tropical diseases such as yellow fever. Among American troops in World War 1, disease deaths were higher than combat deaths, 63,000 to 51,000. To be complete, other armies had much lower rates of deaths from disease, about half of all combat deaths. The Americans joined the war in 1918, and were caught by the Great Flu Epidemic. By World War II, disease deaths in most armies were 10% of battle deaths. Even though it was fought in the tropics, the Vietnam War saw less than half as many deaths from disease as from combat. Control of disease has been largely from greatly improved public health measures, but also from disease–specific treatments and from vaccination for such diseases as yellow fever. The net effect has been to cut casualties by 60–70%, compared with historical wars.

Soldiers die from accidents away from the battlefield. These range from training deaths to motor vehicle crashes going to or from the battlefield. These are smaller than either disease or combat deaths, but are still significant.

Finally, soldiers die from wounds. To give one example, 50% of amputations during the Civil War resulted in death. Only 5% of amputations in World War 1 ended in death. The chances of dying from a battle wound dropped markedly from 1865 to 1918. The difference? There was an organized military medical system, including front–line surgical care, early evacuation, and sophisticated rear area hospital. There were many technical improvements including management of shock, intravenous fluids, sterile surgical technique, general anesthesia, improved wound debridement, and the Carrell–Dakin technique of wound irrigation (yes, using Dakin's solution). By World War II, the first antibiotics were available, transfusion of plasma and blood was routine, and shock was treated more effectively. Mortality from wounds dropped to a few percent. That's where it has remained across Korean, Vietnam, and the wars of the Middle East.

In talking about military deaths, we must distinguish between casualty and mortality. Casualties include all injuries, from whatever cause, and all illness. Depending on the data source, casualties may also include missing soldiers, although not those who become prisoners of war. But various sources often manipulate the data. In particular, the term, "battle casualties" has long been used to cover up disease and non–battle (accidental) casualties and deaths. If one adds up all battle casualties during the Civil War, for example, the resulting number omits

casualties from disease in military camps. As noted, disease casualties were twice battle casualties.[3]

An important measure of casualty care is the survival percentage of soldiers reaching the health care system, usually defined as the forward aid station. The military care system begins with the corpsman on the battlefield, who can stop bleeding and apply dressings, and who transports the patient to the forward aid station. Only emergency care and stabilization is available there, but patients can be moved fairly quickly to either a Combat Support Hospital or a Forward Surgical Team (FST), where surgical care can be given. From one of these, further evacuation is available to a rear area hospital. Currently, survival of patients reaching the system is around 97%. As helpful as this figure of merit can be today, we don't know what it was before 1900. In the U.S., military medical systems were re–organized after the Spanish American War, that is, between 1896 and 1917. That period saw the development of the Army Medical Corps, the Army Reserve Medical Corps, and the Army Nurse Corps, with early versions of the Dental Corps, Veterinary Corps, and Medical Service Corps. While we can estimate this survival percentage for earlier wars, such estimates are only educated guesses for anything before World War I. And clearly, some wounds are immediately lethal, or so quickly lethal as to preclude treatment. The best casualty care system available cannot save patients who cannot reach it.



4th Field Hospital, near Tripoli, Libya. Partially dug–in tents of third Platoon, opened on January 29, 1943.
Source: https://www.med–dept.com/articles/ww2–military–hospitals–mediterranean–theater–of–operations/



Aid Station 79 Div Bois de Consenvoye
Source: Meuse–Argonne American Cemetery and Memorial

To take a somewhat broader perspective, what can we say about the ongoing human costs of war? Or putting it another way, how do casualties in the wars of the 20th and 21st Centuries compare with casualties in previous wars? A glance at Table 1 shows that in U.S. history, only the American Civil War was comparable to the wars of the last 100 years. It appears to have been much less costly than World War II. But the U.S. population in 1860 was far smaller than in 1940. If we do the math, the Civil War was almost twice as costly as World War II. In fact, during the Civil War, about 1.8% of the entire population of the North and South, were casualties. In World War II, not quite 1%.

This perspective allows us to make two points. First, earlier wars may have been just as devastating to the countries involved as modern war. Casualty numbers have to be considered in terms of the overall population. And second, when even a relatively

small percentage of the overall population is lost to war, there may be a disproportionate impact on the country at large. To take an example, the Korean war (1950–53) had about the same impact as the Vietnam War (1965–73). In each, casualties were about 0.11% of the total population. But the Korean War, coming after World War II, had very little impact. It's often called the Forgotten War. Vietnam, coming after years of peace and great prosperity, had an impact which is felt to this day.

What can we conclude from all this? While casualty care has improved to an extent unheard of even a century ago, modern weapons are increasingly lethal. Modern public health and transportation technology has enabled the formation of far larger armies than ever before. The last 50 years have been relatively peaceful, even counting wars in the Middle East. Many have concluded that perhaps peace can become the norm. But we have now re–learned what our fathers and grandfathers learned during World War II. War cannot always be avoided. The Russo–Ukrainian War has clearly shown that it doesn't



even take two sides to make a war. It only takes one aggressor. War continues to be a scourge upon us.

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From Courtroom to Clinic: Child Advocacy in Action

by Taylor Smith, BS & Colin Smith, BS

One of the most important roles of a physician is that of patient advocate. This role is widely considered a professional obligation in medicine and holds such importance that formal advocacy training has been a requirement of pediatric residency programs for over twenty years and is now being incorporated into graduate medical education curricula across several other specialties.[1,2] The authors are husband and wife, both fourth year medical students pursuing careers in primary care. We developed a passion for advocacy through our work as a Court Appointed Special Advocate (CASA) team.

A CASA is a trained community volunteer appointed by a judge to advocate for children who are in the family court system due to abuse and/or neglect. We each spent 30 hours in training learning about types of child abuse and neglect, how to communicate with the various parties involved in the care of these children, and the intricacies of the family court system. As CASA volunteers we are responsible for advocating for these children to receive essential therapeutic, educational, and medical services in addition to advocating for safe permanent placement. While these responsibilities align with that of Missouri's Department of Social Services–Children's Division, caseworkers are overwhelmed, having on average 25–plus cases while the recommended case load is 13 to 15.[3] Case turnover rates for caseworkers are up to 60%, reflecting the temporality of their relationship to cases. CASA volunteers are in a unique position to stay on cases until closure and focus on being the voice for their assigned children by championing these responsibilities. As we entered our clinical rotations in Rolla, Missouri, we quickly saw how advocacy in the courtroom translates to advocacy in the clinic.

Advocacy training for CASA volunteers and physicians alike include topics such as child development, warning signs of child abuse and neglect, cultural competency, and the impact of adverse childhood events such as domestic violence, poverty, and substance abuse. Both are also trained to complete appropriate documentation. In many ways, the court reports we write for our CASA cases parallel the SOAP (Subjective, Objective, Assessment, and Plan) note format used by medical professionals. In both instances, we are tasked with gathering the history, investigating the story we are told, determining facts, analyzing data, and developing an assessment and plan. This serves as a guide in making a recommendation reflecting the best interest of the child. When advocating in both the courtroom and the clinic, we must take into consideration the immediate and long–term impact of any interventions. The ultimate goal is to help families establish safe environments for their





Taylor Smith, BS (left), and **Colin L. Smith, BS** (right), are medical students at Kirksville College of Osteopathic Medicine, A.T. Still University, Kirksville, Missouri, and CASA of South Central Missouri in Rolla, Missouri.

MSMA Alliance Leaders Share CASA Experiences



Mary Shuman, BSN
MSMA Alliance Past President

An attorney affiliated with Children's Mercy Hospital in Kansas City was the featured speaker. His topic was abused children. The horrific photos were of children with third degree burns from being thrown on hot grills and burning coals, tossed in scalding water—all at the hands of their parents. A woman in the audience shared that she was the director of an organization that advocated for abused and neglected children. I introduced myself to her. I was all in and I still am. I am a CASA.

Sammy Jo was one of my earliest cases. She was four years old. Mom and dad's parental rights had been terminated. Sammy Jo was placed in multiple foster homes. She was always the new kid in countless schools. I kept a 'Sammy box'. I saved her school papers, photos, essays, and poetry. We agreed that the box would stay with me, for safe keeping, until she had a place of her own. She graduated high school from a juvenile detention center. I was there to cheer her on. Her diploma went into the Sammy box. She was released from juvie. She had aged out of the children's division system. She was on her own.

I helped her enroll at the local university. Late one night she phoned me from CVS. She was hysterical. She was wearing her only pair of jeans and her period had started. She didn't have money to buy tampons. I met her. We shopped for that and other essential needs like toothpaste and shampoo. Giddy teen girls worried if they would be asked out on a date. Sammy Jo worried where she would stay—she was homeless. She got caught up with a dangerous crowd. She was sentenced to prison. Monthly, I would visit her at Chillicothe Women's Correctional Center.

March 18, 2020, the Kansas City Police Department released the name of a 27 year–old woman who had been identified as the victim of a deadly shooting. It was Sammy Jo.

I attended her funeral. I still have the Sammy box filled with memories. She was a gifted writer—poetry was her favorite.

November 17, 2022, the 5th Circuit Court of Missouri presented me a 25–year service award. I can't retire—I have six active cases.

The United Nations human rights system has a mandate that focuses on preventing torture of prisoners. Vulnerable children should be so lucky. Underpaid and overworked children division workers come and go. CASA stays.

children to thrive as well as addressing preventative measures to ensure brighter futures.

Whether advocating for permanent placement, tutoring, therapy, or medical services, we have discovered one of the most important aspects of this work is including both the child and the caregiver in the conversation. Children may not appreciate the intricacies of their circumstances, but educating them and their caregivers in a simplified, understandable manner is essential to ensuring success. In an unfortunately similar way, the recommendations made in the best interest of the children and patients we care for are simply that—recommendations. A unique mutual barrier exists in these two environments; buy–in of third parties. For parents and court systems alike, recommendations only go as far as the cogency of the argument. In these situations, a decision–maker may ask, "Does this child really need this intervention?" Going beyond mere suggestions is the crux of advocacy. Putting forth effort to defend a recommendation through education, clear expectations, attainable goals, and clear definition of how the recommended interventions will improve the long–term outcome for the child is fundamental in effective advocacy.

All in all, our experiences in the courtroom have provided a stark parallel and instilled a deep appreciation for the gravity of the recommendations we will make as future physicians. Purposefully advocating

MSMA Alliance Leaders Share CASA Experiences



Sue Ann Greco, BSN, MSN
MSMA and AMA Alliance
Past President

My road to becoming a CASA actually started in 2001 when I began studying for a certificate in Legal Studies. During student introductions in my very first class, one of the students described how she was going through classes to become a Court Appointed Special Advocate. I had never heard of this position before and was very intrigued as I had been a pediatric nurse and had a little bit of familiarity with the foster care system. However, this was not the time for me as I was venturing out on a path to become a legal nurse consultant.

In 2010 I was between jobs and heard a public service announcement about CASA by Missouri's First Lady, Mrs. Jay Nixon. It reminded me that this was something I had wanted to do. Ironically, I had spent the last year volunteering at a Catholic Charities social work agency that provided case work for abused and neglected children. My task was to copy and organize case files. After reading some of the files, I knew that becoming a CASA was what I needed to do. I applied and began the training and received my first case that spring.

As a new CASA I was asked what type of case I would like. Since my background was in pediatric nursing, I said I would be willing to take on a case where the child had health issues. I was given a case where the child had multiple health issues and handicaps. I have been told several times that not many CASA workers would have taken on such a case, but for me it has been very comfortable and rewarding. I am still on the same case 12 years later. The most rewarding aspect of having been on this case is that I am the person on the team who has been on the case the longest. We have gone through multiple social workers and placements. It is very rewarding to me to be able to have the history with this child that I do.

Over the years I have spoken to many CASA volunteers. Everyone I know finds this volunteer position to be challenging but rewarding. Case work can take anywhere from 4 hours to 15 hours a week. We are required to complete 12 hours of continuing education credit each year. It is a great position for someone who is retired and looking for something rewarding to do. Some of the CASAs I have met have been CEOs of companies. However, you do not need to have any particular background, you just need to have a heart.

for the best interests of each patient is paramount. Physicians especially must fulfill the role of advocate in order to provide the highest quality patient–centered care. We would like to encourage fellow student doctors and other medical professionals to seek out opportunities to practice advocacy outside of medicine alone through opportunities such as CASA. Every child in the foster care system can benefit from the constant support of a trusted adult as they navigate the family court system. The need for CASA volunteers is great, with nearly 700,000 children becoming victims of abuse and neglect annually and only about 250,000 of them having CASA volunteers.[3] For more information on becoming a Missouri CASA volunteer, we encourage readers to visit MoCASA.org.

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MSMA Members in the News

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

Missouri Medicine Announces Global Indexing Access

One of the most important reasons for *Missouri Medicine's* national reputation and ability to attract quality manuscripts and have academic departments eagerly commit to producing our signature theme issues is our global reach via MEDLINE, PubMed, Scopus Elsevier, EBSCO, and now ProQuest databanks.

Over the course of the last decade, *Missouri Medicine* began a long, rigorous qualifying procedure to have all our content linked to global indexing services. Except for the *New England Journal of Medicine*, this is exceptional for a state medical journal.

This year, the Journal was invited to be indexed by ProQuest Health & Medical Collections/EBSCO Information Services. ProQuest is a comprehensive medical information resource for researchers, students, faculty, and healthcare professionals. In addition to biomedical content from MEDLINE, the collection aggregates content in all forms of media to support the learning, teaching, and research needs of institutions. This includes medical reference ebooks, instructional videos, dissertations, and working papers.

In 2021, *Missouri Medicine* became indexed by Scopus/Elsevier where 20 of our Journal articles were in the top 10% most viewed publications in 2012–2016. Our issues dating from 1945 to current are now in Scopus, which indexes from more than 25,000 multi–disciplinary sources including journals, book series, and conference papers that have an International Standard Serial Number. There are nearly 82 million records in Scopus dating from 1788 and over 17 million author profiles. This ensures that the meticulous work of published authors will be retrievable and appear in internet searches world–wide. Access to Scopus is by subscription only. Please check with your campus librarian to confirm access.

Missouri Medicine was approved in 2017 for full issue content in PubMed Central. The Journal has been linked to PubMed (abstract only and originally called Index Medicus) since the early 1940s. In 2018 MEDLINE recertified *Missouri Medicine*. All of us at *Missouri Medicine* thank MSMA and its members for 119 years of encouragement, participation, and support. Our Journal is widely respected and our publication have an international following.

Missouri Medicine Editorial Board Members Receive Distinguished Service Award

Two members of the *Missouri Medicine* Editorial Board are receiving the Distinguished Service Award for their valuable and highly regarded input and manuscript reviews.



Christopher R. Carpenter, MD, MSc, who has represented Statistics & Methodology for five years, is leaving Missouri for a position at the Mayo Clinic in Rochester, Minnesota as Vice Chair of Implementation and Innovation.



Howard M. Rosen, MD, FACE, ECNU, who has represented Endocrinology on the board for nearly 15 years, is retiring.

Missouri Medicine wishes both physicians congratulations on their futures. Replacements will be announced in the January/February issue.

Thank You Non–Editorial Board Contributors

Missouri Medicine would like to publicly thank the following invited non–Editorial Board experts who have done peer–review of submitted manuscripts in 2022: Phillip Boysen, MD, An–Lin Cheng, PhD, **John Daniels, MD**, James J. DiNicolantonio,

PharmD, Sean Gratton, MD, **Charles M. Lederer, MD**, Louis S. Martone, MD, **David McKinsey, MD**, **Lenard Politte, MD**, Rithwick Rajagopal, MD, Gloria Seo, MD, **Eric A. Voth, MD**, and Melissa Toyos, MD.

Missouri Medicine Members in the News



The Liberty Hospital Board of Trustees has named **Raghu Adiga, MD**, its President and Chief Executive Officer. Dr. Adiga has served in this role in an interim capacity since June 2022. He is recognized as one of the region's leading Infectious Disease specialists.

At its recent Annual Meeting, the Kansas City Medical Society appointed officers for 2023.















Among them are MSMA members top row l to r: **Carole Freiberger–O'Keefe, DO**, President; **Scott Kujath, MD**, Past President; and Members–at–Large l to r: **Samuel Caughron, MD**, **Brad Garstang, MD**; **Sarah Hon, DO**; **Joanne Loethen, MD**; and **Stephen Salanski, MD**.



Congratulations to MSMA member **Larry Hollenbeck, MD**, who was honored with the Lifetime Achievement Award at the Kansas City Medical Society's Annual Meeting in October.



MSMA member **Christine Livek, MD**, has been elected Secretary/Treasurer of Lake Regional Health System's medical staff. Her term began in October 2022 and will last for two years.



At its recent Legacy Dinner, the Cass Regional Medical Center Foundation presented **Richard Price, MD**, with the Foundation Award. The award honors those who have demonstrated steadfast dedication to the mission of Cass Regional Medical Center and to improving the quality of health care in Cass County. Dr. Price has been in practice at Harrisonville Medical Clinic for more than 42 years.





Kudos to MSMA members **Gabe Soto, MD**, (left), and **Bryan Beck, MD**, of SoutheastHealth. The heart team is the first in the region to offer minimally–invasive therapy for patients with atrial fibrillation who are at risk of ischemic stroke. The procedure is performed in Southeast Hospital's Cardiac Catheterization Lab.



Long–time MSMA member **Clifford Talbert, Jr., MD**, has been honored by the Saint Francis Foundation with its Healing Hands Lifetime Giving Award, in recognition of his long–term support and leadership giving. Dr. Talbert recently retired after many years of practicing Internal Medicine in Cape Girardeau.



Davin Turner, DO, has been named the Chief Administrative Officer of Mosaic Life Care in St. Joseph, where he formerly served as Chief Medical Officer. Dr. Turner is a Family Medicine specialist and has served in several administrative roles since 1996.



Kathleen Weaver, MD, has received the inaugural William "Bill" Johnson Advocate for Public Health Award. The award, established this year by the Audrain County Health Department, is offered in the name of Johnson, the first administrator of the former Audrain City–County Health Unit. Dr. Weaver, an Orthopaedic Surgeon in Mexico, received the award for her leadership and for playing an integral part in the county's response to the pandemic.



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In Memoriam

William Huse, MD – Obstetrics & Gynecology – Overland Park, KS – 10/10/2020
Momoko Oyama – Medical Student – St. Louis, MO – 6/14/2020
William Marshall, MD – Family Practice – Fayette, MO – 9/25/2021
John H. Kelly, MD – Internal Medicine – St. Louis, MO – 9/28/2021
George Richardson, MD – Family Practice – Sarasota, FL – 11/1/2021
Abbiah Reddy, MD – Urology – Orange Park, FL – 1/18/2022
Ismael Aguilo Rodriguez, MD – Internal Medicine – Webb City, MO – 2/19/2022
Perry U. Hunsley, MD – General Surgery – Salina, KS – 4/26/2022
John C. Perryman, MD – Internal Medicine – Kansas City, MO – 7/7/2022
Thomas M. Macdonnell, MD – Family Practice – Marshfield, MO – 7/10/2022
Robert Pavlu, MD – General Practice – Carrollton, MO – 7/22/2022
Gene A. Schillie, MD – Obstetrics & Gynecology – Shawnee, KS – 9/5/2022
Christopher Thomas, MD – General Surgery – Shawnee Mission, KS – 9/7/2022
William F. Sasser, MD – Cardiovascular Surgery – St. Louis, MO – 9/25/2022
Charles B. Wheeler, MD – Pathologist – Overland Park, KS – 10/25/2022

MSMA Remembers Two Great Pro–Patient, Pro–Medicine Physicians

MSMA remembers Drs. Macdonnell and Wheeler and attending the Annual Conventions, testifying during the Reference Committees, and being a Friend of Medicine in the General Assembly.

Thomas M. Macdonnell, MD, known as "Dr. Tommy," died July 10, 2022, just six months short of his 100th birthday in Marshfield, Missouri.

He was involved in many civic organizations and boards during his lifetime but is best remembered as a World War II hero, a state representative, and an obstetrician.

Dr. Tommy enlisted in the U.S. Army in 1943 at the age of 20 and took part in D–Day as part of the Normandy Invasion. He was a sharpshooter and half–track gunner in the First Infantry Division also known as "The Big Red One." He was one of the few in his group that survived the carnage at Omaha Beach and was hit in the hip by shrapnel.



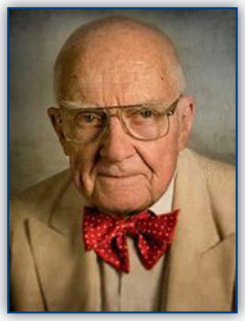
Dr. Tommy also took part in the Battle of the Bulge where a land mine resulted in more serious injuries to his skull, ribs, vision and hearing. For his service, he received two Purple Hearts and the Silver Star.

Coming back Dr. Tommy followed in his father's footsteps by becoming an obstetrician in Marshfield where he delivered more than 4,500 babies. In 1989 a large group of them honored him by turning out in the town square to have a photo made.

When he first started in the business with his father he was sent on house calls where he would charge three dollars for in–town visits and five dollars for out–of–town calls.

Dr. Tommy was elected to the Missouri House of Representatives in 1986 where he authored the Clean Indoor Air Act that would become law in 1992.

That law not only banned smoking in most public places but also prohibits the sale of tobacco to anyone under the age of 18.



Charles B. Wheeler, MD, a physician and one–of–a–kind politician, died Oct. 25, 2022, at a skilled nursing facility. He was 96.

Dr. Wheeler served as Kansas City mayor from 1971 to 1979.

With a distinctive voice, straight–arrow reputation and penchant for bow ties, Wheeler was elected Jackson County coroner in 1964 and western judge of the former Jackson County administrative court in 1966. After his two terms for mayor, he made a comeback in 2002 when he ran for Missouri Senate and won, partly attributable to yard signs that bore a silhouetted profile bearing the words "Dr. Wheeler – Integrity."

Before and during his years in politics, Dr. Wheeler, a pathologist, ran Wheeler Medical Laboratories on the St. Luke's campus.

During his mayoral years were the opening of the Harry S. Truman Sports Complex and Kansas City International Airport.

Another landmark achievement was helping convince the Missouri General Assembly and other state elected officials to establish the University of Missouri–Kansas City. Construction of the medical school began in 1972 on land contributed by Kansas City at 22nd and Gillham, which soon became known as Hospital Hill. Ground was broken on nearby Truman Medical Center in 1973, and the publicly financed hospital opened in 1976.

A Kansas City native, he got his bachelor's degree from the University of Louisville and a law degree from the University of Missouri–Kansas City. After graduating from medical school at the University of Kansas, he served as flight surgeon to the original aerial acrobat team, the Thunderbirds. **MM**



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NOTE: No city indicates MSMA Resident Member

MM



Register at www.maops.org/VOC

Correspondence

National News: Why the Hospital Closed in Mexico, Missouri

The massive problems leading to the closure of Audrain County Medical Center (AMC) in Mexico, Missouri, have received national attention including recent publication in *USA Today*.

Read here: bit.ly/3iCZv0K

I live and practice in Mexico. The publicly-owned AMC has for many years been the referral center for a large area of mid-Missouri. In 2013, in response to changing economic circumstances, the hospital was sold to SSM-Health. Later SSMH divested of its mid-Missouri hospitals (AMC and St. Mary's Jefferson City). After numerous pledges and promises of quality and financial stability, AMC was purchased by Noble Corporation. The nationally known problems leading to closure of AMC are extensively outlined in the *USA Today* article.

It is imperative that Mexico and its large referral area have an emergency room and hospital. Our present medical situation was inconceivable to our former physician community. Our critical and emergent care is presently serviced by several ambulances that transfer patients to Columbia. On some ultra-critical occasions, a helicopter is used. This is far from ideal and has created increased morbidity and mortality.

Like most of our physician community, my general surgery practice has been existentially challenged. My patients and I have had to do an inordinate amount of time-consuming travel. I've done surgeries in Jefferson City and Moberly Regional Medical Center, outpatient surgeries at Columbia Surgical Associates and endoscopies at the Surgery Center of Columbia. All have graciously welcomed me and my patients. I am working on surgical privileges at Boone Hospital and the University of Missouri-Columbia Medical Center. I have not been able to expedite the ponderous credentialling process, even given the sudden AMC closure and the needs of our Audrain community.

I presently see patients in my office several days per week. I am one of the last solo, non-employed private practice physicians in Mexico. I refer out radiology, lab work, and subspecialty care if needed.

The few physicians in our community are employed either by the federally funded Arthur Center, or the University of Missouri. Since our primary care physicians are not working and most clinics are closed, surgical referrals are dwindling. With rapidly rising overhead and staff expenses, I have not been taking personal remuneration.

This ordeal has been devastating to our physician community and the patients we serve. It is an economic and quality of life blow to Mexico and surrounding communities. The Audrain medical and civil leaders have unrelentingly searched for a way for our closed hospital to reopen. At the time of this correspondence, we have a highly respected potential buyer. We hope to announce the sale and reopening of AMC in the near future.

Joseph A. Corrado, MD, FACS
General Surgeon, Mexico, Missouri
MSMA Past President

How Much of a Donated Dollar Goes to Healthcare or Research?

As recently as 30-plus years ago, most hospitals were not-for-profit and often run by religious organizations. They were called community hospitals. The public, as well as community and business leaders, financially supported hospitals generously. They served on the board of directors and took great pride in their hospitals. Some community hospitals affiliated with academic medical centers and had internship and residency programs. There was a community spirit which permeated these local teaching hospitals. At the community teaching hospital where I practiced for many years, each patient room had a bronze plaque on the door with the name of a family that donated a significant amount of money to the hospital.

In the 1990s, things began to change and for-profit hospitals appeared. Today there is very little difference between for-profit and not-for-profit hospitals. For-profit hospitals provide about the same amount of charity care as not-for-profit hospitals. Yet not-for-profit hospitals pay no property taxes while for-profit-hospitals pay property taxes. This taxation difference can be a substantial sum and a major financial burden for the cities in which not-for-profit hospitals are located.[1]

For example, in one recent study, not-for-profit and for-profit hospitals had similar unreimbursed

Medicaid costs as a share of expenses. While another study showed that for-profit hospitals actually provided more charity care than not-for-profit hospitals.[2] Yet not-for-profit hospitals often avidly solicit monetary donations from the public. They compensate their fundraisers handsomely. Charity Navigator (www.charitynavigator.org) is an internet source for the amount of money hospitals spend on fundraising salaries versus actual medical care. Incredibly some hospitals' fundraising fees are egregiously as high as 70 to 80 percent of donated money.[3]

St. Jude is the largest health care charity in the country. Pro Publica, a consumer watchdog organization, did a detailed study of St. Jude focusing on its fundraising efforts.[4] Each year the hospital sends out hundreds of millions of letters, many with heart-wrenching photos of children receiving cancer treatment. It advertises heavily on television. It has hired celebrities to endorse the hospital. In 2020, St. Jude's raised a record two billion dollars. It has 5.2 billion dollars in reserve.

Since 2017, only about half of the $7.3 billion dollars St. Jude has received in contributions went to the hospital's patient care and research. Of the remainder, 30% was spent on fundraising and 20% to its reserve fund. It should be noted that although St. Jude advertises that care is free for those who cannot afford treatment, much of the cost of treatment is paid by the families' private insurance or by Medicaid.[5]

Although families may not receive a bill from St. Jude, they still sustain significant financial stress, primarily the loss of income as parents take leave from their jobs to be with their child during treatment. In these cases, St. Jude recommends that families apply to other charities or for government help. The head of one of the charities recommended by St. Jude has stated that St. Jude families have the same money problems as the families of other children's hospitals, even though he said St. Jude's marketing creates the public perception that it alleviates these burdens.[6]

The fundraising and investment arm of St. Jude known as ALSAC has 2,188 employees. More than 400 of its employees are paid over $100,000 annually. In 2020, St. Jude raised a record two billion roughly equal to the total raised by all the nine children's hospitals ranked ahead of it in quality. St. Jude's reserve has grown by 58% over recent years. It has shifted its portfolio to financial products such as private equity funds designed to generate larger returns than stocks, bonds and mutual funds.[7]

Marty Makary, MD, an academic gastrointestinal surgeon and author, in his book "The Price We Pay" notes that hospital charges are notoriously inflated sometimes over 20 times what is paid by Medicare. He cites how his own not-for-profit teaching hospital, Johns Hopkins, sends unpaid patients' bills to collection agencies. How does this practice differ from the practices of for-profit hospitals?[8]

When not-for-profit hospital finances are exposed and the practices and compensation of fund raisers scrutinized, one can reasonably question why the public would donate any money to hospitals.

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Arthur Gale, MD
General Surgeon, Retired, St. Louis, Missouri

Do Fish Oil Supplements Reduce A-Fib?

Since we debated DiNicolantonio and O'Keefe about the use of fish oil supplements (FOS) to reduce cardiovascular diseases in *Missouri Medicine*,[1,2] new data have emerged regarding a potential side-effect of FOS—atrial fibrillation (AF). Recently, Gencer et al. published a meta-analysis of seven randomized, placebo-controlled clinical trials of FOS that reported AF as an endpoint.[3] This well-conducted meta-analysis revealed a statistically significant increase in AF in subjects receiving FOS, with the greatest risk associated with high-dose therapy (i.e. 4 g daily). However, the AF data were not adjudicated (i.e. rigorously confirmed) in four of the trials included in the analysis. Furthermore, AF was a secondary, tertiary, or exploratory endpoint in all but one of the trials, and bias attributable to informative censoring may have over-estimated effects of FOS on AF.[4] Thus far, the only FOS study that included AF as a primary endpoint was the VITAL Rhythm Study,[5] a large, randomized, placebo-controlled clinical trial which showed that daily treatment with eicosapentaenoic acid (EPA) 460 mg and docosahexaenoic acid (DHA) 380 mg had no significant effect on incident AF among adults aged ≥50 years during a median follow-up of >5 years. However, VITAL Rhythm did not exclude the possibility that high-dose FOS increases AF risk.

What are reasonable conclusions that can be drawn from currently available data regarding FOS and the risk of AF, and how should the data guide everyday practice? First, it is clear that FOS do not reduce AF, as had been postulated from epidemiologic data.[6] Secondly, the statistically significant, dose-dependent association of AF with FOS revealed in Gencer's meta-analysis is cause for significant concern, as prescription of high-dose EPA is increasing based on results of the REDUCE-IT trial.[7] Third, when discussing initiation of FOS with patients, clinicians should make them aware of the possible connection between high-dose FOS and AF (particularly patients with risk factors for developing AF), and clinicians should be on the lookout for AF in patients taking FOS. Nevertheless, clinicians can also inform patients that, when using primary endpoints from clinical trials as the main guide, as should be the case, there are currently no definitive data implicating FOS as facilitators of AF, nor are there data suggesting that FOS increase the risk of stroke, the most significant complication of AF. Lastly, clinical trials involving high-dose FOS and AF as a primary endpoint are needed to shed more light on this important issue.

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Retraction

The authors of the following article: Chockalingam, A., et al., "Home-Based Arm Cardiac Rehabilitation in Disabled Veterans." Mo Med. 2021 Jul-Aug;118(4):387-392, PMID: 3437376 wish to retract this from *Missouri Medicine.*

Data utilized in the publication was associated with IRB#1155797 which was approved by the MU IRB serving as the IRB of Record for the Harry S. Truman Memorial Veteran's Hospital, Columbia, Mo. On October 15, 2012, the IRB notified Dr. Chockalingam that no data related to IRB#1155797 could be used or published. The publication of the data in this article has been determined to be serious and continuing noncompliance. This noncompliance has been reported to both the Office for Human Research Protections (OHRP) as well as VHA Office of Research Oversight (ORO).

On behalf of the authors, I respectfully request a retraction of this article from *Missouri Medicine*.

Anand Chockalingam, MD, FACC, FAHA, FASE
Professor of Clinical Medicine,
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Columbia, Missouri

Errata

In the July/August 2022, 119:4, *Missouri Medicine*, the conclusion of the article by Kate Lichtenberg, DO, "Reversing the Decreasing Life Expectancy, A National Health Priority" can be found on page 333.

In the July/August 2022, 119:4, *Missouri Medicine*, in the article by Maulik, Devitka, MD, et al., "Preexisting Thyroid Disease in Pregnancy: A Brief Overview" on page 361, the article's authors should have stated: "If data regarding a specific practice location or similar patient population is not available, both ACOG and the ATA recommends the following adjustments: 1) subtracting 0.4 mU/I from the lower threshold for nonpregnant range for TSH; 2) subtracting 0.5mU/I from the upper threshold for nonpregnant TSH range; and 3) upper range of T3 and T4 increased by 50% after 16 weeks gestation. Regarding the upper range of TSH, the target range with the subtraction of 0.5 mU/l is equivalent to around 4 mU/l for most centers and above original recommendations of 2.5 mU/l or 3.0 mU/l.[1,4] **MM**

Use of Laboratory Tests and Their Prognostic Value in Patients with Stable Chronic Obstructive Pulmonary Disease

by Sohaib Khatib, MD, Taher Sabobeh, MD, Fouad Jaber, MD, Khalid Abdalla, MD, Som Singh, BS & Gary Salzman, MD

Our literature review supports using CRP, troponin, anemia, and PaCO2 to predict mortality in patients with stable chronic obstructive pulmonary disease.



Sohaib Khatib, MD, (above), **Taher Sabobeh, MD**, **Fouad Jaber, MD**, and Khalid Abdalla, MD, are Resident physicians in the Department of Internal Medicine. **Som Singh, BS**, is a medical student. **Gary Salzman, MD**, is an Attending physician, Department of Pulmonary and Critical Care Medicine. All are at the University of Missouri–Kansas City School of Medicine, Kansas City, Missouri.

Abstract

Chronic obstructive pulmonary disease (COPD) is not merely a lung disease as the name indicates. Patients with COPD experience associated complications with systemic inflammation, heart strain, muscle wasting, poor functional performance, and psychological issues. An assessment of these patients based only on lung function tests or functional capacity would be inadequate. Many studies have reported the significance and prognostic value of several laboratory tests. Troponin, C–reactive protein (CRP), hemoglobin, and carbon dioxide are older tests but compared with the newly developed tests, they are relatively inexpensive to measure and widely available. This article will review laboratory tests used for COPD and discuss their prognostic value. The laboratory tests that can identify high–risk patients will be discussed. We will explore the role of these tests in clinical practice.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the United States.[1] With over 10 million cases of COPD diagnosed in 2018, COPD places a heavy burden on the health system.[2] Patients with COPD experience episodes of worsening symptoms and a reduction in lung function identified as exacerbations. Severe exacerbations will require hospitalization. The disease has a variable progression over time, and the major subtypes (emphysema, chronic bronchitis, and chronic obstructive asthma) have interrelationships between the closely related disorders that cause airflow limitation, this provides a foundation for understanding the spectrum of patient presentations.

The pulmonary function tests (PFTs), which usually include spirometry, measurement of lung volumes and diffusing capacity of carbon monoxide in addition to arterial blood gas analysis at rest have historically been used to measure the physiologic impairment in the lungs to support the clinical diagnosis of COPD. However, spirometry is only a single factor in determining the severity of the disease as nearly 10% of patients with clinically diagnosed COPD with emphysema findings on chest computed tomography (CT) scan had normal PFTs.[3]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, body mass index (BMI), the severity of airflow obstruction, dyspnea, and the exercise capacity index (BODE index) have also been used to identify high–risk patients and to guide treatment protocols.[4] While these scores predict to some extent high–risk patients with COPD, important factors such as systemic inflammation, associated morbidities, and heart disease are not included in the existing scoring criteria.

Laboratory testing has been developed as simple reliable tests to identify patients with COPD at higher risk for decline, recurrent exacerbations, and death.[5] Studying these tests may allow for phenotype recognition, better COPD stratification, and earlier interventions and tailored management.[6] Multiple studies have been performed evaluating the association of troponin, C–reactive protein (CRP), carbon dioxide (CO_2), and hemoglobin levels in patients with stable COPD with all–cause mortality. This review explores the prognostic value and clinical utility of these tests.

High–Sensitivity Troponin and COPD

Troponin is a cardiac muscle marker of injury and is one of the cornerstones for acute coronary syndrome diagnosis. New troponin assays including high–sensitivity troponin (hs–TN) and troponin I are more specific for cardiac muscle injury. Elevated high–sensitivity troponin has been observed in non–cardiac primary conditions including renal failure, pulmonary embolism, and sepsis. The rise in troponin may indicate myocardial damage rather than infarction.[7] The suggested pathophysiology may be related to increased myocardial stress. Circulatory overload, hyperdynamic circulation and increased pressures may lead to cardiac muscle overstretching and troponin leak. Pulmonary vascular resistance elevation in COPD may lead to increased right ventricular afterload. Even a slight elevation in pulmonary vascular resistance may result in right ventricular impairment and increased wall thickness in patients with COPD.[8] Increased systemic inflammation and a prothrombotic state may also contribute to increased pulmonary vascular resistance. COPD is a strong risk factor for cardiovascular events, independent of smoking, this is specifically significant in COPD chronic bronchitis patients. Having symptoms of chronic bronchitis alone increases the risk of coronary deaths by 50%.

In a previous study, elevated high–sensitivity troponin during COPD exacerbations predicted short–term mortality.[9] Establishing the same relationship in stable patients would be more challenging. A review of the literature identified three studies discussing the troponin level in patients with stable COPD. The first study was published in 2016 by Neukamm and coworkers.[10] Two–hundred seventy–five patients were selected and followed for a mean duration of 2.8 years. More than half of the patients (57%) were GOLD class III/IV. Patients with elevated troponin after adjusting for factors including age, kidney function, the presence of Q waves on electrocardiography (ECG), left ventricular hypertrophy, GOLD class, six–minute walk distance, and modified medical research counsel for dyspnea score (mMRC) had higher mortality rates. The hazard ratios (HR) for death were 1.7 (95% confidence interval [CI] 0.8–3.9) and 2.9 (95% CI 1.2–7.2) among patients with hs–TN concentrations of 5.0–13.9 and ≥ 14 ng/L, indicating higher mortality with higher troponin levels. The study excluded coronary artery disease (CAD) by the absence of Q waves on ECG, and this may have led to false negative results.[11]

Adamson and colleagues[12,13] studied 1,599 subjects, a subset of patients with COPD from the Study to Understand Mortality and MorbidITy (SUMMIT) trial with measured serum troponin I levels. These patients were either diagnosed with CAD per definition or at risk and were followed up for median of 18 months. The higher troponin I groups (≥ 4.8 ng/L and ≥ 7.7 ng/L) were at greater risk of cardiovascular events and cardiovascular death with no change in the COPD exacerbation rate after adjustment for risk factors. Inhaled corticosteroids, long–acting beta–2 agonists, or combination therapy did not affect troponin levels.

The latest published input from the COPD and Systemic Consequences–Comorbidities Network (COSYCONET) cohort study by Waschki and colleagues[14] analyzed 2,085 patients with stable COPD (median follow up was 36 months). The study included patients with GOLD stages I–IV. Ninety–six percent of the patients had detectable high sensitivity troponin I levels (hs–TNI). Only 1.8% of the patients had levels greater the reference range of 27 ng/L (cut–off to diagnose myocardial infarction). Patients

with hs–TNI levels ≥ 6 ng/L had increased mortality compared with the lower troponin groups irrespective of the cardiovascular risk factors, but they did not have more COPD exacerbations. Furthermore, patients with a high BODE index and hs–TNI > 6 ng/L had a 2.6–fold higher risk of all–cause mortality compared with patients with low troponin.

These studies have shown that patients with COPD with higher baseline troponin levels are at higher risk for mortality, including cardiovascular death. The cut–off value for troponin elevation associated with increased risk was 4.8 ng/L. A proportional increases in all–cause and cardiovascular mortality was also observed. One of the challenges in these studies has been stratifying patients with a history of CAD, with risk factors (including age, sex, smoking, hypertension, and dyslipidemia), and with electrocardiogram or echocardiography without relying on accurate diagnostic testing including myocardial perfusion imaging. This approach may have underestimated CAD prevalence in study groups.

Adamson and colleagues[13] demonstrated that inhaled bronchodilator therapy did not affect troponin levels. Only 60% of the study patients were on both antiplatelet and statin therapy, and up to 25% of the patients in the study by Waschki et al.[14] were on statins. In one cohort study, successful treatment with statins showed a reduction in lung–related and all–cause mortality in patients with COPD.[15] Daily aspirin use was also associated with a reduced rate of mild and moderate COPD exacerbations, less dyspnea, and better quality of life in a recent observational cohort study.[16] Troponin levels decreased with statin therapy in selected patients with elevated low–density lipoprotein (LDL) but without a history of cardiovascular disease.[17] More studies are needed to evaluate this correlation and the value of following elevated troponin levels in patients with COPD with inhaled bronchodilator, statin, or aspirin therapy.

In conclusion, testing for troponin can identify patients with COPD at high risk for exacerbations and mortality. Starting aspirin or statin therapy in this patient subgroup may be justified to reduce exacerbation risk and mortality.

Anemia and COPD

Anemia is generally defined as a hemoglobin level < 13 g/dL in men and < 12 g/dL in women. However, in patients with COPD, it is difficult to set a clinically meaningful cut–off point because COPD is generally considered a cause of polycythemia in the setting of chronic hypoxemia.[18] The most common type of anemia seen in patients with COPD is anemia of chronic disease (ACD). Different studies have found the prevalence of anemia in patients with COPD to be around 21%–23%, making the prevalence of anemia in COPD comparable to the prevalence of anemia in other chronic diseases well known to be associated with anemia such as malignancy and chronic kidney disease.[19] There are different hypothetical mechanisms to explain the development of ACD in patients with COPD. Specifically, the increased levels of cytokines and leukotrienes suppress the erythropoietin response and shorten erythrocyte life, leading to anemia.[20] Moreover, these cytokines and interferons increase ferritin levels, which trap iron and decrease its availability for hematopoiesis.[21] Anemia is known as a significant predictor of mortality, the hospitalization rate, and the duration of hospital stay in patients with COPD on long –term oxygen therapy (LTOT).[22] However, it is less clear how much anemia could affect survival and morbidity in patients with stable COPD. Therefore, we conducted a literature review and found three studies in which the authors discussed the significance of anemia in patients with stable COPD.

The first study was published in 2006 by Halpern and coworkers.[23] They retrospectively analyzed U.S. Medicare claims data for patients with COPD in the period between 1997 to 2001. They enrolled 132,424 patients with COPD in the study. They found that the prevalence of anemia among patients with COPD was 21%. The primary endpoint of the study was the costs to the Medicare system for all medical care. Patients with COPD and anemia cost 2.2 times more than patients with COPD without anemia for all Medicare payments ($1,466 vs. $649, $p < 0.001$). They also found the mortality rate among patients with COPD and anemia (262 per 1,000 person–years of follow–up) was approximately two–fold the mortality rate in patients with COPD without anemia (133 deaths per 1,000 person–years of follow–up; $p < 0.001$). In this study there were no specific measures of disease severity available. The next study was done by Boutou and colleagues in 2013. They included 294 outpatients with stable COPD; anemia was identified in 46 patients (15.6%). The

authors reported a significant difference in the median survival and survival rates between outpatients with COPD regardless of whether they also had anemia. In patients with anemia, the median survival was 68.7 months compared with 79.8 months in patients without anemia ($p = 0.035$). The survival rates at three and five years were 0.65 and 0.52 for the patients with anemia and 0.8 and 0.68 for the patients without anemia, respectively. Anemia but not the hemoglobin concentration was found to be an independent predictor of mortality in the total population (HR 1.87, 95% CI 1.06–3.29).

Oh et al.[24] evaluated the prognostic role of anemia on the clinical course of outpatients with stable COPD in Korea in 2017. They included 407 patients with COPD enrolled in the Korean obstructive lung disease (KOLD) cohort at 16 hospitals in Korea recruited over nine years. They found anemia to be a significant factor that negatively impacts the survival of patients with COPD: The patients with COPD without anemia (mean survival period = 8.88 ± 0.15 years) survived longer than patients with COPD and anemia (mean survival period = 6.77 ± 0.84 years; $p < 0.001$). They also found that elderly patients, female patients, and patients with a lower BMI and a lower albumin level were more likely to have a significantly lower serum hemoglobin level (all $p < 0.05$). One major limitation of this study was the male–dominant sample (male = 97.3%) as smoking is far more common in Korean males than Korean females.

The most recently published cohort study was in 2018 by Park and coworkers.[25] They identified 7,114 patients with COPD in the period from 2003 to 2013 by using the National Health Insurance Service–Health Screening (NHIS) cohort in Korea. Of these patients, 469 (6.6%) were anemic. During the study period, the mortality rate in patients with COPD and anemia was 46.5% compared with 32.1% in patients with COPD without anemia ($p < 0.001$). In addition, anemia was identified as one of the determinants significantly associated with overall mortality in multivariate analysis. The HR of anemia for mortality was 1.31 (95% CI 1.11–1.54). The decrease in the hemoglobin level was closely related to the decrease in survival rate among patients with COPD and anemia. However, the authors could not exclude patients with comorbidities associated with anemia, which could be a potential confounder.

In summary, all these studies have clearly shown that anemia in patients with stable COPD is a major clinical concern because this has been associated with significantly higher mortality rates among patients with COPD. However, there has been no clear agreement about the role of the hemoglobin concentration in predicting mortality and survival in patients with COPD with or without anemia.

There appears to be several benefits to red blood cell transfusion in patients with COPD and chronic anemia. Schönhofer et al.[26] found that red blood cell transfusion in patients with COPD and anemia leads to a significant reduction in both the minute ventilation and the work of breathing compared with patients with anemia but not COPD. In addition, in patients with COPD and anemia who have difficulty in weaning from the ventilator, blood transfusion may lead to successful weaning.[27] LTOT showed a progressive but non–significant improvement in hemoglobin concentration in patients with COPD and chronic anemia.[28] Additional studies are needed to determine the impact of red blood cell transfusion or LTOT on the survival of patients with stable COPD and chronic anemia.

C–reactive Protein and COPD

C–reactive protein (CRP) is a non–specific acute phase protein and inflammatory biomarker that is elevated in conditions associated with tissue damage, inflammation, infection, and malignancy.[29] Given that COPD is a chronic inflammatory disease of the lungs that involves different inflammatory cells and mediators, several inflammatory markers including CRP have been found to be increased in the systemic circulation of patients with the disease.[30] The inflammatory process in COPD is not limited to the lungs; it also involves systemic inflammation manifested by several systemic complications common in patients with COPD, such as osteoporosis and cachexia.[31] Elevated CRP levels in the presence of a major exacerbation symptom is useful in confirming the COPD exacerbation diagnosis.[32] However, CRP levels were not helpful in predicting survival and mortality in the acute COPD exacerbation event.[33] Determining the role of CRP levels in predicting the prognosis in patients with stable COPD is less clear. Using a high–quality literature review, we identified

several studies exploring the prognostic role of CRP in patients with stable COPD.

The first study was published in 2006 by Man and colleagues;[34] they measured CRP levels in 4,803 cigarette–smoking patients aged 35–60 years with mild–to–moderate airflow obstruction on spirometry using a highly sensitive enzyme linked immunosorbent assay. All–cause mortality increased significantly with increased CRP levels. In addition, the risk of CAD– and cancer–related mortality was significantly related to CRP levels. However, these results were limited to patients with mild–to–moderate disease but not to patients with more advanced disease. In 2007, Dahl et al.[35] selected 1,302 patients with COPD from the ongoing Copenhagen City Heart Study; they followed them for eight years and recorded COPD admissions and deaths. They found that the cumulative incidence of COPD hospitalizations and death was significantly higher in patients with COPD with high CRP values (> 3 mg/L) independent of lung function and smoking.

De Torres et al.[36] evaluated the association between CRP levels and survival in patients with moderate to very severe COPD. They followed 218 patients with stable COPD for a median of 36 months after measuring baseline CRP levels. Their published results revealed that a baseline CRP level was not significantly associated with survival status in patients with COPD with moderate to very severe disease. Although this study was a clinical rather than epidemiological one, it was limited by the relatively small population size. Liu and colleagues[37] investigated the role of CRP levels and BODE scores in predicting mortality in patients with COPD. Their prospective study included 125 patients with stable COPD. They found that both serum CRP concentrations and BODE scores were independent prognostic variables of mortality in the studied population. However, the combination of both precisely predicted the survival of patients with stable COPD. In 2016, Kim et al.[38] conducted a retrospective study to evaluate the factors associated with mortality in patients with COPD at high risk for acute COPD exacerbation. They identified 61 patients at high risk for acute COPD exacerbation out of 606 enrolled in the study. High–sensitivity CRP was one of several factors (including neutrophil percent, lymphocyte percent, and the number of comorbidities) that significantly predicted mortality in patients with COPD at high risk for acute COPD exacerbation (defined as hospitalization at least once in a year).

In 2017, Xiong and colleagues[39] enrolled 409 patients with stable COPD in a prospective, case–control study. They followed the patients every three months during the 24–month follow–up period with routine blood tests, pulmonary function tests, CRP, Erythrocyte Sedimentation Rate (ESR) , procalcitonin, and the BODE index to evaluate the prognostic role of these variables. CRP was positively correlated with mortality. However, the relevance of CRP to mortality was inferior compared with other variables measured in routine blood tests. The patients with COPD included in this study were those with moderate to very severe disease, so the results may not apply to patients with mild disease. In 2018, Mendy et al.[40] analyzed data regarding 431 patients with COPD from the National Health and Nutrition Examination Survey (NHANES) conducted from 2007 to 2010 and the corresponding Mortality–Linked File; they aimed to determine the blood biomarkers that could predict mortality in patients with COPD. They found the CRP level to be a significant determinant of mortality in the studied population. Moreover, the role of the CRP level in predicting mortality could significantly improve with the addition of eosinophil and neutrophil counts.

Celli and colleagues[41] carried out a sub–study of the randomized SUMMIT trial in 2019. They studied the significance of several serum biomarkers in predicting hospitalizations, exacerbations, FEV1 decline, and mortality in patients with moderate COPD. The study showed CRP as a significant factor associated with increased risk of death in patients with COPD. However, CRP was not associated with predicting hospitalizations, exacerbations, or FEV1 decline.

Based on the above–mentioned studies, there are conflicting results regarding the significance of the CRP level in predicting mortality in patients with stable COPD, especially regarding changes in COPD severity. However, the use of the CRP level in combination with other clinical variables and blood biomarkers could help to predict mortality in patients with stable COPD. Therefore, we recommend against the individual use of the CRP level in predicting

mortality in patients with stable COPD, but we recommend combining it with other variables to improve the predictive value.

Hypercapnia and COPD

Elevated arterial CO_2 levels (hypercapnia), defined as an arterial partial pressure of CO_2 ($PaCO_2$) ≥ 45 mmHg in patients with COPD, is observed in stable patients and during exacerbations. According to one study, 28.4% of stable GOLD three and four patients had hypercapnia.[42] Emphysema, airflow obstruction, and respiratory muscle weakness may lead to increased alveolar dead space and hypercapnia.[43] Emphysema patients usually are not hypercapnic until near death and are not frequently admitted for exacerbations of respiratory failure. On the other hand, chronic bronchitis patients usually retain CO2 and become hypoxemic, either acutely or chronically, and this leads to the complications of pulmonary artery hypertension and cor pulmonale. A distinct subset of patients with COPD had temporary, reversible hypercapnia following exacerbations.[44] Many questions followed. Do patients with COPD and hypercapnia have a worse prognosis compared with normocapnic patients? Furthermore, does hypercapnia represent the natural progression of COPD or a different phenotype? We accordingly conducted a literature review.

Costello and colleagues[44] studied 85 patients with COPD over five years. The analysis included arterial blood gas at admission and discharge, the number of exacerbations, and mortality. The patients were divided into three groups according to admission and discharge $PaCO_2$. Interestingly, the reversible hypercapnia group had similar five–year mortality compared with the normocapnia group. Only 24% of patients with reversible hypercapnia developed chronic hypercapnia during follow–up. Patients with irreversible hypercapnia had lower follow–up partial pressure of oxygen (PaO_2) and higher $PaCO_2$ values compared with the other groups with higher long–term mortality.

Dave and colleagues[45] studied 1,224 patients with COPD retrospectively, of which 587 had the alpha–1 antitrypsin deficiency (AATD) diagnosis. During a 10–year follow–up, patients with non–AATD COPD and stable hypercapnia did not show an increased mortality risk compared with normocapnic patients. On the other hand, patients with worsening stable–state hypercapnia had significantly increased mortality (HR 1.65, 95% CI 1.06–2.56, p = 0.03). Yang et al.[46] implemented a prospective cohort study to compare the survival of patients with COPD and chronic hypercapnia with those with COPD and normal $PaCO_2$. Between 1993 and 2006, they enrolled 275 patients with stable COPD, including 98 patients with normocapnia and 177 patients with chronic hypercapnia. They found that patients with normal $PaCO_2$ survived longer than those with hypercapnia (6.5 vs. 5.0 years, p = 0.016).

In 1998, Aida and colleagues[47] studied the prognostic value of hypercapnia in patients with chronic hypoxemic respiratory failure requiring LTOT, as hypercapnia was generally considered an ominous sign in chronic lung diseases at that time. Their study comprised patients in Japan from 1985–1993: 3028 patients with the sequela of pulmonary tuberculosis on LTOT and 4,552 patients with COPD on LTOT. There was an increase of ≥ 5 mmHg in $PaCO_2$ over the six to 18–month follow–up period that was associated significantly with a poorer prognosis compared with those with stable $PaCO_2$. However, there were no differences in mortality between patients with hypercapnia and normocapnia with the sequela of pulmonary tuberculosis on LTOT.

Ahmadi et al.[48] performed a national prospective study in Sweden between 2005 and 2009 to evaluate the prognostic role of $PaCO_2$ in patients with oxygen–dependent COPD. They found that $PaCO_2$ was an independent predictor of mortality (p < 0.001). It exhibited a U–shaped pattern in association with mortality: Mortality decreased with hypocapnia ($PaCO_2$ < 5.0 kPa) and hypercapnia ($PaCO_2$ > 7 kPa). In 2018, Brat et al.[49] implemented a non–interventional multicenter study on patients with COPD using the Czech Multicenter Research Database to investigate the respiratory parameters associated with increased mortality in GOLD category B patients with COPD, which represents the largest portion of patients with COPD in real–life studies. The results showed that hypercapnia ($PaCO_2$ > 7.0 kPa) was associated significantly with mortality in these patients (p < 0.001).

In conclusion, all of the above–mentioned studies agree that the elevation of arterial carbon dioxide

is a significant predictor of mortality in patients with stable COPD. However, there is variable cut–off for $PaCO_2$ values that are associated with higher mortality. Therefore, we recommend using hypercapnia as a valid predictor of mortality in patients with stable COPD, but additional studies are needed to determine the $PaCO_2$ value that significantly impacts mortality rates in patients with stable COPD.

Conclusion

There have been a myriad of studies in which researchers have explored the significance of several blood laboratory tests in predicting mortality in patients with stable COPD. A high troponin level is a reliable predictor of mortality in patients with stable COPD, and we recommend considering starting these patients on aspirin or statin therapy to reduce mortality. Although anemia is significantly associated with higher mortality among patients with stable COPD, we recommend against the sole use of the hemoglobin concentration in predicting mortality in these patients. In addition, studies have shown that the use of the CRP level alone to assess the risk of mortality in patients with stable COPD is not significant. Hypercapnia is clearly associated with higher mortality rates among patients with stable COPD, but no clear $PaCO_2$ cut–off has been found to predict mortality in this population. Our literature review supports using CRP, troponin, anemia, and $PaCO_2$ to predict mortality in patients with stable COPD. However, we highly recommend pursuing the well–established process in the diagnosis and follow up utilizing the complete and focused history and physical examination, complete pulmonary function test (PFT) including routine spirometry, determination of lung volumes and measurement of diffusing capacity of carbon monoxide in addition to the use of noninvasive oximetry and blood gas analysis for follow ups. Currently, there is no indication in the guidelines to employ measurements of laboratory tests in a steady state COPD patient.

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Disclosure

None reported.

MM

A Review of Posterior Fossa Lesions

by Haley N. Bray, MD & Joshua M. Sappington, MD

When a patient presents with hearing loss especially asymmetric or sudden loss, cranial nerve dysfunction, or symptoms that may represent obstructive hydrocephalus it is imperative that the treating physician consider a posterior fossa lesion in the differential diagnosis.



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Abstract

Posterior fossa lesions can occur in patients of all ages. Patients present with subtle findings of hearing loss, tinnitus, headache, cranial neuropathies, imbalance, vertigo, nausea, and vomiting depending on the location and type of lesion. The presentation can be particularly insidious as the most common symptom is slowly progressive hearing loss. Posterior fossa lesions should be included in the differential diagnosis for patients with this presentation and appropriate audiologic testing and imaging should be performed. Management involves collaboration between multiple subspecialties and has evolved significantly over the years leading to increased patient involvement and improved outcomes.

Introduction

Lesions of the posterior fossa may be encountered by physicians of many specialties. An understanding of the clinical presentation, differential diagnosis, work–up, and treatment of these lesions will assist all physicians in the care of a patient with this medical condition. It is imperative that patients suspected of or diagnosed with a posterior fossa lesion are referred to the appropriate specialties.

The posterior fossa is bound by the clivus, petrous ridge of the temporal bones, mastoid portion of the temporal bones, and the occipital bone. It houses the cerebellum, portions of the brainstem including the pons and medulla, and the fourth ventricle.[1] Lesions in the posterior fossa can be categorized by their etiology and include vascular, infectious, traumatic, and neoplastic or by their anatomic location within the posterior fossa. They are either intra and extra–axial which describes whether they exist inside or outside of the pia mater in the brain parenchyma. Intra–axial tumors arise from the brainstem, cerebellum, or fourth ventricle.[2] Tumors of the posterior fossa can be seen in both adults and children with 65% of pediatric brain tumors arising in the posterior fossa.[3]

Many posterior fossa lesions are found is the cerebellopontine angle (CPA) which consists of cerebrospinal fluid (CSF), cranial nerves VII and VIII, the anterior inferior cerebellar artery, and arachnoid tissue. Tumors at this location represent less than 10% of all intracranial tumors in adults and less than 1% in children.[4] The most common pathologies are acoustic neuromas and meningiomas.[4] Lesions in this area are of particular interest to otolaryngologists as they present with otologic symptoms particularly asymmetric hearing loss and require multidisciplinary management including otolaryngology, neurosurgery, and radiation oncology.

Clinical Presentation

The presentation of a patient with a posterior fossa lesion may

be different based on the type and anatomic location of the lesion. Typically, patients present with gradually progressive symptoms and signs including asymmetric hearing loss, tinnitus, vestibular dysfunction, and cranial neuropathies.[2,5] Tinnitus followed by hearing loss are the most common earliest findings. Vertigo is overall uncommon and usually mild however patients more commonly presenting with imbalance.[6] They may also present with symptoms of increased intracranial pressure such as nausea, vomiting, papilledema, mental status changes, and ataxia.[3,6] Any patient presenting with these symptoms should be considered for work–up of an occult lesion.[5] Asymmetric sensorineural hearing loss or sudden sensorineural hearing loss are two of the most common presentations and patients with either presentation must have a contrasted MRI to evaluate for retrocochlear pathology. Due to the increased use of MRI with contrast incidentally diagnosed posterior fossa lesions are becoming increasingly more common.[7] Early identification of tumors, the delineation of their natural history, and the availability of MRI has led to a significant change in management with increased options for patients.[7] Figure 1 highlights the sinister nature of these lesions as this patient's only presenting symptom was sudden hearing loss.

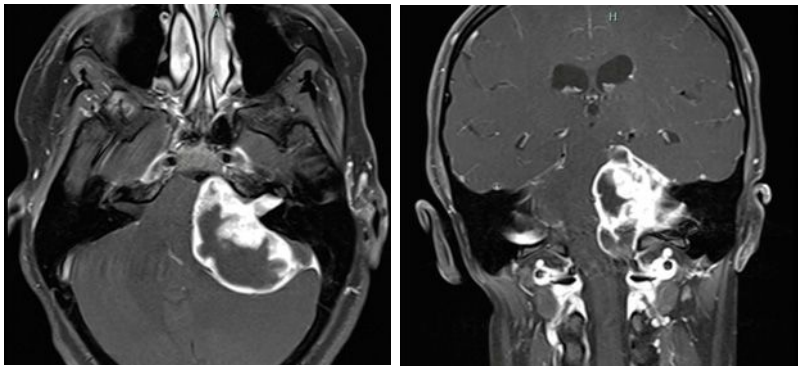


Figure 1. A young individual presented for evaluation of sudden sensorineural hearing loss and was found to have a giant acoustic neuroma. This patient had no other major additional signs or symptoms.

Work–Up

A thorough history and physical examination is the first step in evaluation. Historical symptoms including asymmetric hearing loss, asymmetric tinnitus, vestibular dysfunction, and cranial neuropathies raise suspicion and require further workup for a lesion that is more advanced.[2] A comprehensive physical exam includes a complete head and neck exam, cranial nerve evaluation and microscopic otoscopy.

Audiologic testing is an imperative step in the diagnostic and management algorithm.[5] Involvement of the middle ear can result in conductive or mixed hearing loss. A complete audiologic exam includes routine air, bone audiometry, and speech discrimination. Auditory brainstem response testing is another available test which is performed in cases where hearing preservation is considered and possible.

Both CT and MRI can be used to image the posterior fossa, but MRI with gadolinium contrast is preferred and is the gold standard due to improved soft tissue imaging.[2,3] CT is often used as the first imaging study, especially in patients with findings that are concerning for an emergent diagnosis requiring a quick and easily available form of imaging.[3] With regards to MRI, T1–weighted sequence with contrast is essential in delineating these lesions. The administration of contrast with MRI is exceptionally important in initial diagnosis as many small lesions may be missed without the administration of contrast. T2 imaging may not delineate small lesions as easily due to CSF bathing the CPA and IAC but can be used to monitor known lesions.[8,9]

Table 1 summarizes the various pathologies based upon location and pathology type. Given that most pertinent and common lesions of the posterior fossa and CPA for otolaryngologists are acoustic neuromas and meningiomas these two pathologies will be presented in greater detail.

Acoustic Neuroma/Vestibular Schwannoma

Acoustic neuromas are most common tumor of the CPA, representing over 80% of tumors at this anatomic location.[2] A benign tumor that arises from perineural Schwann cells of the vestibular nerve, are also called vestibular schwannomas.[2,3] They may arise from the superior or inferior vestibular nerve. Within the internal auditory canal, they have a close relationship with the facial nerve and cochlear nerve. They are typically slow growing, well circumscribed, and can cause symptoms by displacement of neurovascular structures.[2] The most common presentation is a slowly progressive asymmetric sensorineural hearing loss. Facial nerve palsy and paralysis are uncommon even in

Table 1. Table containing an differential diagnosis overview of potential lesions of the posterior fossa.[10-24]

Posterior Fossa Lesions	
Intra-axial Neoplasms	Pilocystic astrocytoma Medulloblastoma Brainstem glioma Hemangioblastoma Atypical teratoid rhabdoid tumor Choroid plexus papilloma Ependymoma and Subependymoma Hemangioma Dysplastic gangliocytoma (Lhermitte-Duclos) Langerhans cell histiocytosis
Extra-axial Neoplasms	Acoustic Neuroma/Vestibular Schwannoma Meningioma Cholesteatoma/Epidermoid cyst Arachnoid cyst Cholesterol granuloma Dermoid tumor Non- acoustic neuroma/schwannoma Teratoma Lipoma Chordoma Glomus Tumor/Paraganglioma Endolymphatic sac tumor Giant cell tumor Chondrosarcoma Lymphoma Metastasis
Non-neoplastic lesions	Trauma Vascular lesion Hemorrhagic and ischemic stroke Arteriovenous malformation Aneurysm Nontraumatic subdural hematoma Cystic lesion Dandy-Walker cyst Mega cisterna magna Retrocerebellar cyst Infectious/Inflammatory Abscess Lyme disease Tuberculosis Autoimmune dural lesions

large lesions. Most are unilateral and non–hereditary, but a small percentage of them may be associated with Neurofibromatosis type 1 (NF1) or Neurofibromatosis type 2 (NF2).[2] Bilateral lesions occur with NF2 and are pathognomonic for this genetic condition.[2] Approximately 80% of acoustic neuromas involve the IAC and can be purely intra–canalicular (withing the IAC), purely extra–canalicular or both.[2,3,14] They are isodense or slightly hypodense on unenhanced CT and typically isointense or mildly hypointense on T1 without contrast, and avidly enhance with contrast and mildly hyperintense on T2 MRI.[2,3] The imaging of choice is MRI IAC with and without contrast. Treatment of these lesions has evolved markedly over the years.[15] Treatment depends on the size, location, as well as the associated symptoms and signs. This is especially true as smaller tumors are being diagnosed more frequently with the availability and use of early imaging.[15] Options for management include observation with repeat imaging, stereotactic radiotherapy (SRT), and microsurgical resection (Figure 2).

Meningioma

Meningiomas represent another common tumor in the posterior fossa and are the second most common lesions. They are typically benign, but can be locally aggressive and can invade bone through haversian canals or cause adjacent bone to become hyperostotic.[2] On unenhanced CT 50% are hyperdense and 50% isointense on T1 and T2 MRI.[3] They may also have calcifications and a homogenous enhancement with iodine.[2] On T2 they may be hyperintense and often have a dural tail which may help differentiate them from other CPA tumors.[3] They also have a broad base and the majority extend into the middle fossa.[2] Interestingly patients with meningiomas will often maintain their hearing even with particularly large lesions.

A grading system developed by the World Health Organization (WHO) is widely used and based off of histopathologic appearance.[2] The grading system ranges from Grade I to III with Grade I representing benign lesions that make up 90% of these tumors (Figure 3). Often clinically small meningiomas are indistinguishable from acoustic neuromas and pathologic diagnosis is made during microsurgical resection. Similar to acoustic neuromas management options include observation, SRT and microsurgical resection.

Management

Management starts with ensuring that the patient received a multidisciplinary approach. Depending on the type of lesion, these patients are often referred

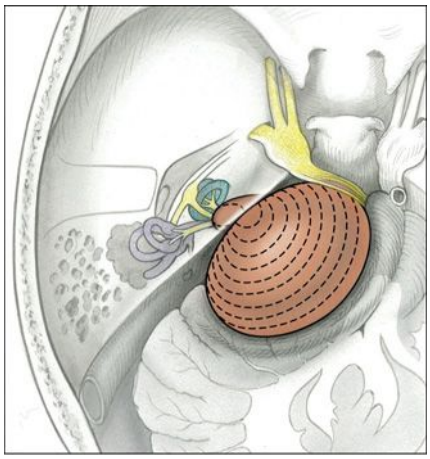


Figure 2. Demonstrating the slow growth pattern of acoustic neuromas. *Image from RK Jackler Skull Base Surgery Atlas.*



Figure 3. Illustration demonstrating the propensity of meningiomas to develop along foramina in the skull base as well as venous sinuses. *Image from RK Jackler Skull Base Surgery Atlas.*

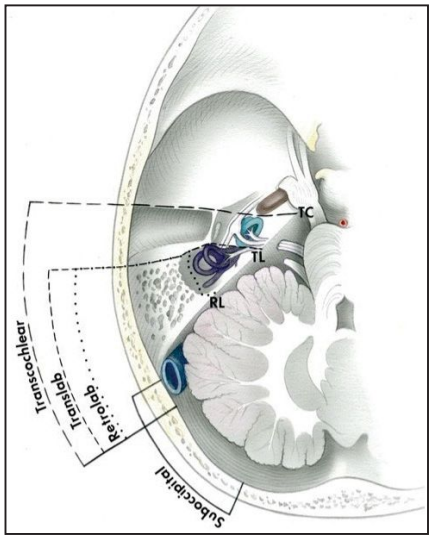


Figure 4. Demonstration of various exposure from several different posterior fossa approaches. *Image from RK Jackler Skull Base Surgery Atlas.*

to neurosurgery and may also require referral to interventional neuroradiology, medical oncology, and radiation oncology. Regardless of the natural history of the particular lesion, it is important to initiate a treatment plan. Patients are provided with information regarding their diagnosis, natural history, and their options for treatment. Additionally, they are involved in the decision–making process in lesion management.

The treatment options that exist for posterior fossa masses include observation, microsurgery, and stereotactic radiotherapy.[15] Treatment decision is based on the type, size, and location of the lesion, whether there are related symptoms or signs, and to a large degree patient's preference. Treatment decisions should be made with the goal of tumor control with maximal patient benefit without creating morbidity.[15] Observation or "watchful waiting" requires a commitment to repeat imaging to monitor for growth. This approach is often utilized in small lesions and lesions in patients who are older or with poor health. The main risks of observation include lesion growth and loss of hearing. Lesions are initially imaged with repeat MRI with contrast with audiogram at six months and if stable are imaged annually with audiologic testing. Indications to pursue alternative treatment include growth of the lesion and changes in hearing which can be a relative indication.

Surgical Management

Microsurgical resection is indicated for large lesions, lesions in young patients, growing lesions, and patients who have failed SRT. There are several microsurgical approaches which are indicated based upon the size of the lesion, location, and patients hearing.[2] For giant lesions these approaches may also be combined. The goal is for gross total resection of a lesion with preservation of vital structures and minimizing any morbidity. This modality is the only curative treatment and patients can benefit from tumor control, management of mass effect, and pathologic diagnosis. Possible complications include CSF leak, meningitis, facial nerve injury, loss of hearing, changes in facial sensation, and injury to the anteroinferior cerebellar artery.[2] All cases utilize facial nerve monitoring and hearing preservation cases utilize electrophysiologic monitoring of the cochlear nerve. Figure 4 demonstrates the various exposures and approaches to the posterior fossa. Approaches for the majority of CPA lesions include translabyrinthine, retrosigmoid, and middle cranial fossa approaches.

Translabyrinthine Approach

The translabyrinthine approach is indicated for a variety of size tumors at the CPA. It provides wide exposure of the internal auditory canal into the CPA allowing for full identification of the facial nerve. Additionally, it has the benefit of having little to no brain retraction and intradural drilling. However, it does result in complete hearing loss and exposure can be limited by the pneumatization of the mastoid.[2] It is recommended

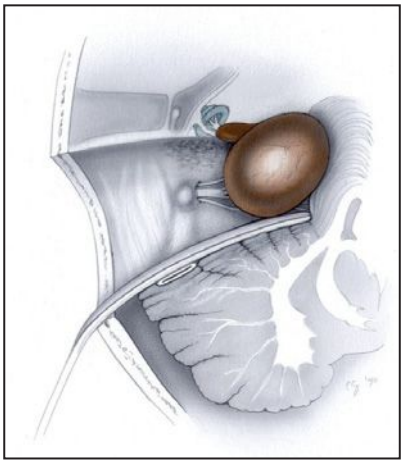


Figure 5. Demonstration of exposure via the translabyrinthine approach. This approach offers wide exposure of the IAC and CPA but sacrifices any residual hearing. *Image from RK Jackler Skull Base Surgery Atlas.*

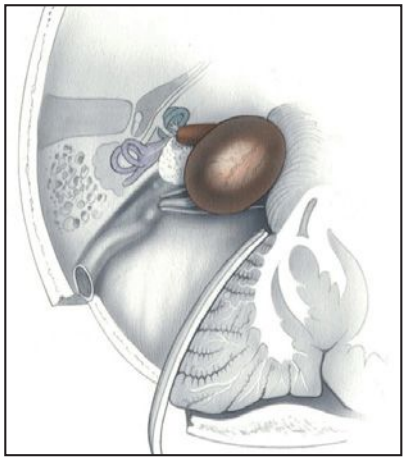


Figure 6. Exposure derived from a retrosigmoid approach. This is a possible hearing preservation approach though tumors that extend laterally into the IAC can be limiting. Additionally, the retrosigmoid approach provides a more panoramic view of the posterior fossa. *Image from RK Jackler Skull Base Surgery Atlas.*

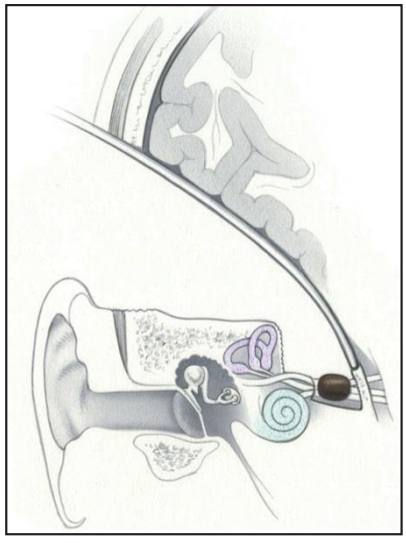


Figure 7. The middle cranial fossa approach is a hearing preservation approach for small intracanalicular tumors with limited medial extension. *Image from RK Jackler Skull Base Surgery Atlas.*

for patients without serviceable hearing and in cases were hearing preservation is unlikely (Figure 5). Reconstruction is performed by placing an abdominal fat graft at the conclusion of the case.

Retrosigmoid Approach

The retrosigmoid or suboccipital approach provides an opportunity for hearing preservation and it provides a wider panoramic exposure to the posterior fossa. The wide exposure of this approach makes it very versatile. Tumor extension into the IAC is an important consideration as violating the inner ear significantly decreases chances of hearing preservation. One particular consideration of this approach is that it requires cerebellar retraction, which could create edema narrowing the surgical corridor.[2] This could lead to long term cerebellar encephalomalacia. Pending the placement of the sigmoid, cerebellum and patient habitus this can result in a tight surgical corridor. In cases without hearing preservation the option of translabyrinthine versus retrosigmoid largely comes down to surgeon preference (Figure 6).

Middle Fossa Approach

The middle cranial fossa approach is a subtemporal extradural approach which is indicated for small intracanalicular tumors with usable hearing. An extended approach is possible though larger tumors are poor candidates for this approach.[2] The limitation of this approach is that tumors that extend to or that are in the distal IAC and the CPA can have limited exposure. This approach requires retraction of the temporal lobe for exposure which has inherent risks including seizure, stroke, and aphasia particularly in elderly patients. Additionally, depending on the nerve or origin of the tumor there is a short term slightly higher risk of initial facial paresis with this approach primarily within the first year of surgery (Figure 7).[25]

Stereotactic Radiotherapy

Stereotactic radiotherapy also known as stereotactic radiosurgery is an additional treatment option for patients. Examples of this include Gamma Knife, CyberKnife, and proton beam radiation. This treatment modality is an option for patients with growing tumors that cannot undergo microsurgical resection, do not wish to proceed with

surgery, or are not too large. The goal of SRT is not to eliminate the tumor but cease growth of the lesion.[26] Ionizing radiation is delivered via a cobalt source or linear accelerator (LINAC) in an exceptionally precise manner to the intracranial lesion.[26] This limits exposure to normal healthy tissue and maximizes dose delivery to the tumor for therapeutic effect. This is accomplished via localization and targeting of the lesion. Treatment planning utilizes data from CT and MRI to localize the tumor plan treatment delivery.[26, 27,28] Patients are typically treated with 12 Gy single dose or 18 Gy fractionated treatments. Control rates for growing tumors is 80–85% vs. 90–95% for all lesions following SRT. Hearing preservation rates are approximately 20% for useful hearing at five years and is an important consultation topic. A negative of this treatment modality is that diagnosis and treatment is based off of imaging and a pathologic specimen is not obtained. A very rare but important consideration is that there have been approximately 20 cases of malignant transformation following radiation which is imperative to discuss with patients.[29] As the tumor is not removed it is recommended that patient undergo annual imaging to monitor for any changes.

Conclusions

Posterior fossa lesions can occur in patients of all ages with particularly innocuous presenting symptoms. When a patient presents with hearing loss especially asymmetric or sudden loss, cranial nerve dysfunction, or symptoms that may represent obstructive hydrocephalus it is imperative that the treating physician consider a posterior fossa lesion in the differential diagnosis. Work–up should always include a thorough history and physical exam, imaging, audiologic testing, and referral to an appropriate skull base center. Once the diagnosis has been made, a management plan can be formulated. Depending on the location, size, and pathology of the lesion different treatment options exist. These include observation, stereotactic radiotherapy, and microsurgical resection which is in stark contrast compared to historical considerations were nearly all tumors underwent microsurgical resection. Treatment options are managed in a multidisciplinary fashion and in conjunction with patient's goals of therapy. This has resulted in improved outcomes and quality of life as well as patient satisfaction.

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Disclosure

None reported.

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