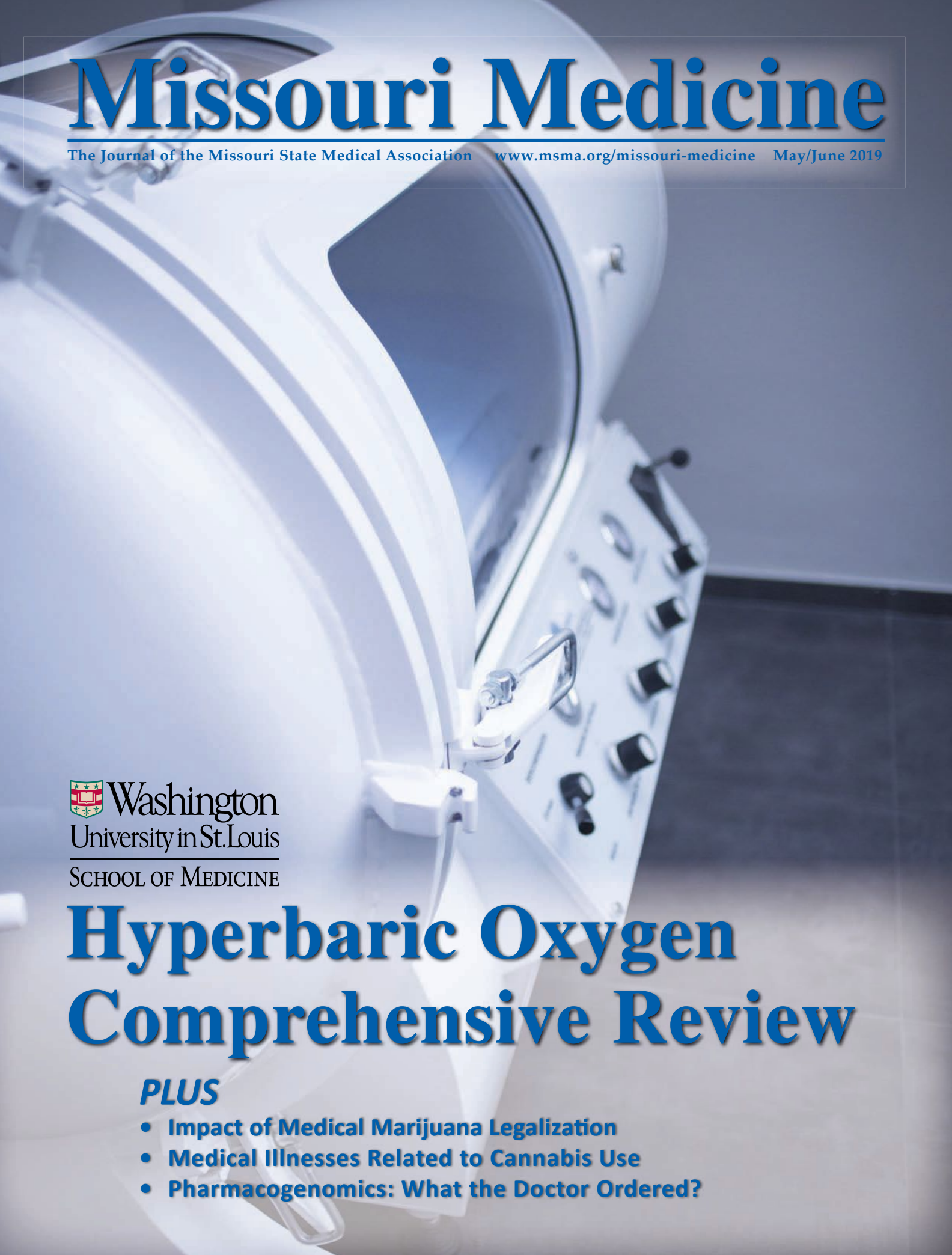
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GUEST EDITORIAL

Marijuana Legalization Will Cause Many Problems for Missouri Law Enforcement and Schools
by David G. Evans, JD 164



PERSPECTIVE

FDA's 'Accelerated Approvals' Are Critical But Raise Thorny Issues
by Henry I. Miller, MD 168

MEDICAL SCHOOL PERSPECTIVE

Washington University: Research, Education, and Innovative Health Care
by **David H. Perlmutter, MD** 173

SCIENCE OF MEDICINE | FEATURE SERIES

Presented by the Washington University School of Medicine
Hyperbaric Oxygen Therapy

Essentials of Hyperbaric Oxygen Therapy: 2019 Review
by John P. Kirby, MD, Jason Snyder, MD, Douglas J.E. Schuerer, MD, John S. Peters & Grant V. Bochicchio, MD 176

Hyperbaric Oxygen Therapy Emergencies
by John P. Kirby, MD 180

Hyperbaric Oxygen Therapy as an Elective Treatment
by John P. Kirby, MD 184

Hyperbaric Oxygen Indictions: Diabetic Foot Ulcers and Intractable Management
by John P. Kirby, MD 188

Hyperbaric Oxygen Therapy and Negative Pressure as Advanced Wound Management
by John Kirby, MD 192

The Diagnosis of Decompression Sickness in Sport Divers
by John P. Kirby, MD 195

Hyperbaric Oxygen Therapy and Radiation-Induced Injuries
by John P. Kirby, MD 198

www.msma.org/engage

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SCIENCE OF MEDICINE

Current Management of Copperhead Snakebites in Missouri
by Kevin T. Baumgartner, MD, Steven J. Fishburn, MD & Michael E. Mullins MD 201

Pleuropulmonary Blastoma: More Than a Lung Neoplasm of Childhood
by **Louis P. Dehner, MD**, Kris Ann Schultz, MD & D. Ashley Hill, MD 206

Physician Suicide: A Call to Action
by Molly C. Kalmoe, MD, Matthew B. Chapman, MD, Jessica A. Gold, MD & Andrea M. Giedinghagen, MD 211

Pharmacogenomics: What the Doctor Ordered?
by Joel C. Eissenberg, PhD & Rajeev Aurora, PhD 217

Emergent Medical Illnesses Related to Cannabis Use
by Karen Randall, DO & Kathleen Hayward, MD 226

REVIEW SUMMARY

Acute Illness Associated with Cannabis Use, by Route of Exposure: An Observational Study
Annals of Internal Medicine 229

161ST ANNUAL CONVENTION REPORTS & HIGHLIGHTS

Meet MSMA's President 232
Meet the MSMA Alliance President 233
State of MSMA - Presidential Address 234
Presidential Inaugural Address 236
Resolutions & Actions 238
Sponsors & Exhibit Sponsors 240
Credentials & Appointments 240
Elections 241
Council Minutes Summary 242
Reports of the Delegate Handbook 246
Financial Statements: Missouri State Medical Association 254
Financial Statement: Missouri State Medical Foundation 254
Financial Statement: Missouri Physicians Health Program 254
Attendance 255

FROM YOUR ASSOCIATION

Correspondence 170
1 Picture = 1,000 Words 171
Member Services Directory 256

MSMA member names in bold

Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

www.msma.org/missouri-medicine











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GUEST EDITOR

Marijuana Legalization Will Cause Many Problems for Missouri Law Enforcement and Schools

by David G. Evans, JD

The marijuana products of today are high in potency and can reach 99% pure delta-9 tetrahydrocannabinol (THC). [1] The THC in marijuana causes the "high" and leads to addiction, mental illness, violence, crime, traffic deaths, and many health and social problems. Research linking marijuana use to psychosis and schizophrenia and acts of violence is uniformly ignored by the proponents of marijuana use. The American Psychiatric Association and other authorities, report that current evidence supports, at a minimum, a strong association of marijuana use with the onset of psychiatric disorders.[2] A recent book by a former *New York Times* reporter details the research showing that the chronic use of marijuana leads to mental illness and violence.[3]

What has been the law enforcement experience in states that have legalized marijuana in some form? California just had to call out the national guard to deal with 22 years of growing marijuana "medicine." In 1996 California passed a "medical" marijuana law. They recently legalized recreational marijuana thinking it would end black market sales. California had over 22 years to get this right. It is a disaster.

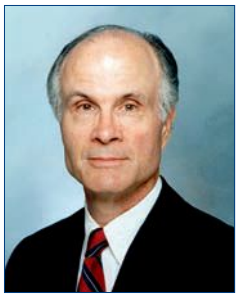
Governor Gavin Newsom, an early backer of recreational marijuana use, is now trying to stamp out California's black market. Newsom announced in February 2019 he would "boost the National Guard's statewide Counterdrug Task Force by redeploying up north to go after illegal cannabis farms, many of which are run by cartels." "So, the black market hasn't been curtailed, but it's probably been accelerated," says a local sheriff. [4] Black market marijuana is cheaper to buy.

Law enforcement in the states that have legalized marijuana know best what they face each day. Several national law enforcement groups oppose marijuana legalization and have written to Congress about it. [5] The National Fraternal Order of Police stated that a joint study conducted by the University of Colorado, Johns Hopkins University, and Harvard Medical School about the impact of legalization in Colorado determined the following:

1. There is evidence of a persistent black market for marijuana which may increase the presence of Mexican drug cartels that are bringing in other drugs like heroin.
2. There are higher rates of traffic fatalities while driving under the influence of marijuana.
3. An increase in marijuana-related poisonings and hospital visits for children occurs.
4. There was no reduction in crime or significant increase in tax revenues.
5. Use of marijuana by children less than 17 years of age is rising faster than the national average and arrests of juveniles for marijuana-related offenses are up 5%.

The National Association of Assistant United States Attorneys noted that citizens in states that have legalized marijuana for medical use have seen the abuse of such laws, which has created many undesirable and unforeseen effects, including:

1. Increased violence directed toward marijuana dispensary owners and employees.
2. Increased burglaries of marijuana dispensaries.
3. Lack of effort on the part of dispensary owners/employees to control unlawful or nuisance behavior in and around the business or to comply with state laws designed to regulate medical marijuana use.
4. Increased loitering, noises, litter, and property damage, smoking of marijuana in public areas.



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5. Increased offenses involving driving while under the influence of marijuana.

6. An influx of criminal elements into the neighborhoods where dispensaries are located.

7. Marijuana distributors operating in school zones or close to schools or parks

8. Increased sales of marijuana to juveniles under the age of 18 or to customers who are young and do not have an illness or a serious medical condition.

The National Sheriffs Associations, the National District Attorneys Association, the National Narcotic Officers' Associations Coalition (NNOAC) noted that states that legalized marijuana have been unable to control the black market for the drug. The Oregon State Police reported that 70 percent of the marijuana transactions remain illegal, despite legalization laws. Marijuana is sold on the street in legalized states and exported in vast quantities to other, non-legalized jurisdictions. There are even reports of foreign drug cartels, including Mexican cartels, moving operations to Colorado to take advantage of lax marijuana laws. According to the California Police Chiefs' Association, there is ample documentation of the many adverse effects of marijuana legalization in addition to the violations of federal law.[6]



Data show that while under the influence of marijuana, people show the same lack of coordination on standard intoxicated driver tests as do people who had too much alcohol.

Legalizing Marijuana Will Cause More Mayhem on Missouri Roadways

Data show that while under the influence of marijuana, people show the same lack of coordination on standard intoxicated driver tests as do people who had too much alcohol. The more difficult and unpredictable the task, the more likely marijuana will impair performance. [7]

Colorado and the State of Washington Data Since the Legalization of Marijuana

In Colorado, 55% of marijuana users surveyed by the Colorado Department of Transportation said they believed it was safe to drive under the influence of marijuana. Within that group, the same percentage said they had driven high in the past 30 days, on average 12 times. A recent analysis of federal traffic fatality data by the *Denver Post* found that the number of Colorado drivers involved in fatal crashes who tested positive for marijuana has doubled since 2013. [8]

In April, 2017, the Governors Highway Safety Association (GHSA), the national association of state highway safety offices that address behavioral highway-safety issues including drug impaired driving, reported that:

- In a 2014 roadside survey in the state of Washington conducted primarily in evening hours, 44% of the drivers reported that they had driven within two hours of using marijuana in the past year.
- In Colorado, marijuana-related traffic deaths increased 48% in the three-year average (2013-2015) since Colorado legalized recreational marijuana compared to the three-year average (2010-2012) prior to legalization.
- In a survey of drivers in Colorado and Washington who reported any marijuana use in the past month, 43.6% reported driving under the influence of marijuana in the past year and 23.9% had driven within 1 hour of using marijuana at least 5 times in the past month.[9]

AAA Foundation for Traffic Safety Report on the State of Washington

The Washington Marijuana Legalization and Regulation Initiative 502 was approved in 2012. It legalized the production, possession, delivery, and distribution of marijuana. In 2016, the state of Washington Traffic

Safety Commission (WTSC) reported the results of THC toxicology tests. From 2010 through 2013, the estimated number and proportion of drivers involved in fatal crashes who had a detectable concentration of THC in their blood ranged from a low of 48 (7.9%) to a high of 53 (8.5%). The number and proportion both doubled from 49 (8.3%) in 2013 to 106 (17.0%) in 2014. Analysis of trends over time before and after Initiative 502 took effect indicate that the proportion of drivers positive for THC was generally flat before Initiative 502, but began increasing significantly approximately 9 months after the effective date of Initiative 502. [10]

Colorado Data from the Rocky Mountain High Intensity Drug Trafficking Area Report

The Rocky Mountain High Intensity Drug Trafficking Area is a federal project that gathers data on drug trafficking and facilitates cooperation and coordination among federal, state and local drug enforcement efforts to enhance combating the drug trafficking problem locally, regionally and nationally. According to their 2017 report, marijuana-related traffic deaths when a driver tested positive for marijuana more than doubled from 55 deaths in 2013 to 125 deaths in 2016. Marijuana-related traffic deaths increased 66% in the four-year average (2013-2016) since Colorado legalized recreational marijuana compared to the four-year average (2009-2012) prior to legalization. The number of toxicology screens positive for marijuana (primarily DUID) increased 63% in the four-year average (2013-2016) since Colorado legalized recreational marijuana compared to the four-year average (2009-2012) prior to legalization.[11]

On September 12, 2018 a new Colorado report compiled by the Rocky Mountain High Intensity Drug Trafficking Area found that marijuana-positive traffic fatalities have increased since marijuana legalization. Drugged driving went from killing roughly one person every 6.5 days to now killing someone every 2.5 days.[12]

Michigan

Of the nearly 800 of Michigan medical cannabis users surveyed, 51 percent admitted to driving while "a little high" and 21 percent said they had driven while "very high." [13]

Marijuana Use, Mental Illness, and Violence

Marijuana use can trigger psychotic symptoms (from observable clinical studies of purified THC) in 40% of people with no family history of psychosis. Regular recreational marijuana users had psychotic disorders at a greater rate than any other recreational drug. More than cocaine, methamphetamine, amphetamine, LSD, PCP, or alcohol. The risk of negative mental health effects is increased about five times by regular use of high potency marijuana. A recent survey of the elements illustrating marijuana as a causal factor for psychosis was published in the journal *Addiction*.[14]

Recent science shows a clear relationship between marijuana use and violence. Violent episodes, particularly domestic violence, should be investigated to ascertain any involvement with marijuana. Marijuana use can also be a predictor of violence and thus preventing marijuana use can possibly prevent violence. A recent article in the *Journal of Addiction Research & Therapy* states:

> "According to research studies, marijuana use causes aggressive behavior, causes or exacerbates psychosis and produce paranoias. These effects have been illustrated through case studies of highly publicized incidents and heightened political profiles.
>
> Ultimately, without the use and intoxication of marijuana, the poor judgment and misperceptions displayed by these individuals would not have been present, reducing the risk for actions that result in senseless deaths.
>
> Import to these assertions, is that the current marijuana is far more potent in THC concentrations, the psychoactive component. Accordingly, and demonstrated in direct studies, more potent marijuana results in a greater risk for paranoid thinking and psychosis. In turn, paranoid behavior increases the risk for paranoid behaviors and predictably associated with aggressive and violent behaviors.
>
> Marijuana use causes violent behavior through increased aggressiveness, paranoia and personality changes (more suspicious, aggressive and anger).
>
> Recent illicit and "medical marijuana" (especially grown by care givers for medical marijuana) is of much high potency and more likely to cause violent behavior.
>
> Marijuana use and its adverse effects should be considered in cases of acts of violence as its role is properly assigned to its high association.
>
> Recognize that high potency marijuana is a predictable and preventable cause of tragic violent consequences.

Marijuana is currently a growing risk to the public in the United States. Following expanding

public opinion that marijuana provides little risk to health, state and federal legislatures have begun changing laws that will significantly increase accessibility of marijuana. Greater marijuana accessibility, resulting in more use, will lead to increased health risks in all demographic categories across the country. Violence is a well-publicized, prominent risk from the more potent, current marijuana available."[15]

A recent study showed that compared with never-users, those who use marijuana and are exposed to it effects were associated with a higher risk of subsequent violent behavior, as indicated by convictions or self-reports. This effect persisted even after the study controlled for other putative risk factors for violence. The study discovered a bi-directional relationship between marijuana use and violence. Marijuana use predicted subsequent violent behavior suggesting a possible causal effect.[16]

Marijuana Related Educational Problems in Schools

Legalization has also triggered disturbing changes in the attitudes and actions of young people. In Colorado, there is more marijuana in schools than teachers and administrators ever feared. Drug violations reported by Colorado's K-12 schools have increased 45% even as the combined number of all other violations has fallen. There has been an increase in high school drug violations of 71% since legalization and school suspensions for drugs increased 45%.[17] Marijuana is the number one substance found in suicides of young people in Colorado who are 10-19 years old. [18]

Legalization of marijuana is not a wise choice for those concerned about public health and safety and our schools.

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Disclosure

The author serves as Senior Counsel of the Cannabis Industry Victims Educating Litigators (CIVEL). CIVEL educates attorneys on how to represent the victims of the marijuana industry. Visit www.civel.org **MM**

FDA's 'Accelerated Approvals' Are Critical But Raise Thorny Issues

by Henry I. Miller, MD



The obstacles to developing and getting a new drug to market are daunting. The process can take upwards of a decade, and in 2014 was estimated on average to cost $2.55 billion. It's likely to be significantly more now.

Because those time and cost barriers can spell the difference between life and death for patients suffering from diseases without good therapeutic options, the FDA's "accelerated approval" regulatory pathway is critically important. This "quick-on, quick-off the market" mechanism for medicines to reach the marketplace can work to the advantage of drug companies and desperate patients alike.

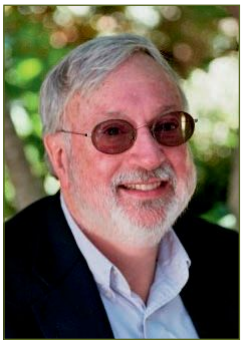
Introduced in 1992 and modified in 2012, accelerated approval allows the FDA to base approval of drugs for "serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint." In other words, marketing approval can be based on clinical trials that do not yet show an improvement of a definitive endpoint such as increased longevity, reduction in the incidence of heart attacks or healing of an infection.

A "surrogate endpoint" is a marker of some kind —a laboratory test, radiographic image, physical sign or other finding—thought to correlate with definitive clinical benefit. Examples include the lowering of blood pressure or improvement in a laboratory value such as "good" cholesterol. Similarly, an intermediate endpoint is "a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug," such as the shrinkage of a tumor.

After accelerated approval, the drug sponsor (company) must perform confirmatory trials to prove that the medicine is effective in meeting a definitive clinical endpoint, at which time the approval is converted to a standard, unconditional approval. If the studies fail to provide such confirmation, the FDA can pull the drug from the market.

The vast majority of drugs marketed after accelerated approval are found in subsequent studies to be safe and effective. And given that only medicines for serious conditions that address an unmet medical need are eligible for this pathway, accelerated approval offers significant benefits to patients by making important medicines available far earlier than would otherwise have been the case.

A journal article (G. Raghu et al. doi:10.1001/jama.2018.6129) by a large multinational team that



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reported a mid-stage (Phase 2 of the usual three) clinical trial of human pentraxin 2, a new drug for a serious lung disease called idiopathic pulmonary fibrosis (IPF), illustrates that the issues surrounding accelerated approval are not always straightforward.

IPF is marked by scarring, or fibrosis, of the lungs, the cause of which is unknown. Over time, the scarring gets worse and it becomes hard to take in deep breaths and the lungs cannot take in and transfer enough oxygen to the bloodstream.

During the past few years, the FDA has approved two other drugs on the basis of clinical data showing that they slowed the rate of deterioration of a surrogate endpoint—measurement of forced vital capacity (FVC)—the largest amount of air that a person can blow out after taking in the biggest breath possible. But neither of them convincingly enhances survival or quality of life.

The Raghu et al. clinical trial, which involved 117 patients and compared pentraxin 2 to a placebo, found that the drug was superior in two ways: the rate of deterioration in FVC was slowed, and there was a marked effect on how far a patient could walk in six minutes: the distance achieved by patients in the drug-treatment group decreased less than two feet during the 24 weeks of the study, while the distance patients in the placebo group could walk decreased an average of 104.3 feet.

The improvement over placebo of these two endpoints—FVC and the six-minute walk—for a serious disease without good therapeutic alternatives would seem to make pentraxin 2 a good candidate for accelerated approval.

Even in the absence of definitive evidence of prolonged survival, the drug could make a big difference to the retention of lung function and mobility of the roughly 100,000 Americans who suffer from IPF. So, why not grant accelerated approval for pentraxin 2 now?

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Marijuana Effect on Vascular System

The articles in the November/December edition of *Missouri Medicine* by John C. Hagan, MD (Big Tobacco, Big Opioid, Big Weed: The Successful Commercialization of Habituation & Addiction) and Elizabeth Stuyt, MD (The Problem with the Current High Potency THC Marijuana from the Perspective of an Addiction Psychiatrist) gives an excellent entry for the article by Skubramaniam and Lavie (March/April 2019) concerning the cardiovascular effect of marijuana. The medical, social, commercial, and legal issues involving cannabis are similar to the history of tobacco and alcohol that we have been dealing with for the past many years.

The adverse effects of nicotine and marijuana on the vascular system are similar and mediated largely by vascular spasm, elevated blood pressure, and endothelial damage via inflammatory and blood clotting factors. Controlled scientific clinical studies are difficult to perform on cannabinoids because of ethical reasons and most are based on observational and not experimental data. It is difficult to keep the risk of bias out of these studies.

Cardiovascular diseases progress over many years and longitudinal studies are not possible. Certainly, those patients with cardiovascular problems are most vulnerable and might be at a higher risk by augmenting the process with marijuana. It is imperative that we better understand the risks to weigh against the benefits.

A review by Riva et al. (Riva D, Ghasemiesfe M, Korenstein D, Dascino T, and Keyhani S. "Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes" Ann Intern Med 2018 Feb 6: 168(30; 187-194) did extensive observational review of the literature and found no change in metabolic factors related to vascular disease or clinical outcome in users and non-users. The results are difficult to interpret in that the variability of age, duration of use, socio-economic factors, potency of the agents, route of administration, and other uncontrolled variables verses the beneficial results will keep this discussion going for years.

Meanwhile marijuana commercialization, for both supposed medical and recreational use, continue to flourish. With controlled studies, medical use benefits will be easier to define than the recreational physiological and behavioral results. The authors are to be commended for their insightful articles on this very important medical and social problem.

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Tainted Talc and Ovarian Cancer

In the March/April 2019 issue of *Missouri Medicine*, I read with interest the article "Ovarian Cancer and 'Tainted Talc': What Treating Physicians Need to Know" by Rachel Casey, JD, and Timothy Larkin, JD. It describes the current debacle of the tort system in Missouri, specifically St. Louis, surrounding plaintiffs and their contingency fee tort lawyers seeking monetary and punitive damages for plaintiff's ovarian cancer. The premise of these plaintiffs lawsuits has been that talcum powder produced by Johnson & Johnson caused their ovarian cancer. The authors describe the recent strategy shift by plaintiff's attorneys to attempt to place the blame on potential "contaminants" in talc rather than the talc itself. This new strategy is driven by the overwhelming scientific research developing that there is no credible evidence that talc causes ovarian cancer. Therefore, talc tort lawyers need to look to alternative junk science to convince gullible jurors to accept the most tenuous putative causation and award ludicrous monetary judgements (i.e. "win the tort litigation lottery"). They found their new 'bogey man' culprit when it was purported that many years ago talc might have been contaminated with trace amounts of asbestos, a known carcinogen associated with lung cancer and mesothelioma, but never with ovarian cancer. Tort lawyers never really have to prove cause and effect,



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just invoke the evil name "asbestos" and the easily agan mislead jurors will be convinced. The specious link is based on junk science created by avaricious pseudo-scientists whose conclusions and testimony are secured for a generous expert witness fee. The proliferation of rumor on social media further aids the tort bar. A similar story is now ongoing worldwide with the vaccination debate. Seems to be working well so far!

Ovarian cancer is a difficult disease. It is tough to diagnose early as there are no good screening tests. It is often diagnosed in advanced stages where the treatment subjects patients to toxicity, miserable side effects, possible treatment failure and death. This is perfect scenario for a patient looking for someone or something to blame and the equally perfect environment for tort lawyers to flourish filing individual and class action lawsuits that often lead to huge awards.

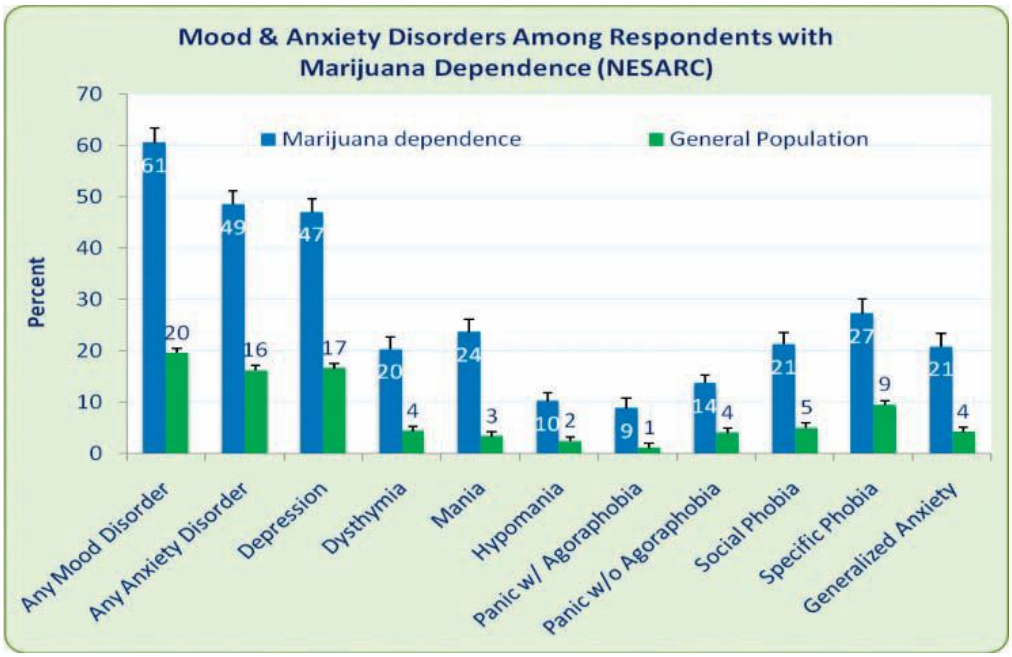
The tort system in this country has been broken for many decades. The tort bar and their political minions are too powerful. Billboards and television commercials invite anyone with an injury or illness to contact a tort lawyer for a free consultation. Million-dollar judgements are flaunted in these commercials. Helping someone who has been negligently injured can be enhanced by courts insisting on strict guidelines for valid scientific research and unbiased expert witnesses. That would make so much more sense. So, too, would be outlawing these mega-million-dollar awards that are unreasonable. These systemic abuses only keep the junk lawsuit industry in high gear. Missouri has become a magnet for lawsuits. An extraordinary number of cases are filed in St. Louis every year. Many of these lawsuits don't have anything to do with Missourians. Out-of-state attorneys come here because they find sympathetic juries more interested in redistribution of wealth than the scales of justice. Out of 13,000 plaintiffs involved in multi-party 2018 lawsuits in St. Louis, fewer than 1,000 were Missourians. Only about 240 lived in St. Louis. Venue shopping clogs Missouri's courts and cost taxpayer's money, without producing any benefit for the citizens of our state.[1] It is time for Missourians to insist that their legislators support further, much needed tort reform, especially venue shopping.

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1 Picture = 1,000 Words



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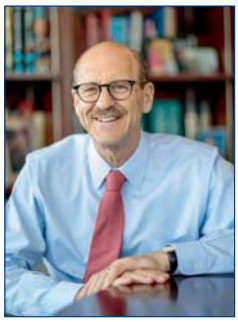
by David H. Perlmutter, MD

We at Washington University School of Medicine in St. Louis are tapping the ever-expanding capacity of our research, educational and clinical engines to improve overall health; to make innovative health care more widely available; and, essentially, to change the world for the better.

With the help of efforts well underway at the school, prospects are encouraging for early detection and prevention of Alzheimer's disease; halting debilitating and costly disorders brought on by aging; and reducing the impact of mental illness and a range of other ailments. Researchers at the university are developing and, in some cases, testing treatments aimed at advancing these critical goals.

Among major projects at the School of Medicine:

- Ongoing studies at the university's Charles F. and Joanne Knight Alzheimer's Disease Research Center to uncover just what it is that causes this destructive disease, with the aim of developing effective treatments and even preventing it from taking root.
- Cutting-edge research at the Andrew M. and Jane M. Bursky Center for Human Immunology & Immunotherapy Programs to advance the great potential of immunotherapy. While the center's main focus is cancer, scientists also are exploring how to employ the immune system to take on autoimmune and infectious diseases.
- A newly announced partnership with Centene Corp. to transform and accelerate research into treatments for Alzheimer's disease, breast cancer, diabetes and obesity. The managed-care company will fund up to $100 million over 10 years for research as part of the School of Medicine's Personalized Medicine Initiative, which aims to develop customized disease treatment and prevention. Innovations that arise from the initiative will be commercialized through the ARCH Personalized Medicine Initiative, a joint venture between the school and Centene.
- Studies at our school's Taylor Family Institute for Innovative Psychiatric Research to explore new targets for mental health therapy and to develop new drugs in an effort to help the many people for whom current therapies don't work.



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National Institutes of Health Funding

In fiscal year 2018, the School of Medicine ranked fourth nationally in funding from the National Institutes of Health (NIH) at about $449 million, up 9.5 percent in each of the last two years. With those funds, our scientists are working to reprogram human cells as potential treatments for disease. They are answering perplexing questions about antibiotic resistance and endeavoring to discover safe, new approaches to treating infection. They are delving into the role of the gut microbiome in malnutrition, finding the underlying causes of preterm birth, and working to develop next-level imaging systems. The work that goes on here is fascinating and inspiring on a daily basis.

Part of the funding for our research also comes from almost $300 million provided by the School of Medicine. That funding is channeled from the school's revenue, which in fiscal year 2018 was about $2.6 billion. The largest stream — $1.27 billion — came from the school's growing clinical practice, Washington University Physicians. Our longtime relationship with our teaching hospitals also continues to bolster the school. About 1,500 faculty physicians represent more than 76 specialties and subspecialties at Barnes-Jewish Hospital and St. Louis Children's Hospital. Both hospitals are nationally recognized, world-class teaching hospitals with a wide network of in- and outpatient health-care services.

As part of the school's commitment to research, we are planning to build a state-of-the-art neuroscience research center on the east end of the Medical Campus. The center, expected to be the biggest such center in the nation, will serve

as a highly collaborative venue, bringing together multiple disciplines under one roof. It is expected to open by the end of 2022.



Washington University School of Medicine Campus - Credit Bob Srenco

Scholarships for Medical Students

We recently announced that the School of Medicine is expanding scholarship funding with a pledge of $100 million over the next decade toward scholarships for medical students, as well as efforts to enhance medical education. This will allow as many as half of our future medical students to attend tuition-free; many others will receive partial tuition support. The scholarship program will begin this fall with the incoming class. A committee will decide, based on financial need and merit, who will receive scholarships and whether they will be full or partial.

We hope that the scholarships will attract students from more diverse ethnic and socioeconomic backgrounds and allow them to begin their medical careers with no or substantially reduced debt. In the very sound words of Eva Aagaard, MD, our senior associate dean for education and the Carol B. and Jerome T. Loeb Professor of Medical Education: "Ultimately, the scholarships will help us build a class that reflects our school's values and allows us to educate the very best future physicians so that they will go on to have an indelible impact on health and society." An important component of this investment is our desire to train medical students to become multifaceted academic physicians so that they are among the leaders shaping medicine and medical education's future.

In conjunction with the scholarship program, our school is working to enhance and modernize the medical education program under the guidance of Aagaard. The new Gateway Curriculum will provide training and support to faculty in how to best teach medical students and trainees. The curriculum will give students more integrated clinical, basic and social studies content and experiences. It will emphasize addressing the social and economic factors that influence individual health.

To advance the ongoing training of our academic physicians, the school also has created the Academy of Educators. Its goal is to foster a culture of educational excellence and an institutionally valued community of leaders in health-science education. Mary Klingensmith, MD, the Mary Culver Distinguished Professor and vice chair for education in the Department of Surgery, is the academy's inaugural director.

The School of Medicine named several other new leaders in 2018, including Sherree Wilson, PhD, to the newly created post of associate vice chancellor and associate dean for diversity, equity and inclusion. Among her goals is to bring talented people from diverse backgrounds into the school community. Her work will expand on the Faculty Diversity Scholars Program started in 2007. To date, that program has funded 33 scholars, of whom 23 currently are on faculty. Among other recently announced changes in leadership, Richard J. Cote, MD, was named the new head of the Department of Pathology and Immunology; Gregory J. Zipfel, MD, will become the new head of the Department of Neurosurgery on July 1; and Michael Avidan, MBBCh (MD equivalent), will take over as head of the Department of Anesthesiology, also on July 1.

As the School of Medicine looks to the future, our goals include transforming health care through research that advances personalized medicine and addresses aging. We will lead in education by reducing student debt, by modernizing our curriculum and by imagining new ways to add much-needed diversity to the field of medicine. As to patient care, our school's community isn't afraid to shake things up to find and deliver new, innovative approaches to treatment that are timely, cost-effective and responsive to the St. Louis region and beyond. **MM**



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Essentials of Hyperbaric Oxygen Therapy: 2019 Review

by John P. Kirby, MD, Jason Snyder, MD, Douglas J.E. Schuerer, MD, John S. Peters & Grant V. Bochicchio, MD

Washington University in St. Louis
School of Medicine

Proper appreciation of what HBO_2 can do and has been rigorously shown to be able to do can guide clinicians to make better choices in the use and referral of patients for HBO_2 across 14 approved indications.

Hyperbaric oxygen therapy (HBO_2) continues to be an opportunity for clinicians to better manage a variety of clinical problems. This thematic issue of *Missouri Medicine* covers the major indicated uses of HBO_2 and its rationale so that clinicians can make better informed choices.

From its beginnings in combating poorly understood pathophysiologies in divers and construction workers under increased pressure environments to its more contemporary applications in wound healing and critical illnesses, hyperbaric oxygen now complements many therapies for better patient outcomes.

We herein give an overview of HBO_2, its emergent uses, common elective uses, presentations of decompression sickness that could present to a general practitioner and also how HBO_2 complements coordinated management of difficult wounds such as Diabetic Foot Ulcers with other modalities like negative pressure wound therapy (NPWT).

This issue of *Missouri Medicine* is meant to familiarize more clinicians about hyperbaric oxygen so that practices can improve.

Here are some basics about HBO_2 and then we will look at HBO_2 emergencies and then several elective uses of HBO_2.



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Clinical hyperbaric oxygen treatment is defined as placing a patient's entire body in an increased pressure environment and having that patient inspire 100% oxygen for a specific diagnosis and for a defined period of time and treatments.[1] The usual minimum acceptable pressure for clinical treatment is 1.4 atmospheres absolute or 1.4 ATA.[2] Atmospheres absolute is a scale that incorporates the total pressure being exerted upon the body regardless of where the body is, i.e. at sea-level or in a pressure chamber.[3] 1.4 ATA can be simplified to be thought of as 1.4 times the usual, environmental pressure any patient's physiology is feeling at idealized sea-level.

HBO_2 treatments are typically delivered in hyperbaric chambers that can be a single patient at one time (i.e. monoplaced Figure 1) or a room sized accommodating multiple patients at the same pressure (i.e. multi-place chambers Figure 2) With improvements in material sciences chambers have gone from mostly metal enclosed multi-place chambers to clear acrylic monoplace chambers. Monoplace chambers are lighter, smaller, easier to install and less expensive to retrofit into existing medical spaces. Additionally, clinicians should appreciate there are key differences in referring patients to HBO_2 centers that are multiplace vs those that are monoplace.

Multiplace chambers are engineered rooms that are filled with compressed air and the patients receive their therapeutic 100% oxygen by donning hoods or masks. Multiplace chambers can have a caregiver in the chamber with the patients and patients can receive hands on care during their treatment sequences. Patients may sit in chairs or lay on gurneys to receive their treatments as a group going down to a defined depth and treatment time common to them all. Monoplace chambers are usually clear acrylic tubes filled with oxygen that an individual patient lies in semi-recumbent or beach chair position and typically watches TV through the clear walls of the chamber. They are typically lighter and less expensive to retro-fit into



Figure 1: Monoplaced Chamber



Figure 2: Multiplaced Chamber

existing spaces than multiplace chambers. The entire interior of a monoplace chamber can typically be filled with 100% oxygen and patients only don a mask or hood to breathe regular air to reset their seizure thresholds or other oxygen toxicities. Monoplace chambers can now allow on-going treatments, including IV fluids or IV medications or physiologic monitoring, as they have specially engineered past through ports for tubing and wires, but typically no one else is in the chamber with the patient. Treatment times and sequences may be individualized.

Typical elective HBO_2 treatments are approximately 90 minutes and run between 2 and 3 ATA depending upon the therapeutic effects desired. Urgent and emergent treatments or other specialty applications may run longer and at greater pressures (often referred to as going deeper due to HBO_2's historical origins in diving). Typical elective treatments are administered Monday through Friday during regular clinic business hours that can vary from center to center. Nationally, for many reasons, only a small proportion of centers can offer treatments for critically ill patients or emergent indications at all hours of the day or night throughout any given week, weekend or holiday. There remains a national shortage of HBO_2 centers with this 24 x 7 capacity to treat sick patients urgently and emergently. Emergent and elective indications for HBO_2 will be covered in separate articles. In either elective or urgent circumstances, a clinician treating a patient with a HBO_2 indication in Table 1[4] should work with their available HBO_2 centers for an evaluation. Table 1 is taken from the UHMS indications list located on their website.[5] Indications for HBO_2 may be a chronic condition and the addition of adjunctive HBO_2 may be completely elective such as those with chronic refractory osteomyelitis. An organized list of the possible indications, by their urgency and pathophysiology and common contraindications for HBO_2 are in Table 1.[5] Clinicians should incorporate the needs of the patients being considered for HBO_2 as well as the capabilities of each hyperbaric facility.

It should be noted that other uses of oxygen from supplemental inhalation or regionally or topically are not meant to be variations in HBO_2 treatments. HBO_2 has specific billing codes and they are not to be generalized to cover other forms of the use of oxygen. Even some whole-body chambers for oxygen delivery, if collapsible and meant for emergency use or transport, may not be intended for routine on-going clinic HBO_2 therapy such that some payer sources may require treatments to be offered only in rigid chambers. Additionally, some states and some regions of the country have different guidelines

Table 1. Commonly Accepted Indications for Hyperbaric Oxygen Treatments

- Air or Gas Arterial or Venous Embolii
- Severe or Symptomatic Carbon Monoxide Poisoning
- Clostridial Myositis and Myonecrosis (Gas Gangrene)
- Selected Crush Injuries, Compartment Syndromes, and other Acute Traumatic Ischemias
- Decompression Sickness
- Selected Arterial Insufficiencies, including Central Retinal Artery Occlusion and the Enhancement of Healing in Selected Problem Wounds
- Severe otherwise Untreatable Anemias
- Certain Intracranial Abscesses
- Selected Progressive Refractory Necrotizing Soft Tissue Infections
- Chronic Refractory Osteomyelitis
- Delayed Radiation-Induced Injury with Bony or Soft Tissue Necrosis
- Compromised Skin Grafts and Tissue Flaps
- Acute Thermal Burn Injuries
- Idiopathic Sudden Sensorineural Hearing Loss

or standards of practice that must be adhered to for HBO_2 treatments to be offered or receive re-imbursement. This review is meant to familiarize clinicians with a broad overview of the basics for HBO_2 and not as rationales for covered treatments. Clinicians are directed to the NCD guidelines[6] for covered conditions that are able to be treated with HBO_2 in Missouri and should be working closely with their local practice compliance mechanisms for good documentation for HBO_2 practices.

At room temperature and pressure near sea-level the air that we breathe is only about 20% oxygen and near 80% nitrogen with other gases simplified to be trace amounts. This means the usual range for a PaO_2 (partial pressure of oxygen in an arterial blood gas) is 75 – 100 mm Hg. [7] If we supplement the fraction of inspired oxygen with either a nasal cannula or a face mask, PaO_2 materially increases well over 100 and can be measured in tissues with $PcTO_2$ (percutaneous transcutaneous partial pressure of oxygen).[8, 9] However, HBO_2 uses not only a high fractional level of inspired oxygen (100%), but also changes the pressure effects that govern how oxygen is both carried by hemoglobin and dissolved into the liquid phases of both blood and body fluids. At ordinary, atmospheric pressures the amount of oxygen (or other gases) that is dissolved into the plasma phase of blood is miniscule. The oxygen content of blood is commonly defined as (Hemoglobin concentration x 1.36 x SaO_2) + (0.0031 x PaO_2).[9] The corrective coefficient, 0.0031, to minimize the quantity of oxygen dissolved in blood goes away as pressure around the body increases and a significant and bio-available amount of oxygen is dissolved into the liquid phases of blood and body fluids. Appreciating that at therapeutic pressures the oxygen that is dissolved into body tissues and fluids is responsible for some of HBO_2 indications allows practitioners to better understand the basic science foundations for them.[10, 11, 12,13] For example, although the retina ordinarily is supported by its own nutrient central artery, HBO_2 offers the only viable treatment to date to help mitigate retinal ischemia. This is because of the central retinal artery flow is compromised or occluded, as HBO_2 is the only available means to get oxygen to retinal tissues through locally dissolved oxygen.[14, 15] It is also the means by which some patients with severe anemia and no capacity to receive hemoglobin transfusions can be improved.[16] It is also the means by which sudden sensorineural hearing loss, responds to HBO_2 treatment with other body fluids carrying nutrient oxygen to otherwise ischemic neural tissues.[17, 18, 19] The effects of HBO_2 go well beyond just driving more oxygen to be delivered into the tissues. The next most obvious effect to take into account is how our bodies react to being at pressure as well. Even simple face immersion in water can reproduce the "diving reflex," let alone when multiple components of the nervous and vascular systems detect a body is at a higher pressure. These include peripheral vasoconstriction, slowed heart rates and at times other rhythm changes, shunting of blood toward the central circulation, and release of stored RBCs in the spleen.[20, 21] Overall there is a shift in body tissue third space free water content back into the intravascular compartment that is then cleared by the kidneys, such that most patients often need to urinate after their HBO_2 treatment. Well-designed HBO_2 centers have their own dedicated bathrooms to accommodate this common need as patient come out of the chamber. Additionally, this shift from extravascular tissue third space to intravascular circulating volume exerts a cardiac load on the heart which needs to pump that increased mass of volume until cleared by the kidneys and this may unmask a congestive heart failure picture in at risk patients. Therefore, referred patient's histories of compromised cardiac output may need further work up, prior to HBO_2, with echocardiography to see that their cardiac function, often using the ejection fraction as a common surrogate, is sufficient for the HBO_2 treatment load.

One of the most important contra-indications to HBO_2 is also related to direct pressure effects on the

patient's body: undrained pneumothoraxes, bullae or blebs. Any contained, enclosed air space anywhere, but particularly in the chest will collapse when subjected to pressure and then re-expand when the pressure is let up. This can convert simple a pneumothorax to a tension pneumothorax. Most HBO_2 centers require a recent chest radiograph to rule out any pneumothorax. If a patient has bullous disease or blebs or other at-risk conditions like emphysema or COPD, then they should be screened with first a CXR and then with further imaging such as CT scanning to better quantify and manage the severity of their disease.

Referring clinicians should also appreciate that during a HBO_2 treatment typically a patient's blood sugar is lowered. This lower blood sugar is also synergistic to lower an individual's seizure threshold while breathing oxygen at pressure. Interrupting the continuous exposure to oxygen for 5-10 minutes at regular intervals will reset their likelihood of a seizure without having to take them out of their pressurized environment. Multi-place chamber patients reset with air breaks by removing their oxygen treatment hoods or masks. All HBO_2 programs should screen for seizure risks, especially in a diabetic patient and those on anti-seizure medications.

To properly screen and manage patients at risk as well as to properly recommend and apply HBO_2 where indicated, several training paradigms exist for clinicians to use HBO_2 well. Current training pathways might begin with immersion CME mini-courses. At a minimum, clinicians should have the beginning baseline standard of a 40-hour accredited training course to supervise straight forward uses of HBO_2. Those interested in a broader range of HBO_2 applications complete a dedicated one-year fellowship in HBO_2 and Undersea Medicine and with a written board certification. Even shy of full board certification there are now several on-line programs, (i.e. the UHMS PATH program) that have high quality CME for physicians to more properly incorporate HBO_2 into their practices.

In conclusion, HBO_2 offers many opportunities to improve specific patient problems across a spectrum of fascinating basic science and clinical evidence. Clinicians should be aware of these included HBO_2's indications as a starting point for how to best incorporate HBO_2 into their practices; and what might be available for patients in sometimes very difficult clinical circumstances. Oxygen, when viewed as a drug, is similar to many drugs that have varied indications with varying levels of evidence for its use. HBO_2 treatments, like all medical treatments, are an added expense and although can be offered in a safe environment still have side effects and potential risks. Individual clinicians and patients are encouraged to look at HBO_2 like other clinical recommendations with a risk-benefit analysis grounded in the best available evidence to choose the best available treatment options to optimize clinical outcomes across the spectrum of indications in Table 1.

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Disclosure

None reported. **MM**

Hyperbaric Oxygen Therapy Emergencies

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Each individual patient must be weighed to see that the additional value of HBO_2 is a good match to improve that patient's long-term outcome.



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Abstract

Emergent indications for HBO_2 are not only for some of the most serious conditions, but also may be the only modality to directly target the patient's pathophysiology. They are to begin emergently or urgently, but may be limited by either the instability of the patient's condition or transfer logistics. Often these emergent treatments involve several treatments in the first 24 hours for best outcomes. If one considers the effects of HBO_2 upon the body while breathing 100% oxygen at pressure many benefits become evident. This article will concisely review hyperbaric oxygen's emergent indications.

Introduction: DCS and AGE

Decompression Sickness (DCS) in Table 1 is one of the most historically well studied indications for HBO_2. We would no longer be ethically able to run a research study on the benefits of HBO_2 with a control arm that didn't have some recompression as it is memorialized as a standard of care for severe DCS.[1, 2, 3, 4] Should a patient have a history of being subjected to being at increased pressure and come out of that pressurized environment with complaints, then DCS should be in the patient's differential diagnosis and HBO_2 offered. The Diver's Alert Network maintain a 24-hour call center should such a DCS event occur: 1-919-684-9111[5]. When identified, oxygen and supportive care should begin and as soon as possible HBO_2 at an appropriate recompression pressure and therapy duration sequence that can be worked out with both local EMS and diving medicine consultations. Treatment can begin with the "4 R's" (Recognize symptoms, Respond with Oxygen, Relay with EMS/DAN, Recompress early).[6] Although major decompression sickness events are easier to identify with antecedent diving as well as classic signs of DCS of joint pain and frank neurological impairment, occasionally sport and amateur divers can have variants that get missed. DCS can occur even with shallow depths of 20 feet and even in certain circumstances in less than 1 meter of water.[7, 8] Treating for decompression sickness can involve longer treatment sequences at higher pressures and therefore deserves coordination with organizations like DAN or with physicians with training in diving medicine.

The most severe examples of DCS are actually where bubbles form in the tissues and vasculature—essentially becoming arterial or venous gas emboli. Although this is very unusual outside of extreme pressure events like submariners escaping from a sinking submarine, in the modern era it happens with medical instrumentations as air gas embolii. Counterintuitively, bubbles forming in tubes meant to have liquid flow through them do not just float along, but obstruct that flow of liquid. In

the body, traumatically rub up against the endothelium causing inflammatory cascade activation.[9,10] A wide variety of exposures can result in arterial or venous gas embolii from head up surgical procedures, exposures of vessels or the lung, cannulations during cardiopulmonary bypass or extracorporeal oxygenation or even during hemodialysis or central line manipulations, endoscopy insufflations — all can inadvertently introduce air into the circulatory system.[11] On top of that, there are patients who have an occult communication between the right and left heart or the arterial and venous systems, and these patients are even more susceptible to arterial or gas emboli causing stroke-like presentations. Patients who may have an occult but still potential mechanism to introduce gas into their vascular system who have stroke like changes in mental status, focal neurological deficits, cardiac arrhythmias than can progress to arrest, tachypnea, hypotension, hypocapnia or pulmonary edema should have a presumptive diagnosis of an air gas embolism entertained[12] Demonstrating the actual gas emboli by imaging even in the face of severe neurological symptoms is not recommended as time consuming and can be falsely negative[13,14] and the diagnosis should be suspected with both the mechanism and exam findings. These patients can have waxing and waning symptoms that can lead clinicians astray.[15] Emergent hyperbaric treatment can be difficult as the patients may have instabilities that preclude any safe transfer and also the numbers of centers that can offer critically ill, intubated patients are themselves limited in the US. Depending upon the nature of the DCS or gas embolism, patients may need to be screened later for other problems like endocardial cushion defects or patent intra-cardiac shunts with an echocardiogram. But like DCS, gas embolism when it occurs should be considered for emergent HBO_2 to achieve the best outcomes.

Emergent Uses from Appreciating Distal Flow and Ischemia Problems

The paradigm of obstructed flow and ischemia to distal tissue beds also explains several other emergent and urgent HBO_2 treatment indications. Acute arterial insufficiencies, traumatic ischemic injuries, and crushes, compartment syndromes all interrupt the usual nutrient, perfusing and oxygenating flow to distal tissue beds. Here is where HBO_2 might have a very important adjunctive effect upon tissues ability to survive and heal. This can be visualized also where a central zone of a thermal burn might be unrecoverable but the surrounding tissue zones with partial injuries are struggling with poor flow, edema, poor oxygenation and excessive inflammatory responses. For this group of emergent indications HBO_2 supports the distal tissues with some level of oxygenation support and also improves collateral flow through effects like edema control and overly harmful inflammatory effects.[16, 17] However, HBO_2 should be coordinated with overall resuscitation and critical care goals, formal vascular restoration of flow where indicated, compartment releases and debridement that make delivery and any subsequent analysis of HBO_2 difficult to do well.

HBO_2 effects also are dependent upon the tissue beds being injured, too. It may be that the difficulties in really proving the value of HBO_2 lies in that some tissue beds are more resilient oxygenating flow problems. As opposed to larger tissue beds it HBO_2 may be effective in smaller, focal applications. For example, central retinal artery occlusion (CRAO) is fortunately not very common, but is very illustrative of some of the best effects of emergent HBO_2 as really the only way to directly supply nutrient oxygen to tissues.[18, 19] The retinal tissues are highly sensitive and need adequate oxygen to maintain their functionality. HBO_2 allows some direct diffusion of oxygen to those otherwise ischemic retinal tissues and buys time for the central retinal artery to recanalize.[20, 21] Furthermore CRAO is a model to consider that HBO_2 may also have its maximal benefit where it impacts upon a relatively small tissue bed, but one where every margin amount of tissue lost has major functional effects upon the visual acuity long term. Like DCS and AGE, these emergent indications need multiple treatments in the first 24 hours and then these treatments can be more spaced out over the subsequent days for full effect. Should a patient present with sudden changes of vision they should undergo a neurological evaluation as well as considering the possibility of CRAO and HBO_2 be offered in coordination in concert with ophthalmology for proper patient selection and on-going therapies such as beginning ambient pressure oxygenation, looking at other contravening factors such as intra-ocular pressures, other pro-occlusion inflammatory conditions like arteritis, capturing the degrees of vision loss and instituting HBO_2 emergently and within 24 hours of symptoms.[22] However, unlike other classes of potential HBO_2 emergent patients, patients with CRAO may be hemodynamically stable and even meet the capabilities of HBO_2 centers that otherwise do not treat critically ill or unstable patients.

The emergent applications of HBO_2 share other common paradigm themes. First it may partly explain the value of HBO_2 in other applications where preservation and healing of small tissue beds may make a big functional outcome difference for patients, such as for CRAO. This may partly explain its value in well selected DM foot

Table 1. HBO_2 Emergent and Urgent Indications[5]
Note some of these extend across a spectrum from emergent to urgent to more elective application.

- Arterial or venous gas emboli
- Decompression illness
- Acute Arterial Insufficiencies such as Central Retinal Arterial Occlusion
- Gas gangrene, clostridial soft tissue infections, other myonecroses and necrotizing skin and soft tissue infections
- Crush injuries, compartment syndromes and other acute traumatic ischemias
- Intracranial abscesses
- Severe anemias
- Flaps and grafts that are failing
- Thermal burns
- Idiopathic sudden sensorineural hearing losses HBO_2 most effective if offered early
- CO and CN poisoning

ulceration patients and in those with intracranial abscesses or even for tissue flaps or localized tissue injury beds. Second, emergent HBO_2 can now be appreciated in how it might salvage that distal tissue bed struggling to remain viable.[23, 24, 25] It will deliver nutrient oxygen where perfusing flow might be less than normal in traumatic ischemias and compartment syndromes[26] and even in thermal burns.[27] This is also the mechanism of action for grafts and flaps where transplanted tissues may be struggling to re-grow their vascular based foundations to survive. As in the other indications, patients with grafts and flaps that are becoming compromised still need to be assessed for other causative factors, but HBO_2 may be an additional tool to help salvage tissue.[28] Finally, CRAO where oxygen is diffused through non-blood flow media like intra-ocular choroidal fluid illustrates how non hemoglobin tissue fluids begin to carry nutrient oxygen at pressure, which is also the mechanism for HBO_2 newest approved indication: Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL). Here oxygen is dissolved into the lymphatics to support the neural functioning of the inner ear in ISSNHL[29] Like CRAO, ISSNHL has few other clinical options and highlights HBO_2 as really the only way to support the nerve tissues of the inner ear in a way that has improved outcomes.[30]

Emergent Indications that Further Capitalize Upon Dissolved Oxygen

Diffusing nutrient oxygen through various fluids explains not only the emergent beneficial effects for CRAO and for SSNHL, but also highlights the effects of HBO_2 for carbon monoxide poisoning and in severe anemias. In both of these indications it is the dissolution of oxygen at pressure that becomes beneficial. HBO_2 also more effectively displaces CO and CN molecules from occupying hemoglobin sites in a shorter time frame. Data continues to accumulate that in certain circumstances, myocardial ischemia or in pregnancy hyperbaric oxygen may have advantages over simple supplemental oxygen for better longer-term outcomes.[31,32]

High Oxygen Tensions May Also Assist in Bacterial Clearances

The last emergent effect grouping emergent indications for HBO_2 highlights another mechanism of action of high-tension oxygen: that it can be directly toxic to certain microorgansims. Gas Gangrene, Clostridial soft tissue infections or other necrotizing skin and soft tissue infections and even some intracranial abscesses are also emergent or urgent indications with a time dependent component if HBO_2 is have its fullest impact.[33] HBO_2 is directly toxic to many of the causative organisms.[34] High tension oxygen environments are often directly toxic to these organisms, inhibit their growth or cause them to down shift into more latent forms and decrease some of their most clinically harmful toxin elaboration. If available, HBO_2 should be considered along with the clinical priorities of earlier diagnoses, immediate aggressive surgical debridement and IV antibiotics along with critical care resuscitation goal directed therapy. The pathophysiologies are often dependent upon the actual organisms causing the necrosis—but share common features of worsening local tissue loss and systemic toxicities that need critical care resuscitation, surgery and antibiotics as first line therapies. Early incorporation of HBO_2 with several treatments in the first 24 hours are recommended to get hyperbaric's full effects. Intracranial abscesses can also be a subset of necrotizing infections, albeit often out of sight in the brain and its closely associated soft tissues, and often with organisms, including fungal pathogens, that feel the effects of higher oxygen concentrations directly.[35] Unlike many soft tissue infections, surgical extirpation of the source abscess may be technically very difficult or morbid. Combining surgery or other drainage maneuvers, antibiotics, neurological and overall critical care support with timely HBO_2 can offer the patient the best possible outcome for infections that may otherwise be resistant to eradication.[36]

All of these emergent or urgent indications are time dependent if they are to be maximally beneficial. HBO_2

should be immediately instituted as soon as feasible for any severe decompressions sickness or gas emboli based upon the patient's history and physical exam. Once distal ischemia of either soft tissues or neuronal tissue reach necrosis this cannot be reversed. Each of these emergent diagnoses need to be suspected based upon the patient's presenting history and physical, some have criteria that need to be established often in concert with other specialties—but all share the common theme of early, emergent if not urgent institution of HBO_2 if it to be maximally beneficial. Often these indications need quick cyclining of HBO_2 with two to three treatments to be given in the first 24 hours of appreciating the HBO_2 indication diagnosis and screening for safety and appropriateness. Hyperbaric oxygen can also be used in infectious emergencies: skin and soft tissue infections, clostridial myonecrosis, and brain abscesses. Often physicians are seeking to decrease mortalities, but it may be more beneficial to consider that hyperbaric's use limits tissue losses for better outcomes. Emergent or urgent HBO_2 remains a challenge for all in terms of picking out appropriate patients, logistically arranging their care for early and repeated HBO_2 sequences as well as simultaneously meeting all the other care needs of the critically ill. Each individual patient must be weighed to see that the additional value of HBO_2 is a good match to improve that patient's long-term outcome.

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Disclosure

None reported.

MM

Hyperbaric Oxygen Therapy as an Elective Treatment

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HBO_2 can be used electively to transition patients from more acute problems to more elective ones.



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Abstract

Hyperbaric oxygen therapies may have grown out of emergencies such as those for Decompression Sickness (DCS), but more commonly in the U.S., hyperbaric oxygen is used for much more elective problems. Wound healing applications lead this trend. Nationally many more hyperbaric centers exist to treat elective problems adjunctively, and this is a concise review of these indications as well as pointing out where even elective centers might be able to broaden their practices.

Introduction

Table 1 lists the HBO_2 indications for elective problems. As opposed to many of the emergent indications where HBO_2 is often a primary therapy and are highly time dependent in terms of getting HBO_2 underway and repeated; many of these elective indications reflect where HBO_2 is an adjunct to other therapies. Elective uses of HBO_2 can be a way to improve the outcomes of patients who otherwise are not responding to initial therapies. Additionally, some of these elective indications still derive some of their applications from emergent indications and are covered here so that clinicians do not miss these as opportunities for better care.

For example, both CO and CN poisonings will be offset and more quickly eliminated by HBO_2 if offered as opposed to allowing either or both of these to be off loaded at regular pressures. CO poisoning may present relatively obviously as an emergency as after closed space fire and loss of consciousness or other severe neurological sequelae or with ongoing fetal or cardiac ischemia necessitating HBO_2. But CO poisoning can also be repetitive and low level with harder to define symptoms. A loading dock worker exposed to the exhaust of lifter-loading vehicle with headaches and fatigue may be suffering from CO poisoning and will get missed. HBO_2 may offer better longer term neurologic outcomes than simple 100% oxygen therapy.[1]

Clearly delineated classes for emergent HBO_2 include those that offset the effects of poor oxygenating arterial flow perfusing tissue beds, such as in a compromised flap. Many elective indications for of HBO_2 extend these effects to small vessel perfusion defects. For example, medical radiation needed to improve cure rates for cancers, often results in progressive fibrosis and resultant non-healing of those previously irradiated tissues. In fact multimodality cancer care has

Table 1. Elective Indictions for HBO_2

- CO and CN Poisonings - while it is assumed that earlier treatments will be better for any patient, there are patients that present in a delayed fashion and may be treated in a time delayed, hence elective fashion for lingering complaints after a CO or CN exposure.
- Decompression Sickness - preferred to be treated as early as possible, like CO/CN poisoning, but often improves even in more elective presentations within the week after the diving incident.
- Chronic Refractory Osteomyelitis
- Radiation Injuries of soft and bony tissue
- Enhanced healing in selected problematic wounds

improved outcomes such that most cancers have better longer term outcomes for more patients than patients needing amputations for diabetic foot ulcerations (DFUs);[2] however patients are surviving to have other sequelae. Patients who often have had a complete cure of their head and neck tumors from a combination of surgery and radiation can have progressive fibrosis of their soft tissues and gums with loss of teeth, exposure of their jaw and even pathological fracture of their mandible—all of which will have better outcomes when HBO_2 is added to their regimens.[3] Patients with on going radiation effects after treatment for head and neck cancers should be referred for HBO_2[4] and this should be coordinated with any planned further operation so that HBO_2 supports optimal tissue healing before and after any procedures.

Therapeutic irradiation is also commonly used in other areas of the body and for other cancers like breast cancer and other soft tissue tumors and for neurologic, gynecologic, colorectal, urologic, and soft tissue cancers. These patients may also have later sequelae from delayed radiation effects such as enteritis, cystitis, bleeding and tissue fibrosis needing surgical resection or revision. All of these have been found to be responsive to HBO_2.[5, 6] Elective hyperbaric when coordinated with other therapies may allow surgical reconstruction of these tissue feasible and protect both the patient and the surgeons from non-healing or other sub-optimal outcomes.

From Radiation Injury to Other More Common Wound Healing Classes

In the U.S., the most common indication to offer elective HBO_2 is now to augment wound healing problems in certain settings. These elective wound healing indications in addition to radiation effects include necrotizing skin and soft tissue infections and their difficulties in healing, failing grafts or flaps, and thermal burns, but also ulcerations from complications from neuropathy and diabetes. Although varying levels of evidence exist across the broad category of enhancing healing in selected problematic wounds,[7] this category shares a common theme that the wound and periwound is locally hypoxic as one of the primary reasons for it not to be healing, but response to supplemental oxygen indicating that it is not a large vessel (i.e. vascular) flow problem and not due to poor central cardiopulmonary mechanics either. Hyperbaric centers commonly employ measuring tissue concentration of oxygen to demonstrate this in the wounds or ulcers that are not healing by placing leads on the skin that measure oxygen partial pressure in the tissues of the wound. Tissue concentration of oxygen measurement is painless as the lead stick on, but does take some time, about an hour and sometimes longer if the patient is to be repositioned, to allow for the patient's tissues to react. Should the patient have low oxygen levels that then improve when given supplemental oxygen is given at room pressures, then HBO_2 could be beneficial. This process can also be repeated in the actual HBO_2 chamber as well to document an adequate response at pressure. Each of the specific kind of wounds have varying levels of evidence and various requirements before HBO_2 can be properly used. One of these is the use of HBO_2 in the management of DFUs. As in radiation changes, diabetes mellitus (DM) over time narrows the small and microscopic vessels such that patient's feet become neuropathic, develop characteristic deficiencies in blood flow and bony stability and develop ulcerations that threaten them with higher amputations and mortality.[8] However, the key to be able to augment a DM patient's healing with HBO_2 is to properly take care of the basics first. Patients should be assisted in giving up smoking, losing weight and having a healthy lifestyle of diet and activity so that their DM is well controlled with an individually acceptable HA1C[9] and frequent accuchecks. The patient's ulceration should be cleaned and debrided and screened for surgically correctable bony arthropathy and arterial inflow augmentation. Any infection either from local necrotic debris or underlying osteomyelitis should



Figure 1. Combined crush injury with chronic refractory osteomyelitis with non-union threatening amputation before hyperbaric. This patient had already failed initial surgical debridements, antibiotics, and stabilization, and had weeping non-healing ulcerations, and non-union of her bone over her internal fixator.



Figure 2. Same patient after combined surgery, antibiotics, and HBO_2.

be sought or removed. The patient's ulceration should be having regular local wound care with a moist supportive dressing for healing. The patient should be off loaded with a good even custom shoe or total contact casting. Should all this be done and the ulceration be essentially middle grade, not to minor nor not so severe so as to be non-recoverable (Wagner Grade 3)[10] and not be healing at 30 days then HBO_2 can be added based upon the patient's safety profile.[11] Much of the data based recommendations both for and against adding HBO_2 have challenges based upon the rigorousness of patients being screened and treated before adding HBO_2 so that only appropriate patients are being included.

Chronic Refractory Osteomyelitis

Similarly, osteomyelitis may also respond very favorably to HBO_2. Recall that some of the most compelling data for osteoradionecrosis began as if high tension oxygen would synergistically attack infection in the bone, but ultimately was found to generate neo-angiogenesis to allow the bone to heal. Although the mainstays for osteomyelitis remain surgical debridement of non-viable or infected bone and any sequestrum, culture driven antibiotics and protective coverage, osteomyelitis responds to HBO_2 both acutely and electively. In the elective setting, HBO_2 has requirements akin to DFUs such that the grossly infected bone needs to be surgically debrided first and that the patient should have failed their first round antibiotics before HBO_2 is offered. Essentially the best data for elective use of HBO_2 is for chronic, refractory osteomyelitis where fundamental care for the osteomyelitis isn't working well. At that point the patient can be re-assessed and HBO_2 added in a coordinated approach

with further bone and soft tissue debridement, re-culturing, off-loading, dressings, nutritional optimization, screening for contractures and control of spasms, and a closure plan for the usually exposed bone.[12]

Severe Anemias not Transfusable

Severe anemia also remains an underutilized opportunity for hyperbaric oxygen to make more of an impact both in acute, if not emergent applications, as well as in subacute or more elective applications. The data behind its rationale is very straightforward and compelling at the basic science level where oxygen delivery goes from being dependent upon hemoglobin concentrations at sea level to near complete replacement of hemoglobin based oxygen delivery mechanisms with HBO_2.[13] Currently the mainstay of patients with conditions of oxygen debts is blood transfusion, both acutely and sub acutely. However, there are occasions where due to a patient's beliefs, such as observant Jehovah's Witnesses, where a patient may not accept blood transfusions or due to factors inherent in the patient's blood where they cannot be safely transfused. There are also times where logistically blood may not be available for transfusion. In these cases, it can be overlooked that HBO_2 has been shown to support the anemic patient[14] as well as build up hemoglobin in concert with other hematinics.[15] Pulsed HBO_2 in concert with nutritional support and other hematinics will increase the circulating hemoglobin.[16]

In conclusion, HBO_2 can be used electively as well as to transition patients from more acute problems—such as when it is added to limit tissue losses and improve resuscitation responses in necrotizing infections or crush injuries—to more elective ones. Often inpatient facilities transition patients from acute indications where patients are given HBO_2 multiple times per day to a tail of treatments where the patient is being transitioned to an outpatient setting and now only needs once a day treatment Monday through Friday to allow better complete healing. Each individual center works with the treating clinicians to work out elective plans to support optimal healing. In this way HBO_2 can improve healing and recovery for a variety of elective problems from radiation injury to the ravages of diabetes to even chronic presentations of some emergencies such as CO poisoning.

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Disclosure

None reported. **MM**

Hyperbaric Oxygen Indications: Diabetic Foot Ulcers and Intractable Management

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Patients who have lower extremity ulcerations, particularly diabetic foot ulcers deserve ongoing efforts to organize care approaches and adjunctive modalities, such as HBO_2, to give them the best functional and durable outcome.



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Abstract

Wound care remains an interdisciplinary specialty that can confront primary care physicians, emergency medicine physicians, and even specialists with increasingly challenging clinical dilemmas as well as an increasing array of possible additional therapies, like HBO_2. As everyone tries to offer what's best, it remains to each individual clinician to weigh the patient's presenting problem, like a lower extremity or diabetes mellitus foot ulcer and potential therapies, such as HBO_2.

Introduction

The U.S. healthcare system continues to have demographic shifts with an increasingly older, obese, and diabetic patient population as shown by CDC tracking.[1] Missouri is in the heavier half of the U.S. Missouri is in the higher groupings of age-adjusted percentages for diabetics in the U.S.[2] Missouri is also a tobacco-growing state with low taxes on tobacco.[3] The net result is more peripheral vascular disease in more patients with more problematic wounds and diabetic foot ulcers (DFUs).[4] Figure 1. Increasingly, both patients and caregivers are looking for more multidisciplinary team work to achieve better outcomes.[5, 6, 7, 8]

Although assembling such a team is sometimes problematic, clinicians should also be aware that there are considerable changes with what really constitutes quality outcomes from traditional metrics like amputation rates. A more modern approach may be to consider what treatment course will restore the patient to more functional ambulation earlier, even if this means an amputation.

Organizing Patient Would and Ulcer Evaluations

Even with greater outcome flexibility, a patient presenting with a lower extremity ulceration should have an organized approach to their initial evaluation and care.[9] Occult problems, even limb threatening ones, can exist as well as simple and less serious ones that need to be found and addressed in severity for ulcers, particularly the multifactorial causes of DFUs.[10] A way to begin is to look at every lower extremity ulcer as having a vascular component. Is the patient having ulceration or wound pain, or limitations in walking, as evidence of worsening vascular status? Often even patients who are presenting with an infection of their leg or foot—actually have poor vascular flow as the reason their foot or leg is infected. The Society of Vascular Surgery (SVS) has recently combined these inter-related factors in an approach called WIfI,[11] and multiple professional societies continue to highlight this public health need.[12]

This organized evaluation begins with a history highlighting both systemic factors, patient background



Figure 1. An example of a first metatarsal head ulceration from diabetes with associated neuropathic skin changes and tendon foreshortening with hammer toes.

health, any smoking or diabetes as well as local factors like worsening leg pain or enlarging tissue losses. The severity of the patient's complaints, the wounds themselves and their dynamic or static character over the recent past should guide the intensity of that patient's work up. Lower extremity ulcerations, particularly DFUs, typically have not only vascular and infectious disease components, but also local mechanical forces. A patient may not be aware that their orthopedic and podiatric stability have changed such that skin and soft tissue are breaking down. It is interesting to see that the American Diabetes Association (ADA) actually groups their DFU recommendations under headings of microvascular complications.[13] DM, and other disease processes, have an insidious effect where microvascular ischemia kills off tissue nerve endings. As this flow is choked off, the nerves for sensory, motor, and unconscious nerve functions are lost, and then the soft tissues and bones change as de-enervated. The skin loses many of its protective character and becomes thinned, shiny, dry, and cracked. It loses its hair and lubricating oils. Poor proprioception can lead to repetitive trauma when the patient no longer steps down securely onto their feet and becomes unaware of the repetitive trauma of standing and walking. Although the patient may not notice, his or her partner may notice that the patient's legs and feet feel cooler in bed and are different in appearance, hair distribution, and nail character. The supporting ligaments weaken or scar, and bones lose their architecture with flattening of the arches, hammer toes, and Achilles' foreshortening even progressing into Charcot pathologies. Repetitive local trauma becomes unsurmountable for the patient to re-heal and pathological responses occur such as callous formation and neuropathic arthropathy. Although it is easy to over focus on the arterial flow in a leg or foot, changes also occur in both venous and lymphatic flow with resultant edema changes as well.

DFU-Focused Evaluation to Justify Adjunctive HBO_2

Patients should be counselled about good general care for tighter glucose control with HA1Cs that are individualized for them.[14] Patients need adequate protein nutrition for healing, even while watching their kidney function. Neuropathic patients are recommended to look at their feet in the morning and in the evening and use a mirror on the floor or their partner to see their all of their feet and never go barefoot. This is especially important for patients who may not realize that they are losing their sensation such that annual foot exams should include fine touch, if not Semmes-Weinstein monofilament document their sensation. Patients who have a history of peripheral vascular disease or who admit to neurological changes or claudication in their feet or legs should undergo bedside Doppler exams or ABIs and formal vascular lab ultrasound testing. Patients should be in protective foot wear with a broad and adequately high square toe box with >3-4 laces, padded tongue and cushioned insole to protect their arch—if not a formal podiatric evaluation and custom footwear.[15, 16]

Once callouses and ulcerations occur multifactorial causes should be sought. There are now several societies looking at optimizing this initial work up for patients, particularly diabetic patients with DFUs, including the

Undersea and Hyperbaric Medical Society (UHMS), the Society of Vascular Surgery (SVS), the American Diabetes Association, the American Society of Podiatric Surgeons, and the American Orthopedic Foot and Ankle Society, among others. This article will attempt to pull information in many sources as they relate to DFUs and HBO_2. One of the really fascinating opportunities in wound care is that the problem of the DFU is a multifactorial one and often deserves input from a dedicated team of interested professionals.

The SVS has been formalizing an approach under the acronym WiFI—"Wound, Ischemia, and Foot Infection."[17] Many referral wound care programs have different variants for this "toe and flow" approach. All are looking at this as there are patients with acute critical limb ischemia—but also with chronic critical lower limb ischemia as well.[18]

This system was designed to combine previous schema for critical limb ischemia and DFUs, and has been validated and is being used to begin to categorize more problems more productively.[19] Just like a clinician might take a history looking at the overall patient and their relevant medical status and inherent risks, this system then focuses on the wound at hand, its extent, any ischemia that might be present and any foot infection present. This complements the basics of a good vascular exam including an assessment of the skin, hair and nails, capillary refill, palpable pulses with bedside hand held Doppler signal assessment, and also neurological exam for losses in fine touch. Patients with diabetic (and other sources of) neuropathy may have quite an on-going problem and feel no pain to warn either themselves or a clinician that they have an ongoing tissue loss problem that may be accelerating.

Often there is an interplay between not just blood and lymphatic flow, neuropathy and arthropathy; but also, diabetic foot ulcerations may have either colonization or frank infection that are polymicrobial, with aerobic gram-positive cocci. Staphylococci and streptococci are common causative organisms. Wounds may or may not need antibiotic therapy. If empiric antibiotics can be targeted at gram-positive cocci in many patients with acute infections, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections may require broader-spectrum regimens and specialized care.[20]

Adding Adjunctive HBO_2 Requires Proper Staging and Patient Selection

In addition to a focused examination of the patient's ulceration, the whole patient needs ongoing assessment as well and the ADA has very helpful guidelines. The ulcer's exam should include utilizing a classification schema in addition to specifying the location, the measured size and depth as well as a narrative describing the layers of tissues involved or lost and any additional signs such as the drainage, odor, undermining and the peri-ulceration character. DFUs can themselves be classified by several systems including the Texas Diabetic Foot Ulcer Classifications, King Classifications, and Wagner Grades.[21] If HBO_2 is to be considered than all the milestones for good care need to be well documented: no good re-vascularizable targets, tissues that are nonviable have been debrided, any infection has been controlled, that the patient's diabetes is under good control and that despite good local care and off-loading that the patient's ulceration has failed to heal for more than 30 days. Much of the data for hyperbaric is swayed by how rigorously are these goals met. Total contact casting has become a mainstay and assists in enforcing off-loading as well as patient follow up. The strongest data for HBO_2 is to add elective HBO_2 for Wagner Grade 3 Ulcerations (a full thickness, deep ulceration with osteomyelitis or abscess evident on exam).[22] Interestingly, although the recommendations for managing DFUs and patients with complex ulcerations in general are becoming more detailed—patient centered outcomes still lead the way. The patient's individual expectations for his or her care and to individualize that care to what the patient can tolerate give more latitude to treating clinicians. For some patients an earlier amputation with an earlier return to walking may

be a better option than prolonged therapies. The future is where larger data sets generate better evidence based wound care recommendations.[23]

Conclusions

Especially if a patient is going to be considered for HBO_2 the overall goals must be that basic care is accomplished first and that the non-healing DFU is neither too minor (less than Wagner 3), nor so far advanced as to be unrecoverable. Many of the controversies surrounding the use of HBO_2 still stem from either over or under inclusion of patient's by their severity. [24] Several schema now exist to more rigorously recommend practice management guidelines for HBO_2 to treat DFU. [25] Continued use of measurements such as tissue concentration of oxygen guide clinicians in addition to the severity of the DFU as to who will most likely respond to HBO_2 and who may not. Including patients who may not respond to HBO_2 skews conclusions about the value of HBO_2. Patients who have lower extremity ulcerations, particularly DFU's deserve ongoing efforts to organize care approaches and adjunctive modalities, such as HBO_2, to give them the best functional and durable outcome.

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None reported. **MM**

Hyperbaric Oxygen Therapy and Negative Pressure as Advanced Wound Management

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Clinical data registries growing out of evolving EMRs will help make more evidence-based decisions for utilizing both hyperbaric oxygen treatment and negative pressure and how they might be used together.



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Abstract

Hyperbaric oxygen therapy shares many characteristics with negative pressure wound therapy (NPWT) from mechanisms of action that are primary, but also adjunctive. Both modalities share parallel challenges as advanced wound management strategies.

Introduction

Wound healing methodologies can remain classically driven, but also have evolved with advances over time. One of the ongoing sea changing currents is the use of negative pressure wound therapies. In many ways negative pressure wound therapies and all their variants share similar mechanisms of active and challenges to their usages as we see in hyperbaric oxygen therapies.

Serendipity

Many physical forces might be exploited to close a wound defect and promote healing. From the simple, classical such as mechanical tension with sutures to the more exotic like chemokines and even electricity in galvanotaxis. Negative pressure wound therapy can be seen in its beginnings as utilizing yet another physical force, vacuum, to close wounds. See Figure 1. However, very earlier on negative pressure wound therapy or vacuum assisted closure was also appreciated to have other helpful effects that went well beyond just pulling wound edges and walls together.[1,2] As negative pressure methods began to be studied more findings suggesting more proposed mechanisms of action were found and put forth. From the cleansing action of pulling wound fluid through and out the wound,[3] to generating helpful local neo-angiogenesis and cellular stimulation.[4] There is always a bit of push and tug between what is believed to be at work, what is really known about what is at work, and what is just being discovered or disproven about various mechanisms of action. This parallels hyperbaric oxygen in many ways. Hyperbaric oxygen attempts to use a very special physical phenomena—pressure changes how oxygen is absorbed and distributed throughout the body. It achieves this—but like the effects of vacuum forces moving tissue planes only begin to describe the effects of negative pressure—hyperbaric oxygen also has other effects.

Organizing Selected Parallels Between NPWT and HBO_2

Both NPWT and HBO_2 have direct effects on tissues and both effect tissue flows in and out of the tissue beds being targeted by

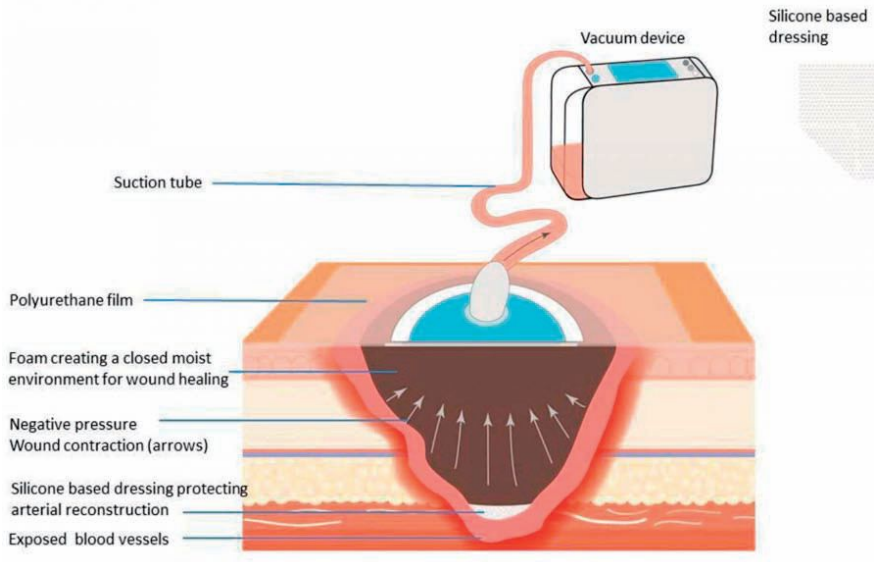


Figure 1. Negative Pressure Wound Therapy
Source: Annals of Vascular Surgery

the modality. For example, both NPWT and HBO_2 improve local flows through diminishing local edema resistance to enhanced flow and driving more perfusing flow into a targeted area.[5,6]

Both NPWT and HBO_2 stimulate neoangiogenesis that can be seen on exam with better quality granulation tissue in the wounds.[7] Both have a variety of mechanisms that are being studied to see why that granulation tissue and neoangiogenesis forms and how to optimize it from the specific microdeformation character of the negative pressure transmission medium to the timing and cycling of hyperbaric with periods of hyperoxemia and hypoxia.[8 9]

Both NPWT and HBO_2 share some common practice pre-requisites for good use in wound healing. Similar to HBO_2 negative pressure wound therapy has several guidelines exist for its use from focused topics such as for DFUs.[10] to overall reviews.[11] Akin to HBO_2 its usages continue to evolve and now include topical applications for incisions. Similar to HBO_2 these recommendations include good practice habits such as to clean and debride the wound of necrotic debris before using negative pressure. Both have specific precautions due to their mechanisms of action such as protecting underlying structures for NPWT or managing hypoglycemia in HBO_2 This is true for HBO_2 to be effective and especially true if both NPWT and HBO_2 are to be combined for synergistic effects. Any infections should be controlled—even though both HBO_2 and NPWT may have their own contributions to assist the body in clearing local tissue infections.

Both HBO_2 and NPWT have prerequisites for safe uses. For negative pressure that means addressing if any suction force is being applied near bowel or vascular structures. For HBO_2 the patient needs to be stabilized to tolerate effects of negative pressure and any risk factors such as diabetes mellitus or seizures are well controlled. Although both may have anti-infective properties, infection and necrosis should be brought under control with surgery and antibiotics. However, both modalities, especially with more negative pressure being combined with irrigation or direct drug delivery, may have more promise in treating active infections than originally thought.

Challenges for both NPWT and HBO_2

However, although both modalities may be used on their own, there may be more benefits in using them together in synergy. But if high quality clinical data is lacking for randomized, prospective, well controlled and adequately powered studies for each of them in isolation—combining them compounds that problem. The question remains how much

synergy is really reached in any combination and can these additional costs of treatment be justified in an increasingly data driven and value based medical economy?[12]

That said, many wound care practices attempt to take the available data and develop practice habits that introduce increasingly more sophisticated (and therefore expensive) advanced wound care treatments to either heal a higher percentage of wounds and ulcerations with fewer complications. If advanced modalities such as HBO_2 or NPWT are not good matches for the patient's problems, then this may also assist patients and clinicians to also consider more palliative care regimens that are safe and acceptable to the patient. Both NPWT and hyperbaric oxygen therapy can be brought to bear in this manner. NPWT can be continued throughout a patient's HBO_2 treatment regimen so long as the actual dressing is protected and that no component, such as an electrical based pump or any other flammable items, enter the chamber according to the practice requirements for that chamber.

It is ironic that medical care now exists in a sea of deceptively extensive EMR-based clinical data. It is deceptive in that although much more data is available—most EMR platforms focusing on compliance, documentation and capturing billing more effectively— aren't easy to use to capture and organize clinical data for meaningful evidence based conclusions. So the day to day clinical experiential data is all there for anyone to analyze, but it still takes considerable human effort to capture it without omissions or duplications and organize it in a way such that biases can be controlled and meaningful evidence based conclusions can be reached in a way that are more generalizable for more clinicians to accept.

Conclusion

Both hyperbaric oxygen and NPWT have become advanced wound care methods with varying levels of evidence that deserve further study. Clinicians can incorporate them into their practices to better manage difficult wounds either alone or in combinations trying to capitalize upon synergy between them. However, ongoing clinical research is needed to better delineate who gets the most value out of these advanced modalities safely and effectively and in manners that merely increase the cost of care for patients. The costs for patients may also be logistical and may also help patients realize that such treatments are not a good match for their particular situation such that other treatment regimens can be pursued. Over time it is hoped that clinical data registries growing out of evolving EMRs will help all make more evidence-based decisions for utilizing both hyperbaric oxygen treatment and negative pressure and continue to explore how they might be used together.

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Disclosure

None reported.

MM

The Diagnosis of Decompression Sickness in Sport Divers

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Treating sport diving patients may be outside of a clinician's usual comfort zone, but there are resources through professional societies to assist both patients and clinicians to seek and receive hyperbaric oxygen treatments.



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Abstract

Hyperbaric oxygen therapy (HBO_2) remains the primary treatment for decompression sickness (DCS)—which can be obviously serious or infrequently more minor and can get missed outside of centers that routinely handling diving medicine. This review will point out the salient items for how sport or amateur divers might present for HBO_2.

Overview

Currently, HBO_2 is so commonly used for wound healing applications that outside of hyperbaric centers near water that often treat DCS, lower grade or sport diving cases of DCS can get missed. Even though treatment with HBO_2 for DCS is one of the most accepted indications and historically has some of the strongest data supporting its use.[1] Cases of DCS can be obvious due to their preceding diving history and classic, immediate symptoms of joint pain and neurologic deficits, but they can also present with atypical symptoms.[2]

There are between 2.7 and 3.5 million scuba divers in the U.S. and more than 6 million worldwide.[3] Clinicians should appreciate that with the popularity of sport diving there is considerable variations in training, experience, supervision, and equipment being used. Often sport dives are organized along several amateur and professional society guidelines, and the first sometimes misleading nugget of information is that a diver ascends having no violation of the safe, planned dive sequence and that other divers with them have no symptoms. It should be noted that DCS, including more minor variants, can be highly variable based upon the individuals state of health and hydration, as well as how other dive factors beyond the depth and bottom time. Temperature of the water and any physical exertion during the dive may also play a role for the individual.[4] So the presenting patient doesn't think DCS is really an etiology for their complaints and leads with no violation of the dive protocol and no one else being symptomatic.

DCS can also occur in relatively shallow depths—in fact there have been isolated cases in children in very shallow, 1 meter depths.[5] Usually depths of about 20 feet are more common for DCS.[6] Children may not intrinsically accommodate with exhaling on ascent and may have more asymptomatic cardiac defects, such as a persistently patent foramen ovale. Anecdotal stories exist of children watching a pool cleaner go about cleaning the bottom of a home's pool using some kind of air delivery circuit and joining that worker where they also breath air at depth and then pop to the surface. This is given as an example where DCS might

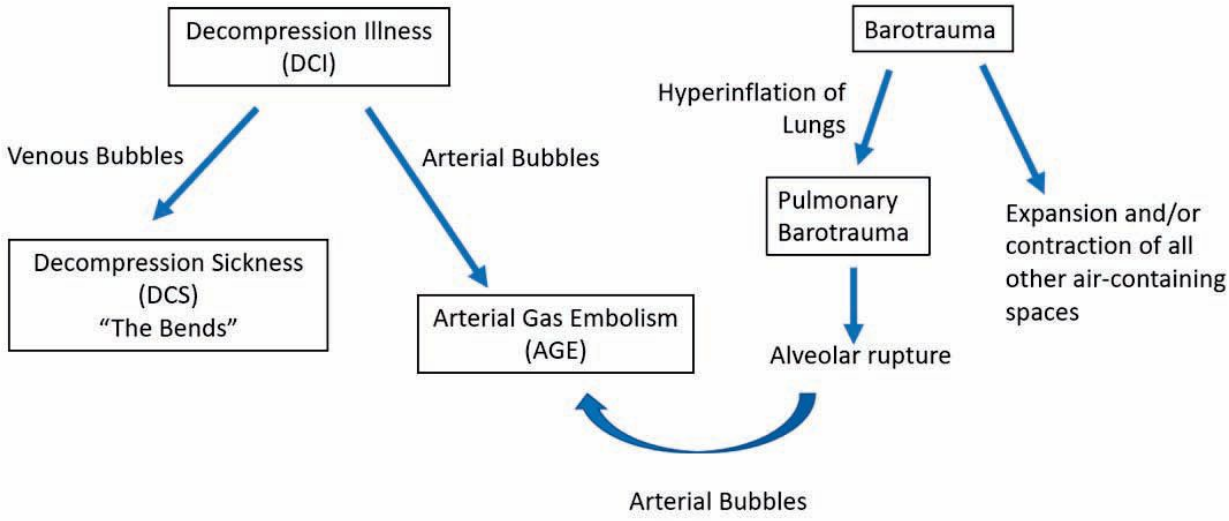


Figure 1. Flow diagram showing the interrelationships between different classifications of diving-related illness.
Source: MedEdPORTAL

be missed if that same child presents with nonspecific malaise and joint pain several days later. Figure 1.

Atypical Presentations Can Present

Lower severity DCS cases often have nonspecific symptoms of pain near major joints, musculoskeletal aches and malaise, numbness and paresthesia and sometimes skin complaints like itching or rashes. Major or Type II DCS have more severe musculoskeletal pain or neurological symptoms (including those related to the inner ear and balance problems, vertigo tinnitus or nausea) or cardiopulmonary complaints.[7] Lower severity DCS can be missed as so atypical and can present to a primary care physician that doesn't often care for diving problems.

Although Missouri is essentially landlocked, diving accidents can and still occur in lakes, rivers, and even in rarified, complex arrangements, like diving in a body of water contained at depth inside of a cave. However, a more common presentation in land locked areas are from sport diving vacations.

Clinicians who themselves are not sport SCUBA divers may not be familiar with diving vacations. Typically a dive vacation is arranged for sport SCUBA divers to fly on a commercial plane to a scenic, warm place to dive as the focus of the vacation package. It is usually recommended and most diving vacations or the dive boat have some affiliation with one of the recognized diving associations. In a typical dive vacation over three to five days, the vacationers go to their deepest depths early if not in the first dive. The usual history is that there were no recognized breaks in the dive plan, no appreciated problems with the bottom time or ascent and someone comes up to the surface and begins having vague, but persistent symptoms like joint pain in the shoulder hips or legs. Typically the presentation is not a classic debilitating one that everyone can immediately appreciate as DCS, but often is bad enough that the patient themselves do not go back for any subsequent descents and/or the dive master refers them back to the resort doctor. It is often the case that neither the patient (who has shelled out for the vacation) nor any of the vacation staff is enthusiastic about labelling it as DCS, and to be fair often the symptoms are often mixed. Often there are tips-offs that can assist in the diagnosis.

Sport Diving DCS Diagnosis Tip Offs

The first is sometimes that patient might insist upon going ahead with the next dive, and when they do they feel better even at a lower depths (recall the first dive is often the deepest) and then feel worse again when they come up. They may notice that they kind of feel better just at the depth of the resort pool as the bench themselves from further real SCUBA diving. During this period they should be concentrating on hydrating themselves well, controlling pain with

NSAIDs, and avoiding alcohol due to its diuretic effects—although alcohol is often consumed in self-treatment. Even before HBO_2, just 100% oxygen can be offered. So the typically low grade DCS sport diver toughs it out for the next several days, feels a little better each day, and then second red flag is the flight home.

Many commercial airline flights may not completely pressurize to sea level as just approximating sea level saves weight and fuel.[8] So if a patient, our sport diver, boards the plan with mild resolving DCS, it gets worse at altitude and then when the plan lands it again gets better. An all too common sequence of events is that the sport diver leaves the work week early for a long weekend diving vacation. They arrive at the resort at the beginning of the weekend and are in the water shortly thereafter. When they come up from that first, deepest dive, even though nothing went wrong, they have symptoms. They are reassured that it isn't likely to be DCS, but to be on the safe side they are recommended not to continue on with the sequence of dives. They tough it out, and just about the time that they fly home at the end of the weekend, they are getting better. Then they worsen on the flight home and again improve when they land. However, often they are now calling their primary care physician Monday morning, who then reaches out to a local HBO_2 center. Sometimes the call doesn't come until later in the week or even the following week.

Calls like this should prompt an evaluation looking for the DCS exposure mechanism and the symptoms in the patient. Most of these patients are themselves very active, healthy, and unless they have had some change in their overall health status, like an opening of a shunt or a popping of a pulmonary bleb have little to no safety contraindications to HBO_2 treatment. All patients should undergo good safety screening for HBO_2. It is recommended that physicians who do not commonly treat patients with DCS contact one of the national societies like Divers Alert Network (DAN) to improve their evaluation exam to minimize omissions (such as more serious complications and not overlook pre-existing conditions like a patent foramen ovale) as well as to plan for treatment options. DAN maintains a 24-hour call center and potentially available facilities, should such a DCS even occur at 1-919-684-9111. Although major cases of DCS might need increased pressures or longer treatment times, often sport divers with less severe symptoms might do just as well with a timely offering of HBO_2 at depths commonly available in even outpatient settings between 2.8 and 3 atmosphere absolute (ATA).

HBO_2 treatment for DCS is one of the shorter sequences of no more than 10 treatments before utilization review. Often sport divers may need only a few treatments for a full recovery. Officially there is no time delay where HBO_2 is withheld where it is too late, but the longer the symptoms persist without treatment the more likely that any treatment will be as successful. It should also be appreciated that the diagnosis of DCS may remain in doubt in a healthy patient without any safety concerns for a trial of HBO_2 and it is the patient's early improvement on the very first hyperbaric treatment that is confirmatory for all.

Conclusions

In conclusion, severe cases of DCS, decompression illness, and arterial gas embolism may be relatively obvious due to their antecedent mechanism of exposure to pressures or gases or instrumentations. Lower grade DCS may present with atypical symptoms in sport divers to general clinicians who should include this in their differential even if no violations of any diving protocol occurred. Nearly all of these patients may be able to be treated in existing facilities as few require more than 3 ATA and often they may even qualify for outpatient treatments. Although treating such sport diving patients may be outside of a clinician's usual comfort zone, there are many helpful resources through professional societies to assist both patients and clinicians to seek and receive hyperbaric oxygen treatments.

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Disclosure

None reported. **MM**

Hyperbaric Oxygen Therapy and Radiation-Induced Injuries

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As HBO_2 increases tissue oxygenation and improves blood flow, it also effects cellular responses for healing.



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Abstract

Initial clinical uses of hyperbaric oxygen (HBO_2) capitalized upon physical effects to drive offending gases back into solution and deliver more oxygen to tissues in early treatments of decompression sickness. HBO_2 has a myriad of other effects, including stimulating angiogenesis and new cellular in growth for healing.

HBO_2 Applied to Patients with Osteoradionecrosis of the Mandible

As incremental improvements in head and neck cancers improved survival with better surgical techniques for more complete tumor extirpation plus better radiation for enhanced local control and even further adjuvant therapies that increased long term survival, patients began living long enough to suffer all the sequelae of osteoradionecrosis (ORN) of the mandible. Patients who had otherwise been cured of their original cancer now suffered ever worsening dentition, including loosening and loss of teeth, and even pathological jaw fractures. These seriously impacted their quality of life for eating, speech, social isolation with open draining sockets, problematic and malodorous wounds and exposed bone and pain.[1,2] As more of these challenging patients presented, it was easy to assume that the exposed bone and soft tissue problems were related to chronic colonization and then resultant infections due to the inherently high bacterial counts in the mouth. Although increasingly stronger antibiotic regimens and surgical dental and bone stabilization protocols were instituted many patients still suffered less than optimal outcomes thought to be related to variants of osteomyelitis of the mandible.[3] At the same time, HBO_2 was accumulating data that high oxygen tensions were toxic to certain bacteria, such as clostridia species, and might also have other cellular effects for better healing in ORN.[4]

Real HBO_2 Effects Irradiated Tissue worked out in ORN and then in other Tissues

This led to an oral surgeon, Dr. Robert E Marx, and others to study if HBO_2 could synergistically improve antibiotic control of surgical complications in ORN.[5,6] Fortunately, in the effort to study the bacterial loads, the pathological bone specimens were carefully analyzed in the course of these trials that included prospective, randomized arms both with and without HBO_2. Although it was expected that those receiving HBO_2 would have



Figure 1. Healed to clean dry scabs, hyperbaric sequence completed at 40 treatments.

lower bacterial counts, lower amounts of bacteria in the bone, and less culturing of bacteria causing problems for healing, there was a different serendipitous finding: the bone samples in the HBO_2 arms all had increased densities of new blood vessels and in growth of cells that were not present before treatment.[7, 8, 9, 10] HBO_2 was having an effect on infection and bone breakdown from stimulating neo-angiogenesis in the bone which allowed the bone to tolerate further surgical manipulation and heal. This was and continues to be a paradigm shift in patient's care after medical irradiation.[11, 12] A process, radiation-induced tissue fibrosis and its hypo-vascularity, was being offset by the stimulatory effects of HBO_2.[13, 14]

By stimulating new blood vessel and cellular in growth, this increased blood flow to allow the bone and soft tissues to heal. This gave head, neck, and oral surgeons increased capabilities and lower incidences of complications for patients. These neo-angiogenesis effects have later been better demonstrated with an array of cellular and cytokine effects and form a more modern way of looking at how HBO_2 treats not only ORN of the mandible,[15,16] but also for laryngeal and soft tissue necrosis in the head and neck[17,18] chest wall necrosis and post breast cancer irradiation syndromes,[19] radiation cystitis[20] radiation proctitis, rads enteritis, and pelvis floor organs including the vagina[21] and neural tissues and the brain.[22,23]

All of these radiation injury effects can be have HBO_2 to augment therapeutic responses for the patient. The effects of radiation can be early or delayed, but should a patient with skin, soft tissue including intra-oral or other mucosal surfaces (uro-genital or GI)[24], bony, or neural tissue are symptomatically changing after irradiation, then adjunctive HBO_2 can be considered.[25] In many ways the radiation induced hypovascularity is similar to the diabetes mellitus induced hypovascularity where HBO_2 has also been shown to be beneficial where the cycling of hypoxia (while in the HBO_2 chamber) and then the slow decay back to baseline hypoxia after treatment is stimulatory for neoangiogenesis.[26]

With the advent of ever larger data registries, more applications of HBO_2 for radiation-induced changes are accumulating. As in other non-healing applications for adjunctive HBO_2 better data will optimize practice guidelines, documented efficacies and also allay some safety concerns as many post irradiated patients may be at risk for tumor recurrence regardless of any HBO_2 offered. Although to date, there is no accumulated evidence for increased cancer recurrences with HBO_2.[27,28] In fact, especially for head and neck cancers, further tracking of recurrences is demonstrating specific differences in tumor biology that predict cancer re-growth such that better HBO_2 tracking may contribute to finding patients at risk for cancer recurrences.[29]

Conclusions

Irradiated tissue responses well delineated in hyperbaric ORN studies are a more modern conceptualization of HBO_2 effects and potential value to patients. As ever increasing sophistication of basic science capabilities to delineate cellular and tissue responses occur, HBO_2 has been found to have effects beyond oxygenation. As HBO_2 increases tissue oxygenation and improves blood flow, it also effects cellular responses for healing.[30] However interesting these basic science mechanism are to consider, modern evidence based recommendations are also based upon clinical evidence and this is where better data registries will make an impact. The cumulative patient and tissue improvements seen in ORN and other post irradiation changes demonstrate the additional, adjunctive value of HBO_2 in other similarly damaged tissue states.

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Disclosure

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Current Management of Copperhead Snakebites in Missouri

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Copperhead snakebites are the most common envenomation in Missouri.



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Abstract

The past two decades have seen changes to the management of copperhead snakebites. We review the current use of antivenom, analgesics, and laboratory testing as well as the declining role of surgical management.

Introduction

Snakebites are common in Missouri.[1,2] The Missouri Poison Center reported an average of 190 snakebites per 100,000 residents between 2001-2005.[1] Of the total 952 snakebites reported in Missouri in this period, 50% were copperhead bites. An additional 40% were unknown venomous snakes, which were also likely copperheads, given their extremely high prevalence in Missouri. This is consistent with national data suggesting that copperheads are responsible for approximately half of reported snakebites.[3]

The optimal management of copperhead snakebite is far from settled. There are several areas of active controversy, including indications for the use of antivenom, need for laboratory assessment of coagulopathy, expected degree of coagulopathy, and appropriate analgesic therapy. In this piece, we will review historical developments in copperhead bite management since the publication of *Missouri Medicine's* last review on this topic and then move to a discussion of current trends in management.

Historical Developments

Much has changed in the two decades since *Missouri Medicine* published a review of copperhead snakebites. In 1976, Krochmal and Anderson reviewed the management of copperhead snakebites.[4] In 1998, Anderson updated this review.[5] At the time of both prior reviews, the only available FDA-approved antivenom for pit vipers was an equine-derived, whole IgG antibody product, Antivenin (Crotalidae) Polyvalent® (Wyeth Pharmaceuticals) with a high risk of serum sickness and anaphylactoid reactions.[6] Both reviews recommended against using antivenom and reflected the prevailing opinion of the time that the risks of the Wyeth antivenom outweighed the benefits for copperhead snakebite victims.[4–6]

Since the 1998 review, there have been several exciting advancements in the management of copperhead envenomation. The most important has undoubtedly been the development and FDA approval of ovine Fab antivenom (FabAV® BTG International, Conshohocken, PA; hereafter FabAV) in 2000. FabAV is an ovine-derived, affinity purified, polyvalent Fab fragment that is derived from the serum of animals injected with venom from eastern diamondback, western diamondback, Mojave rattlesnake, and cottonmouth species.[7] During FabAV production, the enzyme papain removes the highly immunogenic Fc domain from the collected antibodies,



Figure 1. When a Copperhead Comes Calling

Pre-Hospital

- Prioritize scene safety
- Obtain pictures of the culprit snake if possible
- Remove tight clothing or jewelry proximal to the bite
- Do not apply a tourniquet or ice
- Do not use a suction device

Emergency Department

- Obtain intravenous access
- Obtain plain radiographs of the affected part to rule out underlying fracture or retained radiopaque foreign body
- Consider drawing basic laboratory tests: complete blood count, coagulation studies, and fibrinogen.
- Control pain with non-steroidal anti-inflammatory drugs, with the addition of opioids if required
- Obtain expert consultation (with a medical toxicologist or local poison control center) to discuss administration of FabAV and potential transfer to a tertiary care center

which makes FabAV less likely than equine derived Wyeth antivenom to cause anaphylactoid reactions and serum sickness.[8] The Wyeth AV is no longer available as production ended in 2001, and all stocks available in the U.S. expired over a decade ago.

A prospective, multi-center trial by Dart and colleagues demonstrated that FabAV effectively terminated venom effects in patients with mild or moderate rattlesnake envenomations.[9] This trial excluded patients bitten by copperheads and most patients were enrolled in the Southwest, where copperhead snakes are not native.

Fab Antivenom for Copperheads?

The use of FabAV in copperhead bites remains controversial. Historically, many authors advocated avoidance of antivenin in copperhead bites, which are frequently considered mild and unlikely to cause significant morbidity.[10] Lavonas and colleagues noted beneficial effects of FabAV use in copperhead snake envenomations in a case series.[11] However, as Caravati noted in his editorial on the cases series, only a properly controlled prospective trial could produce high-quality evidence of benefit of FabAV in copperhead envenomations.[12]

Gale et al. retrospectively reviewed charts of copperhead snakebite patients in East Texas from 2002 to 2013.[13] Only 13.8% of their patients received FabAV, but those treated with FabAV had more swelling, more pain, and higher snakebite severity scores. Compared to patients who did not receive antivenom, the FabAV treated patients were twice as likely to be transferred from outlying hospitals, four times as likely to be admitted to the hospital, and twice as likely to have an upper extremity bite.

In an uncontrolled, prospective, open-label pilot study, Lavonas et al. saw similar outcomes between patients receiving FabAV and those not receiving it. However, the patients who received FabAV had more severe envenomations than the patients who did not receive FabAV. These studies likely reflected the preference in the early 2000s to reserve FabAV for more severe cases, and highlighted practice pattern variations in copperhead bite management. The goals of this study were to determine the typical duration of recovery following a copperhead snakebite and to test the outcome assessment procedures for the next study.[14]

Gerardo and colleagues recently conducted a multicenter, randomized double-blind placebo controlled trial to evaluate the efficacy of FabAV for the treatment of copperhead bites.[15] They enrolled patients from August 2013 through November 2015. Seventy-four patients received a study drug; forty-five received FabAV, and twenty-fine received placebo. The primary outcome studied was function of the affected limb at 14 days post-envenomation,

as measured by a validated functional scale.[16–18] Patients receiving FabAV had superior 14-day limb function scores than patients receiving placebo (8.6 versus 7.4, difference 1.2, 95% CI 0.1-2.3, p=0.04),[17] and also required significantly less opioid pain medication.[19]

In a secondary analysis of data from this trial,[20] the authors also found that patients who received antivenom early (less than 5.5 hours after envenomation) experienced faster return to baseline limb function than those who received antivenom late. This effect was substantial—median time to full recovery in the "early" group was 17 days, while median time to full recovery in the "late" group was 28 days (p=0.025). In an earlier retrospective review,[21] the same group established that early administration of antivenom did not significantly increase the total amount of antivenom required in a copperhead-predominant snakebite population. They also noted that 80% of "minimal" envenomations progressed to moderate grade envenomations. Taken together, these results suggest that it would be prudent to administer antivenin as soon as possible, instead of observing patients for progression of symptoms prior to administering antivenom. This may benefit patients by promoting faster recovery without substantially increasing the amount of antivenom they receive.

Many physicians are concerned that aggressive use of FabAV in copperhead envenomations may unnecessarily expose patients to the risk of adverse effects of FabAV.[5,13] Fortunately, available data suggest that this risk is relatively low. Schaeffer et al. performed a meta-analysis of safety data from multiple trials of FabAV in rattlesnakes.[22] They conservatively attributed all adverse events to the antivenom and none to the envenomation itself. They estimated that allergic reactions and delayed serum sickness might occur in up to 13% and 8%, respectively, of patients receiving Fab AV. All patients in their analysis received FabAV with no placebo group for comparison, and all patients had rattlesnake bites in the southwestern U.S.

The randomized, placebo-controlled trial of FabAV in copperhead snakebites provided the opportunity to study the events attributable to the antivenom.[15] The secondary safety analysis found that 16 patients treated with FabAV developed at least one treatment-emergent adverse effect related to study treatment, as compared to three patients treated with placebo.[23] There were no deaths, and few serious or severe adverse effects occurred in either the treatment or placebo groups. Most adverse effects were mild skin reactions such as pruritus or urticaria. There were no cases of serum sickness. These findings are consistent with three other independent studies showing low incidence of adverse events following Fab AV use.[24–26]

A newer $F(ab')_2$ antivenom (Anavip ® Rare Disease Therapeutics, Nashville, TN) recently received FDA approval in 2015. Originally developed in Mexico by Instituto Bioclon, it includes two monospecific antibody strains for pit vipers native to South America, Central America, and Mexico, Crotalus durissus and Bothrops asper.[27] A prospective, multicenter trial in the US demonstrated effectiveness of $F(ab')_2$ AV for some North American pit vipers; notably, $F(ab')_2$ is not currently FDA approved for copperhead envenomations.[28] Among rattlesnake envenomations, which often produce coagulopathy and thrombocytopenia, $F(ab')_2$ compared favorably with Fab AV with better control of coagulopathy in the $F(ab')_2$ AV group. Aside from this, the two antivenoms appear to have similar effectiveness.

Among the 114 patients studied by Bush et al., only 21 had copperhead snakebites evenly distributed among the three treatment groups.[28] There was no subset analysis of these patients. Although these preliminary data suggest that $F(ab')_2$ is as safe and effective as Fab AV, we await further clinical experience with $F(ab')_2$ AV in copperhead envenomations.

One may wonder whether the $F(ab')_2$ antivenom raised against two Central and South American vipers will cross react with copperheads. However, the obsolete equine-derived Wyeth antivenom also included antibodies to four pit vipers representing North and South America (three Crotalus species and one Bothrops species). A murine study of the Wyeth antivenom for experimental copperhead envenomations.[29] Mice received an LD90 dose of copperhead venom following pretreatment with either Wyeth polyvalent AV or normal saline. All control animals died, but 14 of 15 AV-treated animals survived to 24 hours. Based upon this study, the published experience with Fab AV, and the preliminary experience with $F(ab')_2$ AV, is reasonable to conclude that $F(ab')_2$ AV will be as effective as Fab AV for copperhead envenomations in clinical practice. Both Fab AV and $F(ab')_2$ AV are similarly expensive, but perhaps some competition in price will make one or both treatments less expensive and more accessible.

The Bleeding Edge?

Laboratory evaluation of patients with North American pit viper bites includes coagulation testing, regardless of geographic location or snake species. These typically include complete blood count (CBC), prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT), and fibrinogen. Several sources recommend these routine tests initially and repeated 6 to 12 hours later for all snake bites within the United States.[30–34]

Coagulopathy and thrombocytopenia indicate the need for antivenom therapy in any snake envenomation, particularly in rattlesnake bites.

Copperhead snakebites differ from rattlesnake bites and generally do not cause coagulopathy or thrombocytopenia. Ali et al. performed retrospective chart review of identified copperhead snakebite cases in Missouri over 14 years and evaluated most extreme values of coagulation studies including INR, PT, PTT, INR, and fibrinogen.[35] They concluded that these laboratory values consistently remained within normal limits with rare, small, and clinically insignificant excursions just beyond the normal ranges. No patients developed bleeding complications. Other reports corroborate this observation.[5,32,36–41]

We advise that copperhead envenomations likely do not require repeated testing if the initial laboratory results are normal and if there is no clinically apparent bleeding.

Snakebites Are Such a Pain

Previous guidelines for the management of pit viper envenomations recommend against using nonsteroidal anti-inflammatory drugs (NSAIDs) to treat pain and inflammation due to concern for platelet dysfunction.[33,34] These arise from expert opinion and are based on the frequency of coagulopathy and thrombocytopenia commonly seen in rattlesnake bite victims but seldom in copperhead snakebites.

We regard NSAIDs as acceptable and safe pain management treatment for copperhead snakebite patients. Copperhead venom is less hemotoxic than rattlesnake venom. In our experience, copperhead snakebites rarely cause clinical bleeding or coagulopathy. Although it may seem intuitive to avoid NSAIDs that might interfere with coagulation, there is little evidence to support this practice. Epidemiologic data on snake bites demonstrate lower rates of thrombocytopenia, hyperfibrinogenemia and coagulopathy in copperhead snake bite patients compared to rattlesnake bite patients.[40] Pham et al. reviewed 147 Missouri copperhead bites treated at Barnes-Jewish Hospital and St. Louis Children's Hospital. Slightly more than half of these patients received NSAIDs in their acute treatment (usually ketorolac and/or ibuprofen).[42] There were no significant differences in laboratory studies between patients who received NSAIDs and those who did not. Two patients had self-limited epistaxis before receiving NSAIDs, and one had microhematuria. All three had no bleeding observed after receiving NSAIDs.[42]

Lavonas and Gerardo jointly endorsed the findings by Pham and Mullins with the caveat that the data only pertain to copperhead snakebites.[43] They also pointed out that NSAID use was common in both the RCT of Fab AV for copperhead bites[15] and among copperhead bites in the comparative trial of $F(ab')_2$ AV and Fab AV[28] without adverse effects.

Do Copperhead Bites Need Surgery?

Snakebite often perceived as a surgical emergency, however data do not support this belief. Toschlog et al. pointed out that although North American crotalid snakebite may produce signs and symptoms that mimic compartment syndrome, it rarely produces true compartment syndrome.[44] A systematic review of copperhead snakebites indicated that fasciotomy and routine surgical consultation are usually unnecessary.[45] Mazer-Amirhshani successfully treated elevated compartment pressures in a 17-month-old child with antivenom therapy without fasciotomy and had no neurovascular compromise.[46] A retrospective review of adult and pediatric patients in the Journal of Surgical Orthopaedic Advances noted that supportive care and antivenom alone were sufficient in the management of snakebites.[47] Current surgical and toxicology literature indicated antivenom is more useful than surgery.[30,37,38,44,46–48] In some facilities, the physician with most experience treating snakebites may be a surgeon; we encourage clinicians to consult early with available local experts in addition to discussing cases by phone with a poison center and/or medical toxicologist.

Conclusion

Copperhead snakebites are the most common envenomation in Missouri. Fab antivenom is safe and effective. Although $F(ab')_2$ is not FDA approved for copperhead envenomation, evidence suggests that it is likely safe and effective also. Coagulopathy is rare with copperhead snakebites, and repeat laboratory testing is unnecessary if initial results are normal. NSAIDS are acceptable and safe analgesics when the clinician is confident that the culprit snake is a copperhead and not a rattlesnake. Surgical intervention is seldom necessary.

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Disclosure

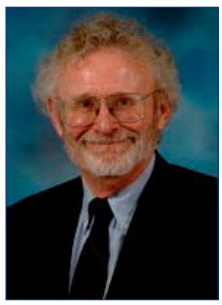
None reported. **MM**

Pleuropulmonary Blastoma: More Than a Lung Neoplasm of Childhood

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Pleuropulmonary blastoma is an established, unique pathologic entity of childhood which serves to validate the continued role of the light microscope in the identification of new diseases in this era of molecular genetics and pathology.



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Abstract

Pleuropulmonary blastoma (PPB), the most common primary malignant neoplasm of the lung in childhood, occurs in the same early age group (0-6 years) as the other more common solid tumors such as neuroblastoma and Wilms tumor. The tumor begins as a cystic lung lesion with the potential over a period of 3-5 years to progress to a high grade multipatterned primitive sarcoma in the absence of a malignant epithelial component. Several years after its initial description as a unique clinicopathologic entity, this and other tumors appeared to have a familial predilection which was later confirmed with the discovery of a heterozygous germline mutation in DICER1 whose protein is a member of ribonuclease III family of enzymes. It is estimated that 75%-80% of children with a PPB have the germline mutation. The other notable finding from our studies is the identification of a family of extrapulmonary neoplasms, including cystic nephroma and Sertoli-Leydig cell tumor of the ovary as two examples, also with DICER1 mutations.

Introduction

Between 1988 and 2009, pleuropulmonary blastoma (PPB) fully emerged as a unique clinicopathologic entity to join the other more familiar dysontogenetic or dysembryonic neoplasms of childhood; this group of neoplasms arise in various organs including the eye, liver, kidney, adrenal and soft tissues, and are known respectively as retinoblastoma, hepatoblastoma, Wilms tumor (nephroblastoma), neuroblastoma and rhabdomyosarcoma. All of these tumors have in common a clinical presentation in children 6 years old or less with a peak generally before 5 years of age. One of the unexplained and contradictory problems was that the presumed dysembryonic neoplasm of the lung, pulmonary blastoma, presented in adults, many of whom were cigarette smokers; the latter neoplasm is now regarded as a type of sarcomatoid carcinoma in the World Health Organization classification of neoplasms of the lung.[1, 2] It was proposed in 1988 with the report of the first 11 cases of a highly malignant neoplasm of the lung and/or pleura, designated PPB, was the true "pulmonary blastoma" of childhood with its clinical presentation in children 5 years old or less.[3] As uncommon as virtually all other malignancies of childhood, PPB is the most common primary pulmonary malignancy in children,

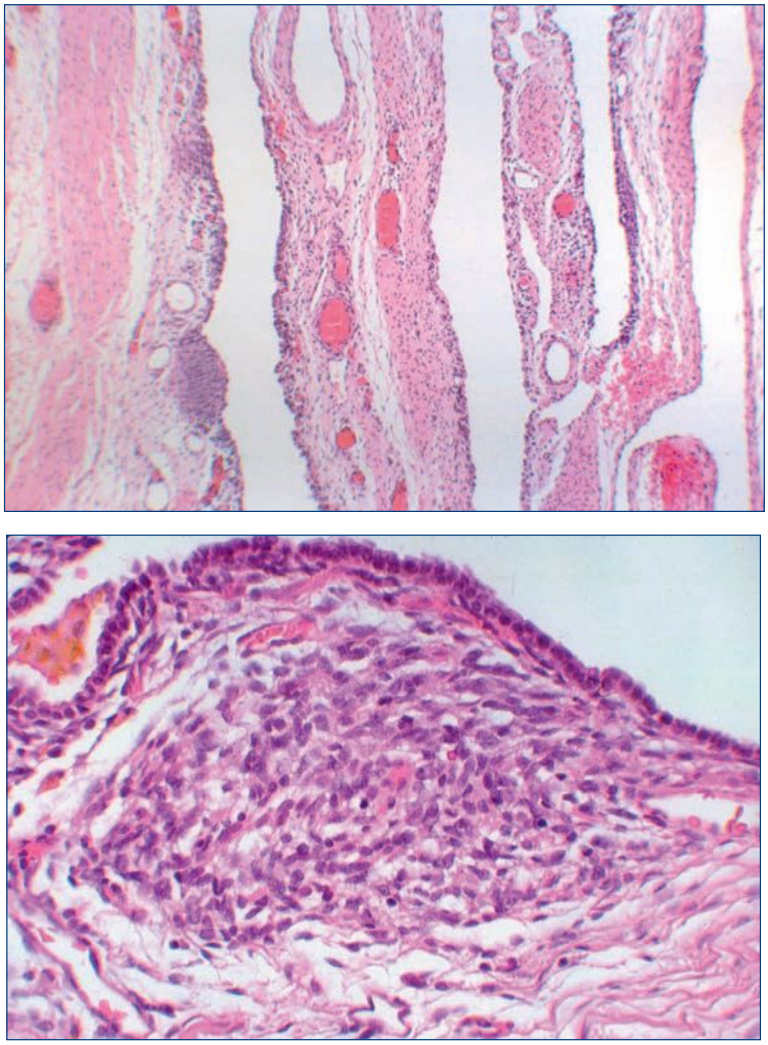


Figure 1. Pleuropulmonary blastoma, type I.
A. This partially collapsed multicystic architecture displays the rather innocuous features with a small hypercellular nodule of fetal cartilage.
B. A focus of embryonal rhabdomyosarcoma within the stroma beneath the lining cuboidal epithelium is a characteristic microscopic feature.

just as Wilms tumor and neuroblastoma are in the kidney and adrenal in this same age group.[4]

Perspective on Childhood Cancer

When we speak of PPB or any other malignancy of childhood, the entire aggregate of malignant tumors in individuals 0-19 years old at the time of diagnosis in the United States is 15,780 cases per year (less than 15 cases per 100,000) in contrast to the 1,688,780 newly diagnosed cancer cases (exclusive of non-melanoma skin cancers) per year in adults (439 cases per 100,000).[5] In children the five most common malignancies are acute leukemia (30%), tumors of the central nervous system (~25%), neuroblastoma (6%), Wilms tumor (5%) and lymphoma (8%).[6] In adults, non-melanoma skin cancers (5.3 million cases per year), breast (266,000), lung (234,000), prostate (165,000) and colorectum (140,000) are the most commonly diagnosed cancers per year in the United States. Only 13% of all cancers diagnosed in adults are regarded as "rare" (NCI definition <15 cases per 100,000) whereas 100% of all childhood cancers are rare. One of the most dramatic improvements in cancer outcomes over the past 40 years has occurred among the childhood malignancies.[7] The 5-year survival for all childhood cancers was 10% in the 1950s, 60% in 1975-79 and almost 80% in the present era; the improved survival over this period is largely influenced by advances in the management of hematopoietic malignancies.[8]

Pleuropulmonary Blastoma

With this digression, let us return to our consideration of PPB in terms of its pathologic progression from an innocuous lung cyst(s) detected in infancy to a high grade multipatterned primitive sarcoma by 3-4 years of age.[4] Because the earliest stage of PPB is a lung cyst, it is often the case that the initial impression is a congenital lung cyst with congenital pulmonary airway malformation (CPAM) (congenital cystic adenomatoid malformation) as the favored clinical and imaging impression. If the cystic lesion is asymptomatic, there are some guidelines and recommendations if surgery is not immediately contemplated. When surgery is performed, a multicystic structure is noted at the periphery of the lung on the pleural surface which maintains its appearance when placed in fluid to demonstrate the delicate septated cysts. It is important for the pathologist to thoroughly sample the specimen so that the septal structures can be evaluated for the presence of primitive small cells and/or rhabdomyoblasts and diminutive nodules of fetal appearing cartilage; these features may be localized

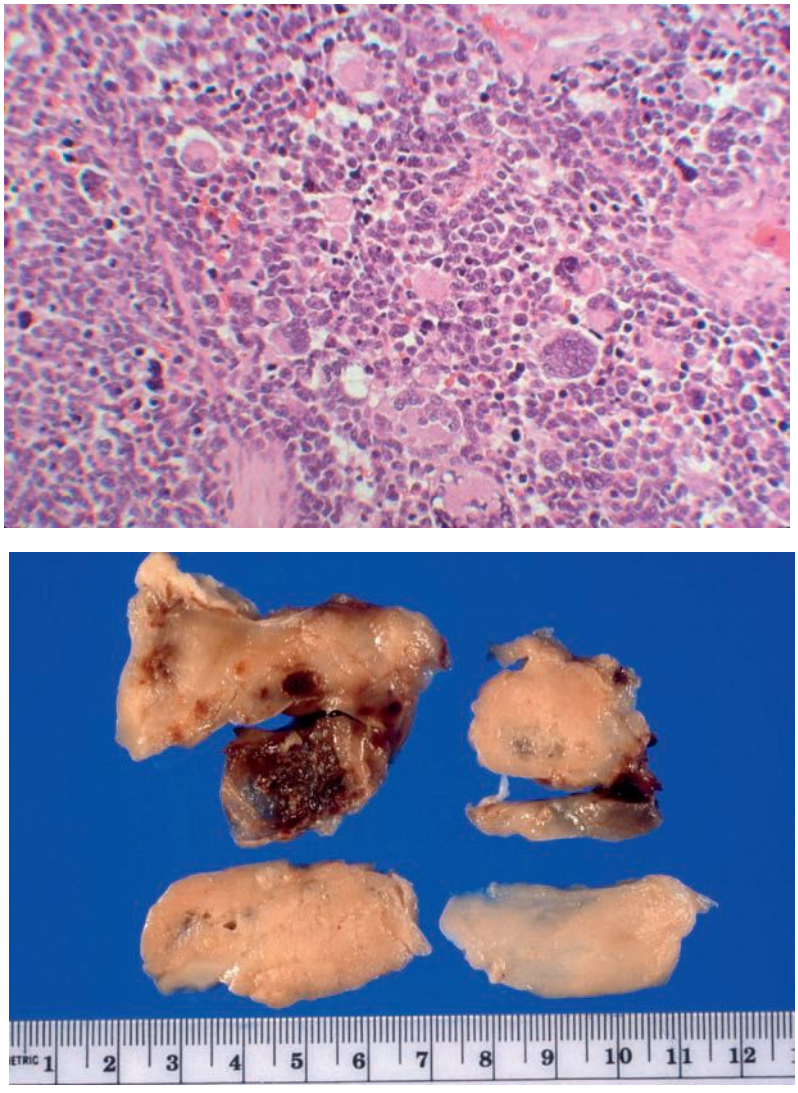


Figure 2. Pleuropulmonary blastoma, type III
A. The tumor occupies the entire thoracic cavity and extends into the mediastinum of this 4-year-old boy who presented with fever and respiratory failure.
B. Multiple resected fragments of this mass show foci of hemorrhage in this tannish-white, solid tumor. C. A mixture of rhabdomyoblasts, anaplastic tumor cells and small primitive malignant cells is one of several microscopic patterns in this complex sarcoma.

within the septa rather than as a diffuse finding so that a thorough microscopic examination is necessary (Figure 1A,B). The critical point for the pathologist is to recognize and diagnose the "congenital lung cyst" as a PPB type 1 and not as a CPAM.[4]

It was only after the mixed cystic and solid PPB type II and the purely solid tumor stage, PPB type III were described that it was appreciated that the exclusively multicystic lesion PPB type 1 was the earliest stage of tumorigenesis . The latter observation was based upon the presence of the residual multicystic lesion in the PPB type II where the solid tumor, whose pathologic features were very similar to the PPB type III, had overgrown and replaced a substantial portion of the cystic component in its progression to the final stage, PPB type III (Fig. 2A-C). As our experience with PPB expanded through the establishment of the International Pleuropulmonary Blastoma Registry (https://www.ppbregistry.org/), it was observed that there was a correlation between the median age at diagnosis and the pathologic type of PPB: type I, 8 mo; type II, 35 mo; type III, 41 mo. The other significant correlation occurred between the PPB type and survival: type I, 94%; type II, 71%; type III, 53%.[9] It is critical to diagnose and manage PPB at the type I stage as evident from these survival figures. Is the eventual fate of every PPB type I that is not diagnosed at this early stage to progress to a PPB type II or type III? We do not have the answer to this question , but we know that PPB type I may present as a multicystic lung lesion without any features of a primitive small cell proliferation or rhabdomyosarcoma; this lesion is designated a PPB type 1r which we have hypothesized represents either the regressive or non-progressive phase of PPB type I. At present, we do not yet know which PPB type I will progress to the more aggressive PPB type II or type III. We have had examples of PPB type Ir with the later development of PPB type II or III .

As additional cases of PPB were submitted to the Registry, it became apparent that there were kindreds in whom other family members had a PPB, renal cystic lesion known as cystic nephroma and other childhood neoplasms.[10, 11] In the course of a diagnostic evaluation for an ovarian mass, a lung cyst or cysts were identified in some cases; the ovarian mass was a Sertoli-Leydig cell tumor and the lung cysts were PPB type Ir.

Table 1. DICER1-Associated Neoplasms

- Pleuropulmonary blastoma (progression of multicystic lesion to PPB type II-III)
- Cystic nephroma (progression to anaplastic sarcoma of kidney)
- Nasal chondromesenchymal hamartoma
- Ocular (ciliary body) medulloepithelioma
- Ovarian Sertoli-Leydig cell tumor
- Embryonal rhabdomyosarcoma of uterine cervix
- Primary peritoneal sarcoma with PPB-like features
- Nodular hyperplasia of thyroid (progression to DICER1 papillary thyroid carcinoma in children)
- Pituitary blastoma
- Pineoblastoma

Several kindreds agreed to participate and have their blood drawn for the purpose of searching for the suspected germline mutation (appropriate consenting and counseling was obtained from each family member in these kindreds). These samples were tested and in 2009, Hill and associates identified germline mutations in DICER1 as the first and only genetic cause for this familial syndrome which is known as the DICER1-related tumor susceptibility syndrome.[12] With phenotype data alone, it was thought originally that 25% of PPB cases were familial, but we now know that approximately 70% of children with a PPB have a heterozygous DICER1 germline mutation, and 84% of those children inherited that mutation from a parent.[13] The remainder of PPBs arise from de novo germline mutations, mosaicism or tumor-limited DICER1 mutations.[13]

Cystic nephroma (CN) of the kidney, a multilocular cystic lesion, occurs in early childhood and is seen in approximately 10% of children with PPB.[11] The CN was the first and most commonly recognized extrapulmonary manifestation in children with PPB.[14] From that observation, an entire family of DICER1-related neoplasms is now recognized and any one of these various tumors can serve as a conduit into the identification of a patient with a DICER1 germline mutation (Table 1). In other words, the possibility that a child or young adult may have a germline mutation in this autosomal dominant disorder may begin with an enlarged nodular goiter or one or more of the several extrapulmonary tumors. We have encountered multiple examples of children and adolescents who presented with one of the DICER1-related tumors, like a PPB, and a CN is discovered or embryonal rhabdomyosarcoma of the cervix with a PPB type 1r in the lung. Others may develop one in a series of metachronous DICER1-related tumors over a several year period beginning with a PPB in early childhood and a nodular goiter and Sertoli-Leydig cell tumor of the ovary in adolescence.

Genetics of Pleuropulmonary Blastoma

The DICER1 tumor susceptibility syndrome appears to represent another example of Knudson's two-hit hypothesis to explain several tumor syndromes with an inherited germline mutation followed by a post-zygotic somatic mutation in the same gene.[15] Some hereditary predisposition syndromes affect one cell type though all of the various somatic cells have the particular mutation. In the case of the DICER1 syndrome, an entire range of cell types are involved in the tumor development from neuroectoderm, bronchoenteric endoderm and urogenital ridge mesoderm.

DICER1 encodes the DICER1 enzyme which is a member of the ribonuclease III family whose function is to cleave long double-stranded RNA into small RNAs (microRNA and small interfering RNA); these small RNAs have critical regulatory roles.[16] The vast majority of DICER1 cancers have biallelic mutations composed of one allele with a complete loss of function, i.e. nonsense codon or small indel leading to premature truncation of the mRNA and protein, and the second allele with missense base substitutions affecting one of five amino acids in the critical RNase IIIb domain of the protein. The combination of these two mutations leads to lack of an entire class of miRNAs; those generated from the 5p end of the precursor miRNA hairpin. The DICER1 protein has a central role in development as a switch so that its function is ubiquitous in organogenesis so that all organs are potential targets in the presence of this critical faulty protein. As a developmental switch in the lung and kidney, dysembrogenesis results in the formation of cysts which in the lung become PPB type I and CN in the kidney. These cysts remain as such or undergo malignant progression to PPB type II or III or anaplastic sarcoma from CN. In the PPB type I, there may be scattered individual cells with aberrant TP53 nuclear staining indicating mutation, but consistently identified to a lesser degree in PPB type II or greater degree in PPB type III with the implication that mutant TP53 has an important role in malignant progression. Table 1.

Future Directions

The understanding of pathogenesis and technical advances in delivery of genes, miRNAs and drugs to tumor cells specifically, opens the door to developing safer and more effective treatments in the future. Our translational research program has developed in vivo models of human PPBs using immunocompromised mice hosts and viable tumor fragments from children with PPB shipped overnight to our laboratory. These mice provide the testing ground for preclinical studies on newly developed drugs. Leveraging the unique genetics of PPB we are also developing a circulating tumor DNA biomarker assay both to improve early detection and also to provide objective evidence of therapeutic effect (or lack thereof). We hope that these advancements will help us as we work to solve the most important problems for PPB drug development. What is the best way to restore homeostasis in PPB cells? Should we replace the missing miRNAs predicted by in vitro studies to halt cell proliferation? Should we attempt to fix the TP53 or DICER1 mutations using advances in gene delivery or CRISPR technology, respectively? And if one or more of those methods are effective, can we solve the problem of delivering to PPB tumor cells specifically?

Conclusions

PPB is an established, unique pathologic entity of childhood which serves to validate the continued role of the light microscope in the identification of new diseases in this era of molecular genetics and pathology. When one of us (LPD) saw the first case in 1977 at the University of Minnesota Hospital, histopathologic features were an unfamiliar mixed spindle cell, small blastemal cell, rhabdomyoblast and cartilaginous neoplasm arising as a pulmonary-mediastinal mass in a 4-year-old boy. It took almost 10 years to collect an additional 10 cases and report them as PPB as the bona fide pulmonary blastoma of childhood.[3] We have made remarkable progress in the 30 years since this initial report. Through the extraordinary cooperation of the affected families, the combined efforts of numerous collaborators and the generous financial support of private and public sources, we continue our efforts in the investigation of this challenging familial tumor syndrome with its polymorphous manifestations.

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Disclosure

None reported. **MM**

Physician Suicide: A Call to Action

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To create the necessary cultural shift, individuals and institutions must not only agree that physician wellness is a priority, but also make tangible changes.



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Abstract

Physician suicide is topic of growing professional and public health concern. Despite working to improve the health of others, physicians often sacrifice their own well-being to do so. Furthermore, there are systemic barriers in place that discourage self-care and help-seeking behaviors among physicians. This article will discuss the relevant epidemiology, risk factors, and barriers to treatment, then explore solutions to address this alarming trend.

Background

Physicians are healers. They perform life-saving surgeries, cure cancers, and conduct groundbreaking research. They also spend nights and weekends on call, documenting in the electronic medical record, and staying abreast of the latest innovations. In the service of others, physicians often forget to care for themselves—and work through illness, including mental illness. Yet, physicians are human, too, and need care like anyone else.[1]

Current literature suggests mental illness and burnout are epidemic in physicians and medical trainees. One study found 20% of medical residents met criteria for depression while 74% met criteria for burnout.[2,3] Burnout—different from but correlated with depression—refers to the triad of emotional exhaustion, depersonalization and feelings of inefficacy resulting from chronic work-related stress.[4] Yet even with high rates of illness and knowledge of mental illness gleaned from their own coursework, physicians and trainees rarely seek treatment. The trend starts early: per Rotenstein et al. while 27.2% of medical students exhibited depressive symptoms, only 15.7% percent sought treatment.[5]

The consequences of this inaction are dire for both physician and patient. Residents with depression were 6.2 times more likely to make medication errors than non-depressed residents.[3] For physicians, avoidance of treatment may result in worsening illness—or even death by suicide. Documentation of increased suicide risk among physicians dates to the 19th century.[6] However, more recently, a 2004 meta-analysis found a modest increase in suicide rates of male physicians relative to the general population—and an even greater increase among female physicians.[7]

This paper will provide an overview of the state of suicide in physicians and medical trainees. More importantly, though, it will focus on solutions: emphasizing the importance of prevention and identification, as well as fostering a culture of wellness and support. The call to action is clear: "Physician, heal thyself."

Epidemiology

Suicide is the second most common cause of death for 10- to 34-year-olds in the United States.[8]

The average age of matriculating medical students in 2017-2018 was 24.[9] Thus, it should come as no surprise that medical students, residents, and attendings—like other Americans—are affected by suicide and mental illness.

Burnout and depression start early in medical training. At the time of matriculation, medical students have lower levels of depression and higher quality of life than age matched college graduates, but within months, their rates of burnout and suicidality exceed age-matched peers'.[10,11,12] There seems to be something inherent to medical school that contributes to reduced quality of life and emergence of mental health conditions.[5] This trend continues or even worsens in residency, fellowship, and beyond.

A 2015 meta-analysis of 54 studies examined the prevalence of depression and depressive symptoms in resident physicians across decades and around the globe.[2] They found a 15.8% increase in depressive symptoms during the first year of residency, across all specialties and countries of training. Over the course of training 20.9% to 43.2% of residents reported depressive symptoms, with symptoms increasing over time. This finding could be extrapolated to fellows, attendings, and other post-training physicians. Currently, the actual data for post-training programs is sparse.

No recent studies have evaluated the incidence of suicide in physicians or medical trainees, but older studies have noted increased risk among practicing physicians specifically. Male doctors have suicide rates as much as 40% higher than the general population, and female doctors up to 130% higher.[13] As discussed above, a number of cross-sectional findings also demonstrate higher rates of depression in medical trainees compared to the general population.[1] This is likely attributable to doctors' immense professional burden and (encouraged) neglect of their own well-being.[13] Given the risks of continued inaction, it is essential to actively address suicide and mental illness in this population.

Risk Factors

Suicide risk is comprised of many factors, including biological, psychological, and social components.[13] Major risk factors for suicide include mental illness and substance use disorders: 90% of individuals who die by suicide suffer from at least one of these.[1] Other notable risk factors include previous suicide attempts, hopelessness, access to lethal means, lack of an adequate support system, and chronic medical disorders.[13]

In addition to general risk factors, the elevated suicide risk among physicians is likely due to population-specific factors. Physicians are trained in toxicology and have readily available access to lethal medications, and depending on specialty, may have additional expertise that can be turned to lethal use.[1] Doctors are also exposed to high levels of personal and professional stress. They must make life-or-death decisions at work and are constantly at risk of malpractice claims. They may face high-stakes conflicts with administration or colleagues, and many struggle with marital conflict or issues at home because of work demands. To make things worse, increasing oversight and regulation has diminished physicians' autonomy, which has been linked to decreased job satisfaction and burnout.[4] Moreover, modern physicians are increasingly burdened by cumbersome electronic health records systems and stringent documentation requirements, which now frequently occupy more of their work hours than direct patient care.[14]

Substance abuse—which is itself a risk factor for attempted and completed suicide—is another occupational hazard. Female physicians have higher rates of alcohol abuse than women in the general population. Addiction is prevalent especially among emergency physicians, psychiatrists, and anesthesiologists.[13] Substance abuse is associated with impulsivity and worsening affective symptoms. Thus, it is hardly surprising that physicians with substance use disorders have elevated rates of suicide attempt and completion.

Additionally, medical training encourages stoicism. From medical school on, physicians are taught there is no room for error and are expected to perform to exacting standards. Physicians are trained to put patients first—often to their own detriment.[15] Trainees may believe they will be faulted for showing vulnerability, and thus avoid asking for help. This self-imposed isolation virtually guarantees burnout.[15] As a result, although physicians are typically better resourced than the general population, there remain significant barriers to seeking help.[1]

Barriers for Physicians

Most people with mental illnesses are untreated or inadequately treated—and physicians are no exception. In fact, in an analysis by Gold, physicians who died by suicide were less likely to be receiving mental health treatment than non-physicians who died by suicide.[16] Many barriers impede access to mental health care across the demographic spectrum, including culture-wide stigma and a shortage of qualified providers. Physicians, though, also face a unique set of challenges.[17]

Firstly, physician suicide is poorly understood. Not only is there inconsistent reporting and a paucity of

descriptive data, but investigative work in this area—including prevention-based studies—has been limited.[7] Secondly, despite extensive training, physicians often struggle to identify depression and other mental illnesses—in patients, colleagues and themselves.[18] Although mental illness can impair an affected individual's insight, the culture of medicine also plays a role in this phenomenon.[1,19] Stoic training environments normalize stress and distress as inherent or even requisite components of physician identity. Sleep deprivation and long hours are viewed as badges of honor. Physicians and trainees are encouraged to see their peers as competition, instead of support. As a result, physicians may feel alone or even like imposters. This lack of social support then correlates with greater burnout.[20] Isolated within competitive training environments, trainees often learn to ignore signs and symptoms of burnout, depression and suicidality. Thus the medical profession sustains a dangerous "culture of silence."[21]

Despite the fact that depression and suicidality are treatable, most affected physicians and trainees do not receive care.[16] Though physicians' propensity to avoid treatment is not yet entirely understood, it is likely multifactorial in nature. Stigma against mental illness remains pervasive in the medical community.[1,17,22] Even among a sample of psychiatrists, who theoretically should be less affected by stigma, 15.7% had self-medicated for depression.[23] Trainees and physicians are also less likely to seek routine medical care when compared to age-matched peers.[24] Twenty-five percent or more of physicians have no primary care provider.[1] This lack of regular medical care means a significant portion of the physician population will not receive routine depression screening. Physicians without primary care providers also miss opportunities for early interventions and mental health referrals that could ultimately prevent suicide.

Even with proper referrals, accessing mental health services is uniquely difficult for physicians and trainees. Many communities have a shortage of psychiatrists and therapists, and wait lists for new patient appointments are often lengthy. Physicians' work schedules often preclude attending appointments during regular office hours, and few health care providers offer extended hours such as nights or weekends. Even when they manage to obtain appointments, physicians may struggle to keep them due to emergencies or other unexpected clinical duties. Affordability is also a concern, particularly for trainees and early career physicians who carry heavy debt burdens.[1] Money becomes an even greater barrier when doctors pay out of pocket – which they often must in order to see a particular provider (ie, to avoid seeing work colleagues), to avoid insurance claims, or minimize wait times. Delivery of psychiatric care to physicians is also complicated, for patient and provider. Most providers have little experience treating fellow physicians, and many doctors are uncomfortable in the patient role, creating a challenging dynamic.

Confidentiality concerns are another barrier to seeking care.[25] Treatment requires physicians make very private disclosures to a mental health professional, who may also be a friend, colleague, or both. Given the stigma surrounding mental illness, shame is common. Physicians may also fear being outed to peers, where stigma may damage reputations and hinder career advancement. Many trainees and practicing physicians avoid care due to fears it will impact their medical licensure, and not without reason.[26] As of 2006, 78% of U.S. state medical boards asked about applicants' histories of mental illness. Only 33% of states focused on functional impairment due to mental illness rather than any lifetime history.[27] Beyond licensing concerns, physicians are also forced to consider the effects of mental health treatment on future cost and availability of professional liability insurance as well as disability, life, and health insurance policies.[28] As a result, some physicians forgo treatment altogether, while others attempt to self-medicate for psychiatric symptoms with potentially devastating results.

These barriers notwithstanding, there are also physician-specific protective factors for suicide that foster resilience. These include access to health care, experience in conflict resolution, family and community support, and religious or other beliefs valuing self-preservation.[1,15] In one 2013 study by Zwack and Schweitzer, interviews with 200 physicians revealed resilience factors including spiritual practice, physician self-awareness, gratification in work, accepting personal limitations, and learning how to better balance and prioritize.[29] Understanding both the risk and resilience factors for physician impairment and suicide is essential for crafting effective solutions.

Solutions

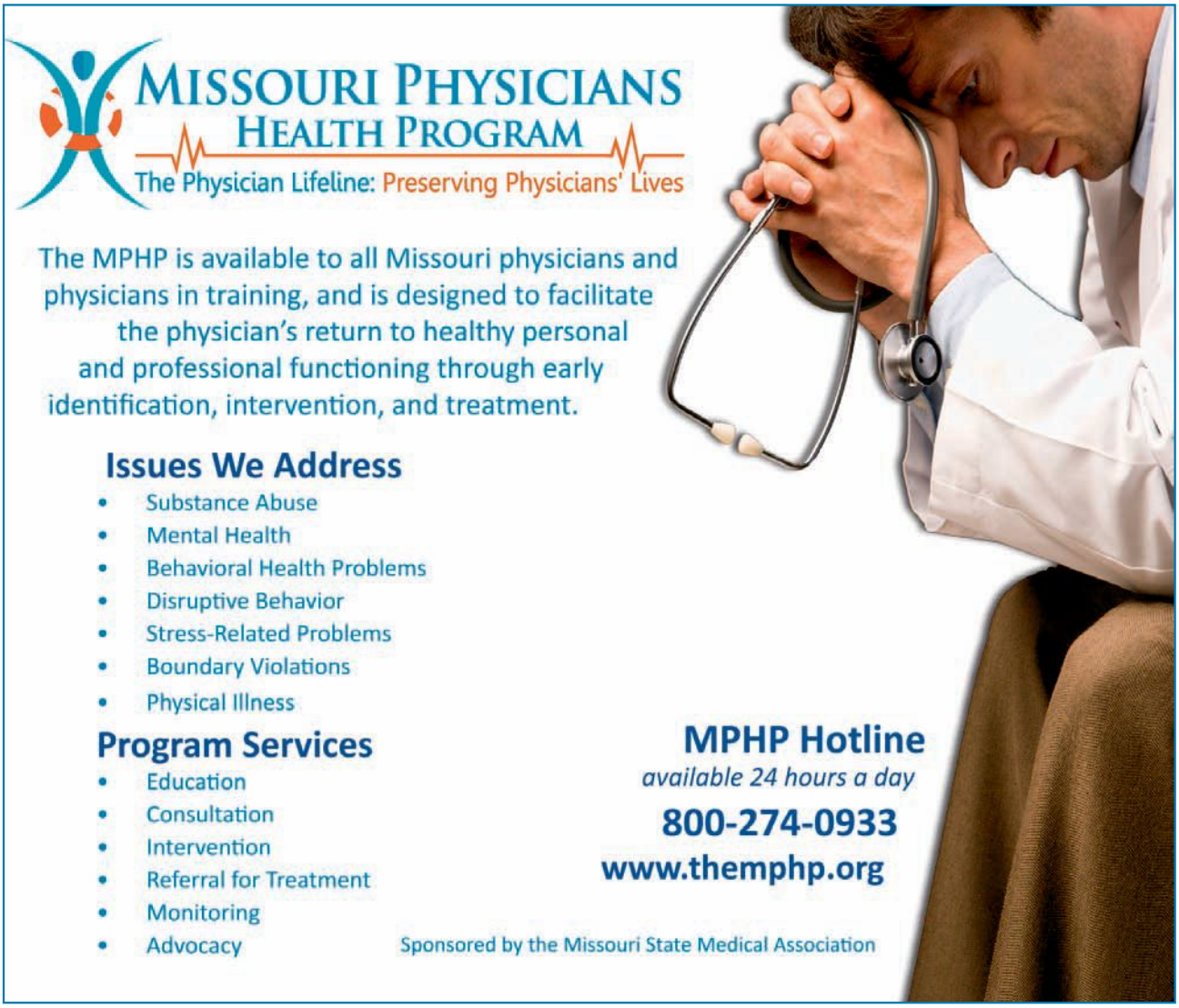
Many potential solutions to the problem of physician suicide have been proposed. These range from interventions on the individual level to large-scale initiatives designed to effect systematic change. However, relatively few strategies have been evaluated empirically.

Ideally, physician mental health should be addressed before physicians are contemplating or attempting suicide. Practicing physicians across all specialties should be taught to recognize signs of depression as well as risk factors for

suicide—both in themselves and others.[1] This can be accomplished through formal inclusion of this information in medical school and residency training curricula, as well as through continuing medical education (CME) courses for attending physicians. The American Psychiatric Association's website provides free wellness education, self-assessment items, and resources for physicians battling burnout, depression and addiction.[30] The American Medical Association also currently offers an online toolkit (Steps Forward) addressing physician distress and suicide.[17]

Medical students and residents with existing mood disorders should be connected with systemic supports early on, as should any physician with newly emerging burnout or mental health problems.[1] As time is a major barrier to accessing care, training programs should have policies allowing time off clinical duties to access mental health services—access itself is something mandated by the most recent Accreditation Council on Graduate Medical Education (ACGME) guidelines.[25] Subsidized or reduced-fee services reduce the financial disincentive for seeking care, especially among trainees and early career physicians.

Training-program-specific mental health clinics and referral networks for trainees are one way of ensuring access to treatment. Clinics with integrated care models can also decrease the stigma associated with seeking help.[19] In these models, primary care doctors not only provide routine health screenings and medical care, but also screen for mental health issues. Patients can then be referred immediately to in-house mental health practitioners as needed. However, creating an entire clinic for every training program is impractical, and physicians and trainees may feel uncomfortable with school or work-sponsored programs.



In these cases, keeping a regularly updated list of external practitioners (accepting new patients, and who take the trainee insurance) is also very useful. Universal well-being assessments (allowing trainees to opt out) is another means to encourage use of available resources.[31]

Physicians should also be supported in implementing lifestyle habits to mitigate symptoms of burnout, including regular exercise, meditation and maintaining a healthy social life.[32] Physical exercise is well known for its health benefits, which include reducing symptoms of burnout and depression.[33] Meditation, and more broadly, mindfulness, has gained popularity in recent years as another approach to enhance personal wellness. Mindfulness, which derives from the Zen Buddhist tradition is defined by Jon Kabat-Zinn as "paying attention in a particular way: on purpose, nonjudgmentally, and in the present moment."[34] Like exercise, mindfulness has been shown to reduce levels of anxiety and depression, and may contribute more generally to resilience.[35,36,37]

Loneliness—prevalent among physicians and trainees—has also been implicated in burnout.[38] Few interventions have specifically targeted this risk factor; however, some residencies and hospitals have implemented planned social events with the aim of improving collegial engagement.[39] Others have tried Balint groups or Schwartz rounds to create space for processing stress and patient care. Impacts on wellness have been mixed.[40]

Regardless of their current state of mental health, physicians and trainees should educate themselves about local legal protections for physicians, as well as the benefits and limits of physician health program in order to effectively advocate for themselves and colleagues.[1,28] Physicians should be aware of licensing requirements and the wording of mental health questions on their state licensing applications. For example, Missouri applicants no longer are asked to disclose mental illness unless it is functionally impairing. Information on the Missouri Physicians Health Program (PHP) is available at http://www.themphp.org/. Increased discussion and awareness also changes culture. Every day more physicians are disclosing their struggles—sometimes in one on one conversations, at other times in widely-read medical journals.[41] Some hospitals are hiring Chief Wellness Officers, suggesting worker wellness should be measured, nurtured and considered as important as the monetary bottom line.

Unfortunately, the actions of individual physicians are insufficient to prevent burnout, depression, and suicide. Changing the stoic culture of medicine will require top-down efforts.[36] These efforts should start at the level of the individual training program or hospital, and the first step is acknowledging and assessing the problem. From there, individual hospitals and physician workplaces can implement changes to strengthen the physician community. For example, employers can implement flexible scheduling, wellness days and other strategies to help busy physicians make time for their own health needs.

Professional organizations and governing bodies are also important change agents—in terms of education and policy. Professional organizations such as the AMA are making efforts to raise awareness and broadcast the benefits of seeking help for depression and suicidality. Groups such as ACGME and the Liaison Committee on Medical Education (LCME) have mandated more extensive mental health curricula for medical students and residents. The AMA and other professional bodies should prioritize development of model policies to help hospitals, malpractice insurers and state boards better manage physicians' mental health needs—and to encourage, rather than stifle, help-seeking. In recent years, many state licensing boards have moved towards nondiscriminatory policies requiring disclosure only of impairment, misconduct or malpractice—rather than any history of mental health diagnosis or treatment.

Researchers also have a role to play in understanding and addressing the issue of physician suicide.[37] It is essential to investigate the evolving patterns of mental illness and substance use disorders in physicians. Research into help-seeking behaviors, barriers to treatment, risk factors and protective factors is also necessary.[1] Future research must focus first on determining the incidence and correlates of physician suicide, utilizing not only psychological autopsies but other more sophisticated techniques. Development of accurate suicide-prediction algorithms is underway, and will help recognize the most at-risk physicians.[42] Lastly, interventional investigations and outcomes research can identify and validate methods to ease the burden of physician burnout, depression and suicide. There is an urgent need for development and dissemination of these best practices.

An estimated 300 physicians die by suicide per year, and rates may be rising.[43,44] Each time, the headlines are saddening—even shocking. Rather than remain in denial, however, it is essential to call for change. To create the necessary cultural shift, individuals and institutions must not only agree that physician wellness is a priority, but also make tangible changes. Otherwise, the ranks of the medical profession will continue to be decimated—and that is a loss for everyone.

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Disclosure

None reported.

MM

Pharmacogenomics: What the Doctor Ordered?

by Joel C. Eissenberg, PhD & Rajeev Aurora, PhD

The growing understanding of genes that control metabolism of specific drugs, combined with a comprehensive genotype of each patient, offers "precision medicine" in a very literal sense.



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Abstract

About half a million adverse drug reactions are reported in the US each year that result in disability, hospitalization or death. The efficacy or toxicity of a drug in a patient can be strongly influenced by their genetics as well as environment. Application of genomics to clinical pharmacology, "pharmacogenomics," promises to transform patient care and health resource utilization in the coming decade.

Introduction

Completion of the human reference genome sequence, together with the advent of inexpensive DNA sequencing and ever more powerful computers, have converged to open a new era of precision medicine. Precision medicine is defined as medical care tailored to optimize efficiency or therapeutic benefit for individuals or specific groups of patients. Applications of precision medicine include defining risk for disease (genomics), defining vulnerabilities of specific cancers (oncogenomics) and defining response to drugs (pharmacogenomics).

The observation that people can differ significantly in their response to the same drug or compound is not new. The Greek philosopher Pythagoras noted in 510 BCE that only some people who ate fava beans developed potentially fatal hemolytic anemia.[1] The English physician, Sir Archibald Garrod, was the first to suggest that genetic variation might underlie variability in drug action.[2] By the 1960s, genetic variability in patient responses to several clinically important drugs had been noted, formalizing the field of pharmacogenetics, the study of how a specific drug is affected by alleles of a specific gene.[3] With the arrival of inexpensive genome sequencing, the single-gene associations of pharmacogenetics have been expanded to surveys of entire genomes, hence pharmacogenomics.

Here, we summarize current insights gained from pharmacogenomics and their potential impact on medical practice.

A Brief Introduction to Pharmacology

A drug therapy can produce one of three responses: first, the patient can have the expected normal response resulting in the lowering of pathology and/or symptoms. Second, a patient can be a non-responder where no beneficial effect on the disease or symptoms is observed. Finally, a patient can have an adverse response ranging from developing a mild cough to mortality. A central goal of pharmacogenomics is to reliably predict from the patient's genome which response is expected. Non-response arises because the drug is unable bind to its target. Non-binding may be due to alterations

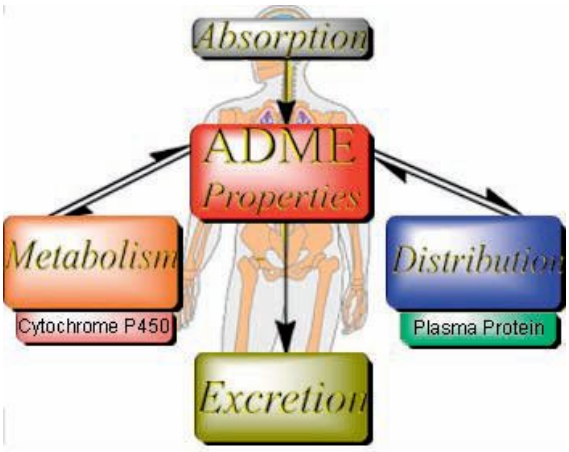


Figure 1

From: https://moulder.temple.edu/research-capabilities/vitro-adme-and-pharmacokinetics

(mutations) of the drug's binding site in the target. Bacteria and especially viruses have high mutation rates to evade seletion pressure of the immune system. Mutations in drug binding sites are more prevalent with antibiotics and antivirals because of the selective pressure of the drug. In addition, these organisms acquire antibiotic resistance genes. Changes in target sequences is also common in antineoplastic drugs because tumors also rapidly accumulate mutations due to genomic instability. Outside these situations, sequence variation in the patient population in the drug target binding site (e.g. in a receptor, kinase, or enzyme) does occur as well that can prevent binding of the drug. A second reason for non-response is that the drug concentration is below the level needed to produce efficacy of inhibition (antagonism) or activation (agonism). In contrast, often (but not always) adverse responses arise because of high concentration, causing off-target effects or directly dysregulating a pathway. The therapeutic concentration of the drug is determined by its absorption, distribution, metabolism and elimination from the body ("ADME" properties; Figure 1). Absorption refers to the process by which the drug moves into the blood from the site of administration. This process is usually passive, but may be carrier-mediated. Distribution refers to the dissemination of the drug in the body, and is governed by blood flow and the ability of the drug to enter cells. This may be mediated by protein carriers in blood. Oral medications are absorbed by the gastrointestinal tract and delivered to the liver through the hepatic portal system, where they may be subject to metabolism by the liver. Metabolism refers to the process by which drugs are structurally altered by cellular enzymes to either activate or inactivate them. Many drugs are delivered as inert "prodrugs" to facilitate their solubility for absorbtion and distribution, to later be metabolized into their active form. Other modifications may inactivate the drug or modify it to promote clearance. Excretion refers to the process by which the drug is eliminated from the body. Drugs may be excreted in their active form or after metabolism, and may leave via urine or bile.

The onset, peak and duration of drug activity depends on all of these mechanisms, which may operate with greater or lesser efficiency depending on the drug, the age or gender of the individual, ethnicity, pregnanacy or variation in various enzymes or transporter proteins.

Consider as an illustration simvastatin (sold as Zocor), one of the most common cardiovascular drugs to treat dyslipidemia and to manage patients at risk for cardiovascular disease. Simvastatin is an inhibitor of HMG Co-A reductase, the rate-limiting enzyme in endogenous cholesterol biosynthesis. The effective dose of active simvastatin in a patient is a function not only of dosage, but of metabolism:

- Organic Anion Transporting Polypeptide 1B1 (OATP1B1) is expressed mainly on the sinusoidal membranes of human hepatocytes and mediates influx of substrates from blood into the hepatocytes. A specific variant form of OATP1B1 results in doubling of the plasma concentrations of active simvastatin, increasing the risk of simvastatin-induced myopathy and potentially impairing its cholesterol-lowering action.[4]
- Simvastatin is taken orally as a prodrug, an inactive lactone that must be hydrolyzed in the liver to produce the active agent, simvastatin acid. Oxidative metabolism of simvastatin lactone in the liver is catalyzed by cytochrome P450 3A4 (CYP3A4) with contributions from CYP3A5, CYP2C8 and UDP-glucuronosyltransferase.[5-7] Inhibition of CYP3A4 by drugs such as itraconazole, verapamil or erythromycin, or by ingestion of grapefruit juice, significantly elevates simvastatin and simvastatin acid concentrations in plasma, again with potentially pathological consequences.[8-10]

Table 1 summarizes examples of medicines that interact with CYP3A4 to inhibit or induce simvastatin activity. With this illustration, it is clear that the efficacy of a drug in a given patient can vary depending on the variants at several or many genes, as well as drug-drug and drug-dietary interactions.

Table 1: Examples of medicines that affect simvastin metabolism through CYP3A4

Interacting medicines	Simvastatin recommendation
Potent CYP3A4 Inhibitors	
Macrolide Antibiotics	
Erythromycin	
Clarithromycin	
Azole Antifungals	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	Combination contraindicated
Protease Inhibitors	
Ritonavir	
Telaprevir	
Boceprevir	
Gemfibrozil	
Ciclosporin	
Danazol	
Moderate CYP3A4 Inhibitors	
Amiodarone	
Amlodipine	
Verapamil	Do not exceed 20 mg/day
Diltiazem	
Nicotinic Acid (>1 g/day)	
Minor CYP3A4 Inhibitors	
Azithromycin	Case reports of rhabdomyolysis. Use with caution and monitor
Roxithromycin	
CYP3A4 Inducers	
Carbamazepine	
Phenytoin	Probable reduction in concentration. Monitor lipid profile
Rifampicin	
St. John's Wort	

Modified from: http://www.medsafe.govt.nz/profs/PUArticles/March2014StatinsAndCYPInteractions.htm

Genetics, Genomics and Inherited Variation in Drug Responses

Twin studies provide strong evidence for a genetic basis for much of the variability in drug metabolism. Briefly, monozygotic twin pairs ("identical twins") are genetically identical, whereas dizygotic twin pairs ("non-identical twins") share only half of the same alleles for each gene, like any full siblings. But unlike singleton siblings, dizygotic twin pairs share the same birth rank, maternal age and generally more similar rearing environments. Thus, greater variation in drug metabolism in dizygotic compared to monozygotic twin pairs is taken as evidence for underlying genetic factors.

Twin studies to measure drug metabolism variability for nearly a dozen different drugs and in four different countries from the late 1960s through the 1970s found that for most drugs, variation in response between monozygotic twin pairs was virtually nil, while variation between dizygotic twin pairs was more similar to the general population.[11] In several cases, pedigree studies point to a mono- or polygenic basis for variation, although the identities of the specific genes and alleles weren't determined. It is likely that the variability in response to specific drugs has a polygenic inputs, even where a single variant provides much of the predictive power.

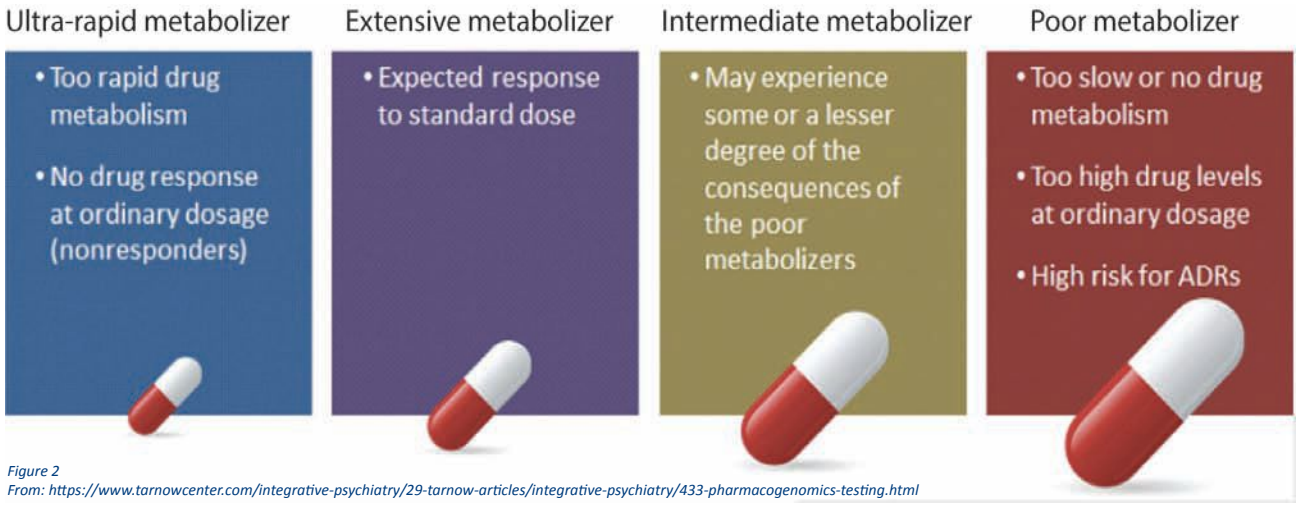


Figure 2
From: https://www.tarnowcenter.com/integrative-psychiatry/29-tarnow-articles/integrative-psychiatry/433-pharmacogenomics-testing.html

The advent of molecular genetics has identified key genetic factors underlying this variability. These factors include ion channels, receptors and, importantly, a family of enzymes that metabolize drugs on their way to the bloodstream, the cytochrome P450 enzymes.

The Cytochrome P450 Gene Family and Drug Metabolism

The human genome encodes 57 cytochrome P450 (CYP450) genes. The products of these genes are heme-containing protein enzymes, most of which are expressed in the liver. The reaction catalyzed by CYP450 enzymes is the oxidation of diverse substrate molecules. Ninety percent of drugs are metabolized by a few members of the CYP450 superfamily: CYP1A2, CYTP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5.[12] Cytochrome P450 3A4 (CYP3A4) is found in the cells lining the small intestine and colon and in the liver, and is implicated in the bioinactivation of about half of all drugs.[13]

The therapeutic efficacy of most drugs, as discussed above, is dictated by the steady-state level of active drug in circulation, which usually depends on how efficiently these compounds are metabolized as substrates of one or more CYP450 enzymes. Accordingly, variants of key CYP450 enzymes that alter catalytic activity can have a significant impact on effective dosing. Variants that lower activity can result in effective blood concentrations of drugs that may be toxic. Variants that increase activity can depress effective blood concentrations of drugs below the level of therapeutic benefit. Individuals carrying specific variants are binned into four categories of drug metabolizers: ultrarapid, extensive, intermediate and poor (Figure 2).

Table 2 summarizes a few examples of therapy recommendations based on CYP450 metabolizer status. The anticoagulant drug warfarin, for example, is used to treat thrombotic disorders but is notoriously problematic for effective dose regulation. Either excessive bleeding or excessive clotting can result if serum levels stray outside the target range. Warfarin is a substrate for the cytochromes CYP1A1, CYP1A2, CYP2C9 and CYP3A4.[14] Would patients benefit from testing for cytochrome genotype before initiating warfarin? The results of clinical studies have been somewhat mixed, but the Clinical Pharmacogenetics Implementation Consortium and the FDA have endorsed cytochrome P450 genotype-based warfarin dosing.[15] As sequencing costs continue to plummet, and additional variant associations are validated, the application of pharmacogenomics to warfarin dosing should become standard clinical practice. Examples of drugs for which pharmacogenomics testing has clinical significance are listed in Table 3.

Pharmacogenetics and Opioid Dependency

Opioid abuse has reached epidemic proportion in the U.S. Over 11 million Americans misused prescription opioids in 2016, and the number of

Table 2. Examples of drugs for which pharmacogenomics testing has clinical significance

drug class	drug	gene with clinically important variants
anticoagulant	Warfarin	CYP2C19 (cytochrome P450) VKORC1 (vitamin K epoxide reductase)
antineoplastic	Irinotecan	UTG1A1 (UDP-glucuronosyltransferase)
	6-mercaptopurine	TPMT (thiopurine methyltransferase)
	Thiopurine, Azathioprine	TPMT (thiopurine methyltransferase)
	Tamoxifen	CYP2D6 (cytochrome P450)
antidepressants	Amitriptyline/nortriptyline	CYP2C19/CYP2D6 (cytochrome P450)
	Nortriptyline	CYP2D6 (cytochrome P450)
	Coxepin	CYP2D6 (cytochrome P450)
	Paroxetine	CYP2D6 (cytochrome P450)
	Sertraline	CYP2C19 (cytochrome P450)
narcotic analgesic	Codeine	CYP2D6 (cytochrome P450)
	Tramadol	CYP2D6 (cytochrome P450)
immunosuppressant	Tacrolimus	CYP3A5 (cytochrome P450)

Modified from: https://www.slideshare.net/NarjesSadr/pharmacogenomics-50413003

opioid-related deaths increased more than four-fold since 1999.[16] 64% of the public reports having been prescribed an opioid for pain, and estimates for the rate of addiction among those taking prescription opioids for chronic pain range as high as 23%.[17]

Twin studies suggest that about half of the risk for opioid addiction is genetic.[18] One approach to genome-wide mapping of risk factors for opioid dependence is genome-wide association (GWA) studies. In this approach, the combination of many different single-nucleotide variants at sites throughout the genomes are surveyed for a population to determine whether certain variants are more common in an at-risk group. Statistically significant associations implicate nearby genes in the risk mechanism. In a 2014 study, Gelernter et al.[19] tested 890,000 variants in 5,697 individuals, including subjects with opioid and/or other substance dependence and controls. Starting with a GWA approach, then refining further by additional analyses, this study uncovered statistically significant associations with four genes required in potassium signaling pathways, as well as genes implicated in calcium signaling and calcium-mediated neurotransmitter release. Subsequent studies confirm these results and expanded the list of candidate genes, including the gene encoding the μ opioid receptor itself, the primary mediator of analgesia by opioids and their therapeutic agonists.[18]

Just as the risk of opioid addiction varies between individuals, so too the response to opioid addiction therapy can differ between patients. Metabolism of methadone and buprenorphine, two of the most widely used pharmacotherapies to treat opioid use disorders, varies among individuals.[20] Both are known substrates for metabolism by cytochrome P450. However, a suite of studies over the past several years have failed to consistently indict variants in the cytochrome P450 genes in altered methadone metabolism, likely owing to small sample sizes.[20] Current correlations between alleles of other genes and methadone or buprenorphine, while intriguing, emerge from underpowered candidate gene studies and thus are not clinically actionable. Adoption of pharmacogenomics strategies, together with larger study cohorts, will likely uncover key factors predictive of individual patient experiences.

Polypharmacy and Drug Metabolism

Polypharmacy, defined as the simultaneous use of multiple drugs by a single patient for one or more conditions, can be beneficial or harmful. For example, in patients with coronary artery disease, the combination of an angiotensin converting enzyme inhibitor, a calcium channel blocker, a diuretic, a statin and an antiplatelet drug is clearly beneficial, as it reduces the risk of a vascular event by two thirds or more.[21] In this case, different drugs targeting different mechanisms converge on the same condition.

Table 3. Examples of therapy recommendations based on CYP450 status

Drug	CYP phenotype	Therapeutic recommendation	Reference
Clopidogrel (heart attack and stroke prevention)	CYP2C19		Ref. 28
	ultrarapid metabolizer or extensive metabolizer	Dose recommended by drug label	
	intermediate metabolizer or poor metabolizer	Increased risk for reduced response to clopidogrel. Alternative antiplatelet therapy recommended if no contraindication (e.g. prasugrel or ticagrelor)	
Tricyclic antidepressants	CYP2D6		Ref. 29
	ultrarapid metabolizer	Avoid TCA use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose. Therapeutic drug monitoring should be used to guide dose adjustments.	
		Dose recommended by drug label	
	extensive metabolizer	Consider a 25% reduction of recommended starting dose. Therapeutic drug monitoring should be used to guide dose adjustments. Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose. Therapeutic drug monitoring should be considered to guide dose adjustments.	
	intermediate metabolizer or poor metabolizer	Avoid TCA use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose. Therapeutic drug monitoring should be used to guide dose adjustments.	
	CYP2C19		
	ultrarapid metabolizer	Dose recommended by drug label	
		Dose recommended by drug label	
	extensive metabolizer	Avoid tertiary amine use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19 such as the secondary amines nortriptyline and desipramine. For tertiary amines, consider a 50% reduction of recommended starting dose, and use therapeutic drug monitoring to guide dose adjustments.	
	intermediate metabolizer		
	poor metabolizer		
Omeprazole (GERD, peptic ulcers, Zollinger-Ellison syndrome)	CYP2C19		Ref. 30
	ultrarapid metabolizer	Be alert to lack of response. For eradication of *H. pylori*, increase dose by 100-200%. For other conditions, consider dose increase by 100-200%. Dose recommended by drug label	
	extensive metabolizer	Dose recommended by drug label	
	intermediate metabolizer	Dose recommended by drug label	
	poor metabolizer		

Modified from: Dong et al., 2018, Ref. 15

Table 4. Examples of potentially clinically relevant CYP inhibitor-substrate pairs

Cytochrome P450 enzyme and inhibitor	substrate
CYP2C9	
Amiodarone	Warfarin
CYP2C19	
Clarithromycin	Omeprazole
Fluoxetine	Omeprazole, Rabeprazole
CYP2D6	
Fluoxetine	Metoprolol
Paroxetine	Flecainide
Perhexiline	Vetoprolol, Venlafaxine
Doxepin	Codeine
Flecainide	Metoprolol, Paroxetine, Codeine
Quinine	Amitriptyline, Codeine, Metoprolol
sertraline	Metoprolol, Risperidone
CYP3A4	
Clarithromycin	Atorvastatin
Diltiazem	Simvastain, Atorvastatin, Methadone
Verapamil	Simvastatin, Atorvastatin

Modified from Ref. 22.

On the other hand, geriatric patients are often treated for a variety of unrelated conditions, leading to problematic interactions. In a 2014 study, Kerr et al.[22] examined the prescriptions of 1045 community-dwelling elderly Australians for co-prescription of CYP450 inhibitor and corresponding substrate drugs, together with assessments for depression, quality-of-life and cognitive status. The study found a 6.2% incidence of potentially inappropriate CYP inhibitor–substrate combinations, and physical quality of life was lower in patients with potential CYP drug-drug interactions. Noteworthy, the most common CYP inhibitor–substrate pairs were the CYP3A4 substrates simvastatin or atorvastatin combined with the CYP3A4 inhibitors verapamil or diltiazem. This combination can result in increased plasma levels of the statins, increasing the risk of myopathy or rhabdomyolysis. A limitation of this study was that patients with several conditions, including psychotic symptoms, were excluded. Many antidepressants and antipsychotics are CYP2D6 inhibitors and/or substrates; thus, this study may have missed these clinically relevant CYP450 interactions. Table 4 summarizes examples of a few pairs of drugs that are either inhibitors of, or substrates for, the same CYP450 enzyme and could be co-prescribed in a clinical setting.

The area of drug-drug interactions deserves more study, but it can be anticipated that one drug can alter the ADME properties of a second drug. However, the drug-drug interactions may not be wholly predictable (or predictable for a fraction of drugs) based on genomic information. This is because one drug may induce (or repress) gene expression of one of the members of a gene family that determines the ADME, but this dynamic change cannot be predicted from the genome sequence, and such drugs should be co-prescribed with caution.

In some cases, individual variation in drug response is due to diet, not genetics.[23] While a comprehensive review of the roles of diet and digestion in drug metabolism is beyond the scope of this review, the effect of grapefruit and certain related fruits (Seville oranges, limes and pomelos) bears remark.

For over 25 years, it has been known that grapefruit can profoundly affect drug metabolism.[24] The furanocoumarins found in grapefruit are metabolized by CYP3A4 to derivatives that bind irreversibly to the CYP3A4 enzyme, inactivating it.[25] In practice, what this means is that grapefruit consumption can dramatically increase the oral bioavailability of drugs that are dosed to be compatible with normal CYP3A4 activity, with adverse affects in some cases. Other foods that can affect drug metabolism included licorice, which can increase risk of digoxin toxicity and reduce the efficacy of diuretics and blood pressure reducing drugs, and chocolate, which in large amounts can increase the effect of Ritalin or decrease the efficacy of Ambien.

Diets can also affect the gut microbiome in a patient. There are emerging reports that demonstrate that changes to the gut microbiome alters ADME and hence efficacy of a drug. Indeed, this avenue of nascent research has been named pharmacomicrobiomics, and is an active area of discovery.[26] While changes in the gut microbiome alter efficacy and toxicity of a drug, it is not determined by the patients' genome. Therefore pharmacomicrobiomics studies are outside the scope of this review.

The Future of Pharmacogenomics

Driving progress in pharmacogenomics will be the major stakeholders:

- Patients and their physician(s) will be incented to obtain personalized pharmacogenomic data to maximize benefits and minimize risk/side effects of the drugs they consume;
- Insurers (private insurers, Medicare, Veterans Administration) will welcome pharmacogenomic data to minimize the prescription of drugs to patients who won't benefit. Precision medicine has the potential to increase efficiency of health care costs (currently over 18% of GDP);
- Drug companies will exploit pharmacogenomics data to target drug development for the largest market. They will also benefit from pharmacogenomics to avoid drug-related adverse effects that could prevent them from maximizing a return on development investment.

At the center of the clinical application of pharmacogenetics is the question of who controls the patient data. Do insurance companies, which end up having to pay for expensive drug regimens, have a right to demand genomic data to support the choice of drug and dosage before approving reimbursement? The emerging view is that there are are two kinds of data: one is the patient's data, which would belong to the patient and require patient permission to use; the second is aggregated de-identified data, which could be available without the patient's specific consent but would be given at the time the sample was obtained for sequencing.

The current state-of-the art is to use next-generation sequencing for targeted genes (panels). Current panels identify 355 variants in nearly sixty genes, and are likely to grow in the near future. These 355 variants cover about 240 FDA-approved drugs [Ref. 1; Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org/genes-drugs/)]. The goal of pharmacogenomics is to extend the benefits of precision medicine to the pharmacy. The predictive power of pharmacogenomics will continue grow exponentially, as DNA sequencing costs fall and detailed reliable risk associations continue to be uncovered. As genome sequencing continues to get cheaper, eventually everyone could have their genome sequence on a card to be assessed whenever a prescription is written. Currently, the modest amount of data connecting specific DNA sequence variants to specific effects on drug metabolism limits pharmacogenomic applications. As more variants that influence the metabolism of specific drugs are discovered, increasingly precise statistical models will be able to weight the respective contributions of these variants to drug metabolism. In this way, patient genomes can be evaluated to set optimal dosing on an individual basis. A barrier for the implementation of pharmacogenomics is the translating of genetic laboratory test results into actionable prescribing decisions. This will require education of patients, health care providers and pharmacists, as well as payers, to effectively use this tool.

Conclusion

The potential of modern pharmacy has been constrained by the fact that different patients react differently to different drugs. Presently, the clinical approach has been to prescribe the drugs that have worked for most people and wait for the outcome. In response to adverse outcomes, dosage can be tweaked or alternative compounds can be substituted. In the case of anti-tumor drugs, the time required to properly tailor chemotherapy to patient metabolism on a trial-and-error strategy could be fatal.

Pharmacogenomics offers an alternative to this ad hoc strategy. The growing understanding of genes that control metabolism of specific drugs, combined with a comprehensive genotype of each patient, offers "precision medicine" in a very literal sense.

An important caveat is that while variants in the protein-coding regions of key metabolic genes can easily be identified using current annotation data, variants that affect expression levels of genes without affecting the gene products can also have important clinical consequences, but are difficult to identify with our current knowledge.

Nevertheless, the future of pharmacogenomics is bright. As Francis Collins presciently observed: " . . . if everybody's DNA sequence is already in their medical record and it is simply a click of the mouse to find out all the information you need, then there is going to be a much lower barrier to beginning to incorporate that information into drug prescribing. . . . And it should improve outcomes and reduce adverse events."[27]

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Disclosure

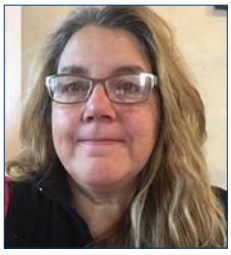
None reported. **MM**



The ED is seeing new medical problems such as acute ingestions, psychosis, chest pain – myocarditis, and cannabinoid induced hyperemesis.[26]

Emergent Medical Illnesses Related to Cannabis Use

by Karen Randall, DO & Kathleen Hayward, MD



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Abstract

As more states rush to legalize the use of cannabis products, both medically and recreationally, there are more medical harms being seen in emergency departments (ED). The tetrahydrocannabinol (THC) concentration today is much stronger than the concentration from the 90s. In the 1990s most typical "joints" contained 1-3 mg of THC. Today, plants are being raised and modified to produce a higher concentration of THC. In turn, the amount of cannabidiol (CBD) is decreasing. Previously, people would smoke 1-3 mg of THC. The typical joint in Colorado contains 18 mg of THC or more. Currently, in the ED, we see patients who self-report smoking 2,000 mg or more of THC in a day. In 2015, 2.6 million individuals started cannabis use, 45% were 12-17 years of age.[3] This brief report includes some of the more common illnesses that have been seen over the last four years of legalization in Colorado, and is by no means inclusive of all the potential problems that can occur. Among the many untoward effects being seen, illnesses that will be discussed are: cannabinoid associated hyperemesis, acute psychosis, cannabinoid catatonia syndrome, acute myo-pericarditis and ingestions.

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS), once thought to be rare, is now being seen almost daily. The exact mechanism for the causation of symptoms is unclear, but thought to be due to the endocannabinoid receptors in the GI tract. Most commonly affected are the heavy users (those that smoke 20 or more times/month).[2,3] CHS has been seen with primarily THC, but there are reports of CHS with CBD. Young people, typically between the age of 18-40 are presenting with frequent bouts of acute nausea, vomiting, and moderate to severe abdominal cramping.[9] Patients present with the combination of screaming and loud vomiting, which has led to the term "scromiting". Patients may report that their symptoms are temporarily relieved by hot showers. They may recurrently present to the ED. Many have had CTs, GI evaluations, and endoscopy. Testing results are usually negative. Endoscopy may show gastritis or esophagitis from the repeated vomiting. Our ED has had two recent cases of pneumomediastinum related to the repetitive vomiting from hyperemesis. Hyperemesis symptoms are very resistant to typical antiemetics (ondansetron, promethazine, etc) and over the last four years, treatment with Haloperidol 5 mg or Olanzapine 5 – 10 mg IM, seems to work more effectively.[6,7,8] It takes longer for onset of action but patients have far better control of their symptoms with either of these two medications. Patients are at risk for acidosis, decreased serum bicarbonate, and acute renal failure due to significant dehydration. Significant alterations in electrolytes can be seen. Most patients refuse to believe that cause of their symptoms is cannabis products (traditional thoughts are that cannabis is the treatment for nausea and vomiting) and are very reluctant to stop using. The treatment of choice is abstinence for a prolonged period of time (typically over several weeks and sometimes, months).

Acute Psychosis

Case report: 16 y/o male presents to the ED after having had a psychotic break while on vacation in a nearby state. Family drove him home, fearing that they could not put him safely on a plane. While in the ED, the patient was behaviorally controlled. There is no family history of psychosis, schizophrenia, or other mental illness. The patient himself has no history of mental illness. He was evaluated and admitted to the off-site adolescent unit. While there, he had another psychotic episode. He attacked three health care workers, stabbing a security officer in the process. He was tased three times without behavior control. He was ultimately chemically sedated. Repeated drug screens were positive for cannabis only. He was treated and released and within two weeks, had another psychotic episode, and attacked family members with enough force to cause subdural hematomas in one.

Case report: 72 y/o female presents to the ED with acute psychosis, yelling, and hallucinating. The patient was visiting from out of state and was staying with her grandson, a bud tender (working in the marijuana industry). She started with edibles. Initially, she had no response to a single serve edible, so continued to eat several. She acutely started yelling, was actively hallucinating, and was combative. She was brought to the ED and she was sedated with lorazepam. She was observed for several hours prior to returning to baseline.

There is a clear association of acute psychosis with cannabis use. A large systematic review shows that there is an increased risk of psychosis, with a dose-dependent response effect and greater in those who use more frequently.[1] A 15- year longitudinal study done in Sweden shows that there is an increase in relative risk of developing schizophrenia among high cannabis users compared to those who do not use.[2] The ED has been seeing more episodes of acute psychosis in the ED where cannabis is the substance being abused.[25]

Acute Cannabinoid Catatonia

This is typically seen in older patients with acute excessive ingestions. I have seen four cases thus far. One patient was brought to the ED as an acutely altered person. He was awake, eyes were open, but he was not responsive to commands or to painful stimuli. He was brought in as a stroke secondary to his mental status changes. He had a non-focal exam. CT, CTA head and neck, and MRIs were negative. The patient was essentially catatonic for at least 10 hours. Labs and EKG were unremarkable. Vital signs remained stable/normal with normal oxygenation throughout his ED stay. At the end of an expensive work up, family added the ingestion of THC butter history. Butter is THC extract to use in baking products. He ingested the equivalent of 22 cookies. Each cookie has six 10 mg doses. This gave the patient an estimated total of 1,320 mg total THC ingested. He was observed for several hours and gradually improved. This pattern of presentation seems to be typical for older patients with a larger, acute ingestion. Vital signs typically remain stable and care is usually supportive. There have been some case reports of patients responding to intravenous naloxone infusions.[4,5] Acute excessive ingestions are most likely to happen with edibles.

ACS, Acute Pericarditis

In our ED, there have been at least three cases of young men, with substernal chest pain, + EKG changes

and elevated troponins. The age ranged from 19-23. None had significant risk factors other than heavy cannabis consumption. Past medical histories were negative. These patients were admitted and troponins were trended. They all had low positive troponins. All left the hospital with a diagnosis of myopericarditis. [18] Additionally, there have been case reports of acute coronary syndrome (ACS). In humans, cannabis is known to cause elevated blood pressure, tachycardia (elevated heart rate can persist for hours after cannabis use)[17], peripheral vasodilation[13] As patients use more cannabis consistently, the risk of ACS increases, especially in men. Mitterman et al. – Determinants of Myocardial Infarction Onset Study cohort – interviewed 3882 Acute MI patients. They conclude that smoking marijuana was associated with a 4.8 times increased risk over baseline, within one hour of marijuana use.[19] Patients who present to the ED with chest pain, despite the age, need to have EKG, troponins, and more formal evaluations when there is a history of recent and/or chronic cannabinoid use.

Acute Ingestions

Ingestions typically occur with edibles. Acute intoxication secondary to ingestion of edibles has been seen in both the young as well as older patients. Colorado State laws require packaging labeling with dosages. However, the appearance of the edibles (cakes, candies, cookies, chocolate, etc.) makes the product attractive and this has lead to acute accidental ingestions. For adults, acute toxic ingestions occur secondary to excess ingestion of product. Many may take one edible (portion size in Colorado is 10 mg) and then continue to consume edibles because they are not feeling the "high". With edibles, onset of euphoria is delayed and first pass metabolism leads to unpredictable onset and quality of the effects felt. However, once ingested, the person is on an unalterable course until the THC is metabolized. This can lead to a sudden onset of acute alteration in consciousness and acute changes in behavior.

A case to illustrate: a family driving from out-of-state to Colorado for vacation, stopped at the border of Colorado, and the mother purchased edibles. She ate one, not feeling the effect, ate at least two more. Suddenly, while riding in a car moving down the highway, she became acutely psychotic, began screaming and trying to get out of the car. She was brought to the ED, sedated and observed for several hours. She ultimately recovered and was discharged home after a prolonged ED stay.

Summary

The ED is seeing a variety of problems related to the use of cannabis products. Most of the literature on cannabis and side effects is based on low potency THC. Since legalization, in Colorado, the potency has dramatically increased and consumption is often in the grams (as opposed to mg's previously). More people are consuming higher quantities of THC on a daily basis and with this use pattern, we are now seeing increased harms and side effects. The ED is seeing new medical problems such as acute ingestions, psychosis, chest pain – myocarditis, and cannabinoid induced hyperemesis.[26]

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Disclosure

None reported.

MM

Review Summary

Source: Annals of Internal Medicine

Acute Illness Associated with Cannabis Use, by Route of Exposure: An Observational Study

by Andrew A. Monte, MD, PhD, Shelby K. Shelton, MPH, Eleanor Mills, BS, Jessica Saben, PhD, Andrew Hopkinson, BS, Brandon Sonn, MS, Michael Devivo, BA, Tae Chang, MD, Jacob Fox, BA, Cody Brevik, MD, Kayla Williamson, MS, and Diana Abbott, PhD

Background

Little is known about the relative harms of edible and inhalable cannabis products.

Objective

To describe and compare adult emergency department (ED) visits related to edible and inhaled cannabis exposure.

Design

Chart review of ED visits between 1 January 2012 and 31 December 2016.

Setting

A large urban academic hospital in Colorado.

Participants

Adults with ED visits with a cannabis-related International Classification of Diseases Ninth or 10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM), code.

Measurements

Patient demographic characteristics, route of exposure, dose, symptoms, length of stay, disposition, discharge diagnoses, and attribution of visit to cannabis.

Results

There were 9973 visits with an ICD-9-CM or ICD-10-CM code for cannabis use. Of these, 2567 (25.7%) visits were at least partially attributable to cannabis, and 238 of those (9.3%) were related to edible cannabis. Visits attributable to inhaled cannabis were more likely to be for cannabinoid hyperemesis syndrome (18.0% vs. 8.4%), and visits attributable to edible cannabis were more likely to be due to acute psychiatric symptoms (18.0% vs. 10.9%), intoxication (48% vs. 28%), and cardiovascular symptoms (8.0% vs. 3.1%). Edible products accounted for 10.7% of cannabis-attributable visits between 2014 and 2016 but represented only 0.32% of total cannabis sales in Colorado (in kilograms of tetrahydrocannabinol) during that period.

Limitation

Retrospective study design, single academic center, self-reported exposure data, and limited availability of dose data.

Conclusion

Visits attributable to inhaled cannabis are more frequent than those attributable to edible cannabis, although the latter is associated with more acute psychiatric visits and more ED visits than expected.

Primary Funding Source

Colorado Department of Public Health and Environment.

Source

Ann Intern Med. 2019;170:531-537. doi:10.7326/M18-2809 **MM**

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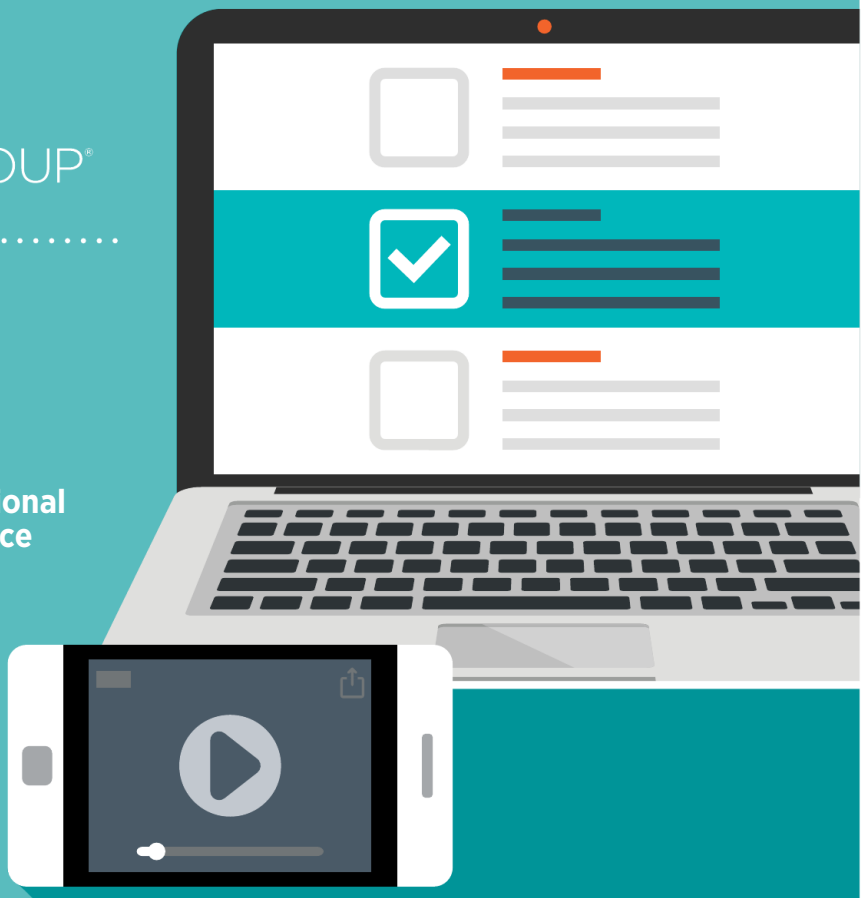
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OFFICIAL MINUTES & REPORTS



Meet MSMA's 2019-2020 President

James A. DiRenna, Jr., DO
Kansas City, Missouri

Contact: james.direnna@blessinghealthsystem.org

James A. DiRenna, DO, FAAFP, Diplomat of the American Board of Ambulatory Medicine, from Kansas City, Missouri, will serve as President of the Missouri State Medical Association in 2019-2020. He was formally installed in Kansas City, Missouri, April 6, 2019, during MSMA's 161st Annual Convention.

Dr. DiRenna was born and raised in Kansas City, Missouri. He graduated from Wentworth Military Academy in the Reserve Officers' Training Corps, serving as the Brigade Commander and a Distinguished Military Graduate. He earned his Bachelor's degree in History and Political Science at Missouri Valley College. He took his commission from the U.S. Army serving as a Second Lieutenant and attended Armor School in Fort Knox, Kentucky.

After returning from Vietnam, Jim DiRenna attended Park College and Northeast Missouri State to acquire the necessary courses to become a candidate for medical school. He attended his Allopathic and Osteopathic medical programs at the University of Missouri–Kansas City and North Texas State University. He then traveled to the University of New Jersey for his post graduate studies, becoming Board Certified in Family Medicine in 1991.

Returning to Kansas City, Dr. DiRenna joined his father James A. DiRenna, Sr., DO, (General Surgeon), at the DiRenna Clinic, Inc. This clinic from 1954 to 1985 was a modified Health Maintenance Organization for the three Brotherhood of Teamsters local unions in the Kansas City metropolitan area. Dr. DiRenna, Sr. moved on to administration at Park Lane Medical Center, while Dr. DiRenna, Jr. and the clinic remained in Raytown as a family practice clinic with the addition of multi-specialties. In the 1990s Dr. DiRenna, Jr. expanded to two clinics with one in the northland and one in Raytown. With the support of the Greater Kansas City Building and Construction Trades and Operating Engineers Local 101, Innovative Health Services (IPA) was established, involving 200 physicians and six hospitals.

Under managed care growth, it became clear there was a need for involvement in both political and medical community affairs. In 1993, Dr. DiRenna sought representation for Osteopathic physicians with the Kansas City Metropolitan Medical Society (KCMMS). Conversations with Larry Rues, MD, from Baptist Medical Center and members of the KCMMS Board were welcoming, and a board seat for Dr. DiRenna was added. He realized that managed care was an issue competing in the world of medical economics at the local, state, and national levels. Advocacy for medical awareness and honoring the role of the physician–patient relationship became his focus.

The inability of controlling tort reform and impending insurance crisis in Missouri led Dr. DiRenna as an individual physician to seek collaboration in joining a group of family practitioners in St. Joseph, Missouri. In 2004, in a cooperative effort, he became an employed physician with Comprehensive Family Care–Heartland Health, later to become Mosaic Healthcare. With his interest and fellowship in urgent care medicine, he helped develop the first urgent care center for Heartland Health in St. Joseph.

A long-time supporter of organized medicine, Dr. DiRenna currently serves on six medical association boards and committees for state and national medical organizations. His awards and affiliations include Physician Emeritus and Life Member of the Missouri Society of the American College of Osteopathic Family Physicians, receiving their Family Physician of the Year award in 2013. In 2011–2012, he was President of the Missouri State Board of Registration of Healing Arts. He served as Chief of Staff of Park Lane Medical Center from 1994–1999, and was on their Board of Directors from 1998–2001. Norman Vinn, DO, President of the American Osteopathic Association, recognized Dr. DiRenna as "a Guardian of the Osteopathic Profession."

He is a long-time avid supporter of the Royals, Chiefs, as well as Golden Gloves boxing. He also serves as the Curator for the DiRenna Award, given to the top male and female high school basketball players in the metropolitan area.

As a retired Army Colonel, Dr. DiRenna proudly served as a Combat Officer in the Vietnam War and a Medical Officer of the 325th General Hospital and 139th Medical Group where he was Chief of Professional Affairs and Liaison to the Fifth Army. He received the Combat Infantry Badge, Air Medal, Purple Heart, and two Bronze Stars for his service. His last duty was supporting Operation Enduring Freedom.

Under his tenure as Missouri State Medical Association President, Dr. DiRenna will focus on collegiality, collaboration, and communication among Missouri physicians and medical students. He will promote his belief that medicine is a profession – not just a job. **MM**

Alliance Installs 2019-2020 President

Gill Waltman

St. Louis, Missouri

Contact: gillian.waltman@gmail.com



Gillian Waltman, 2019-2020 Alliance President, was born and raised in England, the oldest child of Michael and Sheila Roper-Hall, both still living independently at home at almost 95. Gill has one sister and two brothers, all still in England. Her father is a retired ophthalmic surgeon and the family has a strong tradition in the medical field with several generations of physicians.

Gill, still known as 'Roper-Hall' in her professional world, was educated in England and did her specialty training in binocular vision and eye movements at Moorfield's Eye Hospital in London.

She came to the United States in the 1970s to pursue a fellowship in neuro-ophthalmology at Washington University – where she heard a lot about a very shy, very bright young cornea surgeon and former resident and was away at the time serving as a major in the U.S. Army at Walter Reed Hospital. She and Steve Waltman met at an ophthalmology conference in Las Vegas.

After a short transatlantic romance, Gill returned to Washington University to accept a position in the Department of Ophthalmology where Steve was already back on the faculty, and they were married soon after. The Waltmans have lived in St. Louis since then. Steve rose quickly through the academic ranks at Washington University establishing the cornea transplant service and Eye Bank for the bi-state area and becoming a full professor at a young age.

Gill and Steve have two children; Belinda and Michael now in their mid-30s. Belinda is a physician, currently Medical Director of a Los Angeles County Health initiative for the underserved. She is married to Matt, a biophysicist doing stem cell research at Caltech in Pasadena, and have two children. Mike is a business strategist for a series of startup companies in the Bay Area. He and his wife Michelle (an entrepreneurial culinary expert) have one child.

Gill is currently a full Professor of Ophthalmology at Saint Louis University. She is a prolific author, and an experienced reviewer and board examiner who is internationally recognized for her clinical expertise and research experience in the field of adult strabismus and neuro-ophthalmology. She considers herself an "ambassador" for the university and the profession as she travels around the U.S. and abroad.

Gill is also involved in other activities. She plays a lot of tennis, loves to hike with her women's hiking group, and is on the board of the Saint Louis Chamber Chorus serving as vice president for the past four years.

Between her busy schedule at the hospital, with lots of work travel to present papers at various conferences, regular family visits to California, England and Long Island, and heading off on exotic trips with Steve (now all seven continents), Gill has always found time for the Alliance. She became a member back in 1986 when Chris Bohigian was president, being elected to the board a year later when she was elected as the SLMMS Alliance Vice President for Health. Since then she has held numerous positions as an officer at the local and state level.

She has been on the SLMMS Alliance board in various positions and held three consecutive terms as its president from 2003-2006 and was co-president more recently from 2015-2017.

Gill has held leadership positions as MSMA Alliance Vice President for Health, Legislation, and many years as Recording Secretary before being elected as the president-elect. **MM**

State of the Association: Presidential Address

by Joseph Corrado, MD, MSMA President

It has truly been an honor and privilege to serve the Missouri State Medical Association this past year as your president.

I have cherished every minute. With my wonderful wife Donna, at my side, we were able to visit and be part of each of the eight adjoining state medical societies at their annual conventions, along with every county medical society in Missouri to which we were invited. Being in solo private practice, at times this was not easy. We have been to every corner of our great state and have shared part of our terrific journey with you in the photos published in *Missouri Medicine*, and cherish the many new friendships we have made along the way. We really have a dynamic and exceptional medical community here in Missouri and echo the same optimism and sense of camaraderie as my predecessors have. It is great to have actually been to your individual cities and towns. One really can appreciate caring physicians in their natural habitats.

That's not to say that there are not challenges ahead and change is upon us, as I have eluded to in prior discussions but we are blessed to have an extremely competent and professional staff serving our every needs of the organization and I feel very confident that this well hold true for many more years to come, as Mr. Pat Mills continues his inaugural year also. We are in great hands!

So, what's been going on this year? As more bills than usual have received hearings and been voted out of committee and received floor debate and with little collaboration between the two branches of government, things became adversarial, which in turn resulted in an unexpected resignation at the Governor's mansion.

As the 2019 session is underway, with the new Governor, Mike Parson has touched on several issues in his State address, including rural access to healthcare, increased funding for mental health, telemedicine improvements, and the problem of the opioid epidemic.

MSMA's lobbyists are busy at the Capitol this year advocating on behalf of physicians and carrying out the policy considerations of this House of Delegates. Our lobbyists have worked tirelessly to advance a package of prior authorization reforms that would reduce the burdensome PA requirements on physician offices and staffs, and increase timely access to necessary treatments.

House Bill 751 and Senate Bill 298 were authored by MSMA. Both have received hearings and have been voted out of their respective committees. Now, they await floor debate by the entire House and Senate. If passed, these bills would:

- require insurance companies to inform a physician immediately once a prior authorization decision is made.
- prohibit any changes or limitations to a prior authorization for 45 days.
- provide a definition of "medical necessity" to be used by physicians and insurers for purposes of prior authorization.
- require insurance companies to adopt an electronic prior authorization system by 2021 to help eliminate the current overly-burdensome paper/fax machine/telephone system.
- allow physicians and patients to access insurers' prior authorization clinical criteria.
- requires a physician, who practices in the same or similar specialty, to review prior authorization appeals.
- makes a prior authorization certification a guarantee of payment.

Another issue gaining steam as the legislative session continues is the debate over advanced practice registered nurse scope-of-practice. MSMA is comfortable with the status quo.

The APRNs are seeking to put a broad scope-of-practice definition into the law that would allow the Board of Nursing to develop a list of all the things APRNs would be allowed to do, such as "order and interpret diagnostic tests." MSMA is opposed to this. We feel the collaborating physician is in the best position to know what clinical tasks their APRNs are competent to perform. A scope-of-practice list, developed by Jefferson City bureaucrats, can only interfere with this relationship. And allowing some APRNs to perform tasks they are inadequately trained for can negatively impact patient care.

Finally, don't forget about a statewide prescription drug monitoring program. MSMA continues the push to make Missouri the last state to adopt a PDMP. House Bill 188 is in the Senate and will surely receive some debate before the legislature convenes in May.



Drs. James DiRenna, Joe Corrado, and Charles Van Way presented a "Roll of Honor" dedicated to the nine MSMA physicians who lost their lives during the Great World War 1914-1918. Doran Cart, Senior Curator, National World War One Museum and Memorial, is placing the brass plaque inside the Museum.



David McKinsey, MD, (and co-authors Joel McKinsey, MD, and Maithe Enriquez, PhD) received the Art Gale Freedom of Expression Award from MSMA President Dr. Corrado.

Our lobbyists are hopeful that this is the year we add a PDMP to the list of clinical tools a physician can utilize to assist patients with opioid use disorder. However, a number of senators remain opposed to the creation of a statewide prescription database. They will attempt to add amendments in order to derail the bill. For example, an amendment that forces all physicians to check the PDMP every time they write a prescription is something MSMA is stridently opposed to. Passing PDMP will not be easy.

These are just three of more than 600 pieces of legislation that our lobbying team tracks during the legislative session. For more information, please refer to the MSMA Legislative Committee's Report to the House of Delegates, which can be found in your Delegate Handbook under tab B.

The importance of grassroots lobbying has never been greater than it is today. Missouri physicians must become more active in the legislative process.

When our lobbyists ask us to contact our legislators on an issue, we must act!

When the MSMA White Coat Day arrives on our calendar, we must act!

When we are given the opportunity to create a personal relationship with our senator or representative, whether through a campaign contribution or a simple handshake, we must act!

I know that we, as physicians, are incredibly busy. But, at the Capitol, insurance companies want to keep us from being paid, trial attorneys want a cut of what we do get paid, and mid-level providers want to take over our practices.



Harvey Tettlebaum, JD, received the *Missouri Medicine* Distinguished Editorial Service Award from *Missouri Medicine* Editor John Hagan, MD.

WE MUST ACT! I encourage you to seek out the MSMA lobbyists at this convention. They have plenty of ideas on how you can help.

In closing, I again wish to thank all of you for giving me the honor to serve as your Missouri State Medical Association President this year. Although it started under unusual circumstances, I hope that you will agree with me that we have had a great year together. It has been most fulfilling and rewarding and I certainly have no regrets.

Ciao e dio vi benedica! "Good Bye and God Bless" **MM**

Presidential Inauguration Address

by James DiRenna, DO, MSMA President

I am truly humbled, proud and excited to be selected, nominated and accepted by the membership present to become the president of the Missouri State Medical Association for its 161st year of existence.

As I look around the room – I am amazed. I see friends, acquaintances, and peers that I can honestly say are here not only for a medical gala but every one of you has a trusted story with me which is attached to your presence and depth of friendship. I am honored and grateful.

I sincerely welcome you.

When I sat down to write my thoughts for tonight, it came to me not to address the philosophy of medicine or the many issues we read and strategize about for our practices but go right to the core of how I see medicine today.

I love the little clichés we speak that go to the heart of the subject cutting through the maze and landing on a sincere focus with the meaning and purpose of that thought. Such as "Do no harm," "Don't criticize another physician until you walk in their shoes," and "It is what it is." These are statements that are basic, carry foundation and have closure.

A recurring theme throughout my career and one that has been an honor to watch how our profession is able to communicate, collaborate, and have good camaraderie. These three gifts will be my mantra for our next year.

I had the opportunity as Chair of the MSMA Council to be responsible for the entertainment for our dinner the evening before our board meeting. This would be a discussion with theme or question about a topic. I went from table to table with a microphone asking physicians, spouses, children, and guests their view and opinions of the evening's topic. The session was light, humorous and full of surprises.

At the last meeting I asked the group – "If you had the opportunity to have a one on one with Dr. Corrado – what would you want to discuss?"

About 30-40 subjects were brought up. Some agreed with others on topics. Much thought came from this cross section of people with subjects as varied as points on a compass. These are just a few that came to mind: more affordable healthcare, why physicians bring their work home with them at night, membership and losing physicians in Missouri, opioid crisis, and the much belabored – getting rid of daylight savings time, should physicians have more advocacy in helping patients, medical student debt, EMR problems and solutions, program burnout, which now I am leaning toward the new discussion of calling it moral injury.

The dinner meeting lasted a bit over two hours. Some of the subjects mentioned would have taken weeks to process, analyze, and prepare conclusions. Even with this group known to be medically involved, it showed young and new physicians to Missouri they had an association that was strong in its commitment, had resources available and ready to assist physicians and their patients showing a mechanism of understanding and process. This type of involvement is a collaborative effort to support organized medicine.

Ladies and gentlemen, in addition to being the Show Me state - Missouri is a collaborative state. We are known for being creative and producing progressive ideas in healthcare. One good example was the cooperative political and medical effort behind the assistant physician bill. This legislation formulated a new license for Missouri enabling graduate medical students who did not make the residency match to be licensed in a collaborative manor with a physician mentor while having the direction, guidance and time to be employed and seek future residency programs.

I learned about advocacy the usual and customary way – walking through the halls of the Capitol in Jefferson City. Medical school is nothing compared to the education you receive at the capitol during session. I had a true mentor with my father who was medically and politically involved, but the actual process and mechanism of legislation was better explained to me by the late Sen. Ronnie DePasco. The doctors who were involved in the political battles felt lobbying was a privilege, even considering a degree of nobleness – they were messengers with high ideals from home which could advance across the state.

It was my pleasure to be involved in the white coats ceremony at Kansas City University of Medicine and Biosciences and the White Coat Day last month at the capitol in Jefferson City. White Coat Day offered us the opportunity to give Missouri legislators our views on prior authorization, protecting physician payments, improving access to care, scope of practice, and ending the opioid crisis.



AMA President Barbara McAneny, MD, with MSMA President James DiRenna, DO.



2019-2020 Officers, from left: Alex Hover, MD, Council Chair; George Hruza, MD, President Elect; James DiRenna, DO, President; and George Hubbell, MD, Council Vice Chair.

My adventure with MSMA started in 1993. I was involved with moving through the healthcare environment, making clinical rounds at multiple hospitals due to insurance criteria. These requirements were discussed in detail during meetings at Jackson County Medical Society who changed their name to Metropolitan Medical Society which we know as MetroMed. Kansas City is known as District 7 of the Missouri State Medical Association. Being on staff at Baptist Medical Center in Kansas City, I was an active member in the family practice department while chairing the committee of credentials at Preferred Health Professionals, a physician organization involved with Baptist Medical Center. There, I was reunited with a dedicated physician who was chair of the Goppert residency program at Baptist. Dr. Larry Rues and I were grade school friends from St. Francis Xavier at 52nd and Troost. Discussions started and a request was made for a board seat at MetroMed for the Jackson County Osteopathic Medical Society. I was granted a voting board position. So my camaraderie lesson began on the playground. The physicians of District 7 gave me the opportunity of moving through leadership positions where I became a vice counselor and counselor. I would like to thank Drs. Lancer Gates, Betty Drees, Mark Taoromina, Rebecca Hierholzer and Charles VanWay for their cooperation and support on my road to the presidency. I've had the distinct pleasure in working with Patrick Mills and his staff at MSMA. They've always been very supportive, knowledgeable and helpful with any request. I'd also like



2019-2020 Alliance Officers, from left: Diana Corzine, Sana Saleh, Gil Waltman, Kirk Doan, Jennifer Gast, Kelly O'Leary, and Kathy Weigand.

to acknowledge our legislative leader Jeff Howell and Heidi Geisbuhler for the energy and work that is produced in their department. Our lobbyists do a great job for us in the capitol.

I am honored for this recognition and will serve you to the best of my ability. To my patriots and friends in the military, I say never forget. In the end it always come down to "You are what you do; not what you say you will do."

We practice the art of medicine which is problem-oriented medicine. The definition of a good clinician is one who is accessible, available, accountable, and affordable. In my career within the boundaries of the standard of care in the midwest, I have practiced medicine with a passion as an art and a profession - not just a job.

Thank you and now let's celebrate! **MM**

161st House of Delegates Resolution Actions

Below are the resolutions and actions taken at MSMA's 161st (2019) House of Delegates. For more information, contact Patrick Mills at pmills@msma.org or call 800-869-6762.

Resolution 1 – Chronic Traumatic Encephalopathy
(Referred to MSMA Council)
RESOLVED, that the Missouri State Medical Association (MSMA) take a position that tackle football should not be played before the age of high school; and be it further

RESOLVED, that the MSMA would support any legislation to this effect introduced in our state.

Resolution 2 – Addressing Healthcare Needs of Children of Incarcerated Parents
(Substitute Resolution Adopted)
RESOLVED, that our Missouri State Medical Association encourage the American Medical Association to support comprehensive and evidence-based care that addresses the specific healthcare needs of children with incarcerated parents and promote earlier intervention for those children who are at risk.

Resolution 3 – Creation of a Women Physicians Section with the Missouri State Medical Association
(Amended Resolution Adopted)
RESOLVED, that our Missouri State Medical Association create a Women Physicians Section (WPS); and be it further,

RESOLVED, that the Women Physicians Section serve to enhance leadership among Missouri's women physicians, better engage women physicians in the MSMA, address issues unique to the practice of women physicians, and advocate on behalf of women's health issues and the health of women physicians.

Resolution 4 – Support for Bleeding Control Training in Schools
(Amended Resolution Adopted)
RESOLVED, that the Missouri State Medical Association support legislation encouraging the training of high school students and teachers in life-saving bleeding control techniques.

Resolution 5 – Sexual Health Education in Missouri Public Schools
(Amended Resolution Adopted)
RESOLVED, that our Missouri State Medical Association support the implementation of age-appropriate, medically accurate comprehensive sexual health education that stresses the importance of abstinence in preventing unwanted teenage pregnancy and sexually transmitted infections, teaches contraceptive choices and safe sex, and integrates sexual violence prevention, including conversations about consent, and the social and economic impact of teen pregnancy; and be it further,

RESOLVED, that our MSMA opposes the sole use of abstinence only based sex education.



Reference Committee A. Clockwise from top left: William Taylor, MD, Springfield; Frances Mei Hardin, MD, Columbia; Brian Biggers, MD, Springfield, Chair; Rebecca Hierholzer, MD, Leawood, Kansas; and William Dorzab, MD, Raytown.



Reference Committee B. Clockwise from top left: Priya Jain, UMKC Medical Student; Diane Jacobi, MD, Mexico; Fola Fasuyi, MD, Rolla; Ted Groshong, MD, Columbia, Chair; and Steve Smith, MD, Ballwin.

Resolution 6 – Abolishing Prior Authorization Requirements for Opioid Use Disorder Treatment
(Substitute Resolution Adopted)
RESOLVED, that the Missouri State Medical Association support legislation to abolish prior authorization requirements for FDA-approved generic medications for the treatment of opioid use disorders; and be it further

RESOLVED, that the Missouri State Medical Association support legislation to encourage that generic medications to treat opioid use disorders be reclassified on to the lowest cost-sharing tier of a health plan's pharmacy benefit.

Resolution 7 – Supporting Common Sense Climate Change Legislation
(Referred to MSMA Council)
RESOLVED, that our Missouri State Medical Association release a formal statement endorsing that climate change is a real phenomenon with health consequences; and be it further

RESOLVED, that our Missouri State Medical Association will advocate on behalf common sense policies to reduce carbon emissions, reduce environmental pollution, and improve the air/water quality of Missouri; and be it further

RESOLVED, that our Missouri State Medical Association work with relevant stakeholders to lobby for Missouri legislation that will reduce greenhouse gas emissions and improve the environment for the sake of Missouri patients.

Resolution 8 – The Study of Physician and Trainee Suicide Based on the Show-Me Compassionate Medical Education Project
(Amended Resolution Adopted)
RESOLVED, that our MSMA work with relevant stakeholders in the creation of a national database of student, resident/fellow, and physician suicides to track statistics in regards to those who commit suicide and relevant factors surrounding their suicide; and be it further

RESOLVED, that our MSMA endorse resident, fellow, and medical student participation on the Show-Me Compassionate Medical Education Committee.



Running the House of Delegates, from left: Sam Page, MD, Vice Speaker; Jo-Ellyn Ryall, MD, Parliamentarian; and Lancer Gates, DO, Speaker.

Resolution 9 – AMA Delegate Term Limits
(Resolution Adopted)
RESOLVED, that the MSMA Bylaws be amended to create term limits for delegates (not alternate delegates) of the Missouri AMA delegation; and be it further

RESOLVED, that if this amendment to the MSMA Bylaws is approved it will go into effect beginning with the MSMA Convention in 2021 with past service being counted when considering the 2021 Missouri AMA delegation composition; and be it further

RESOLVED, that the MSMA Bylaws, Chapter III. House of Delegates, Section 10 of said Bylaws include: "MSMA members may serve a maximum of eight years as an AMA Delegate; however, term limits are suspended while serving as a member of an AMA House of Delegates Council." **MM**

Miss an Annual Convention General Session?

Presentations for MSMA's General Sessions can be found at www.msma.org/convention-wrap

Credentials & Appointments

The 161st Annual Convention of the Missouri State Medical Association was held at the Westin Kansas City Hotel at Crown Center, Kansas City, Missouri, April 5-7, 2019. Lancer Gates, DO, Kansas City, Missouri, presided as Speaker of the House of Delegates. Parliamentarian was Jo-Ellyn Ryall, MD, St. Louis.

The Committee on Credentials announced that there were 8 Officers, 18 Councilors, and 59 Delegates in attendance for the Opening Session of the House of Delegates.

This report and the minutes of the 160th Annual Convention as published in the May/June 2018 issue of *Missouri Medicine* were approved.

At the Second Session of the MSMA House of Delegates, the Committee on Credentials reported that there were 8 Officers, 19 Councilors, and 86 Delegates in attendance.

Reference Committee A members were: Brian Biggers, MD, Springfield – Chair; William Dorzab, MD, Raytown; Frances Mei Hardin, MD, Columbia; Rebecca Hierholzer, MD, Leawood, KS; and William Taylor, MD, Springfield. Reference Committee B members were: Ted Groshong, MD, Columbia – Chair; Omofolarin (Fola) Fasuyi, MD, Rolla; Diane Jacobi, MD, Mexico; Steve Smith, MD, Ballwin; and Priya Jain, UMKC medical student.

The MSMA Nominating Committee members were: Organized Medical Staff Section – James Conant, MD, St. Joseph, Chair; 1st District – Tom Weigand, MD, St. Joseph; 2nd District – Sandra Ahlum, MD, Hannibal; 3rd District – Edmond Cabbabe, MD, St. Louis; 4th District – Keith Ratcliff, MD, Washington; 5th District – Clark Andelin, MD, Mexico; 6th District – Amanda Turner, MD, Nevada; 7th District – Michael O'Dell, MD, Kansas City; 8th District – Jim Blaine, MD, Springfield; 9th District – Omofolarin Fasuyi, MD, Rolla; 10th District – Douglas Wallace, MD, Cape Girardeau; International Medical Graduate Section – Louis DelCampo, MD, Springfield; Young Physician Section – Sarah Florio, MD, Lee's Summit; Resident and Fellow Section – Nathan Nolan, MD, Columbia; Medical Student Section – Samantha Lund, Washington University. **MM**



Dr. DiRenna stands with William Haynie, MD, Family Physician from Butler, Missouri, and MSMA member since 1963. Dr. Haynie counts the 2019 Annual Convention as his 44th meeting in attendance.

Sponsors & Exhibit Partners

MSMA thanks the following Sponsors and Exhibit Partners who supported the Annual Convention through educational grants.

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- Envision Physician Services
- Home State Health
- Missouri Drug Card
- Missouri Health Connection
- Board of Healing Arts
- Missouri Health Connection
- Missouri Telehealth Network
- MO DHSS - Medical Marijuana Regulation
- MO Physicians Health Program
- MoDocs
- Moneta Group
- MSMA Health Education Foundation
- MSMA Insurance Agency
- NWMO MGMA / GKC MGMA
- Primaris
- ProAssurance
- PSN – Premier Specialty Network
- SHINE of Missouri
- SilverCreek RCM
- Triggerfish Corporation
- U.S. Army Physician Recruiting Service

MM

MSMA Elects Leadership

MSMA Officers

President
James DiRenna, Jr., DO, Gladstone
President Elect
George Hruza, MD, Chesterfield
Secretary
Brian Biggers, MD, Springfield
Treasurer
David Pohl, MD, St. Louis
1st Vice President
Michael Weaver, MD, Kansas City
Honorary Vice President
Sandra Ahlum, MD, Hannibal
Honorary Vice President
Rebecca Hierholzer, MD, Leawood, KS
Immediate Past President
Joseph Corrado, MD, Mexico
Speaker
Sam Page, MD, St. Louis
Vice Speaker
Timothy Swearengin, DO, Rogersville

Councilors

Chair, MSMA Council
Alexander Hover, MD, Springfield (8th District)
Vice Chair, MSMA Council
George Hubbell, MD, Osage Beach (5th District)
1st District
Robert Corder, MD, St. Joseph
2nd District
John Memken, MD, Hannibal
3rd District
Elie Azrak MD, Chesterfield
Robert Brennan, MD, St. Louis
Inderjit Singh, MD, St. Louis
Christopher Swingle, DO, St. Louis
4th District
Kevin Weikart, MD, Lake Saint Louis
5th District
Lisa Thomas, MD, Columbia
6th District
David Kuhlmann, MD, Sedalia
7th District
Betty Drees, MD, Kansas City
Lancer Gates, DO, Kansas City
Marc Taormina, MD, Lee's Summit
8th District
Mathew Stinson, MD, Springfield
9th District
Lirong Zhu, MD, Rolla
10th District
Sharon Wallace, MD, Cape Girardeau
Organized Medical Staff Section
Peggy Barjenbruch, MD, Mexico
International Medical Graduate
Sri Kolli, MD, St. Louis
Young Physician Section
Ramona Behshad, MD, Chesterfield
Resident & Fellow Section
Daniel Young, MD, St. Louis
Medical Student Section
Scott Berndt, Columbia

Vice Councilors

1st District
Robert Weigand, MD, St. Joseph
2nd District
Sandra Ahlum, MD, Hannibal
3rd District
Vacant
4th District
Keith Ratcliff, MD, Washington
5th District
Clark Andelin, MD, Mexico
6th District
Amanda Turner, MD, Nevada
7th District
Michael O'Dell, MD, Kansas City
8th District
Brian Curtis, MD, Joplin
9th District
Omofolarin (Fola) Fasuyi, MD, Rolla
10th District
Douglas Wallace, MD, Cape Girardeau
Organized Medical Staff Section
Hossein Behniaye, MD, Hannibal
International Medical Graduate
Louis DelCampo, MD, Springfield
Young Physician Section
Sarah Florio, MD, Lee's Summit
Resident & Fellow Section
Joanne Loethen, MD, Westwood, KS
Medical Student Section
Priya Jain, Kansas City



Jared Lammert, MD, Columbia, provides testimony during the Reference Committees.

AMA Delegates & *Alternate Delgates

Elie Azrak, MD, Chesterfield
Edmond Cabbabe, MD, St. Louis
James Conant, MD, St. Joseph
Warren Lovinger, MD, Nevada
Charles Van Way, MD, Kansas City

*Joseph Corrado, MD, Mexico
*George Hruza, MD, Chesterfield
*Ravi Johar, MD, Chesterfield
*Michael O'Dell, MD, Kansas City
*Samantha Lund, Washington University

AMA Past President
David Barbe, MD, Mountain Grove

AMA Regional Resident & Fellow Alternate Delegate
Frances Mei Hardin, MD, Columbia

AMA Regional Student Delegate
Manna Varghese, UMKC

Alliance

President
Gill Waltman, St. Louis
President Elect
Diana Corzine, St. Joseph

MM

Summary of Council Actions: 2018-2019

Meeting of March 25, 2018 – St. Louis

Joseph Corrado, MD, Mexico, President, presided. George Hruza, MD, St. Louis, was elected Chair. Alexander Hover, MD, Springfield, was elected Vice Chair. Brian Biggers, MD, Springfield, was elected Secretary. David Pohl, MD, St. Louis, was elected Treasurer.

Meeting of July 22, 2018 - Jefferson City

MSMA has created a tool within the website to help physicians recruit new members and highlight MSMA accomplishments for patients and physicians: www.msma.org/engage. Council members heard all about it during the July Council Meeting at Lake of the Ozarks.

Advocacy

MSMA will be hosting a White Coat Rally Day on March 5, 2019. MSMA members and staff attended an Opioid Policy Advisory Council meeting on July 25. They addressed the issue of letters being sent by MO HealthNet to prescribers. The Board of Healing Arts is reviewing 2018 legislation, Missouri Physicians Health Program, and Colorado's Safe Haven law at its August board meeting. MSMA recommends physicians to serve on that Board. MSMA recently sent letters of concern regarding Missouri HB 1516 (chiropractors billing for services provided to MO HealthNet patients), the U.S. Senate Bill 2575 concerning audiologists' access to Medicare patients, and the APRN Compact. MSMA President, Joseph Corrado, MD, has visited five out of Missouri's eight contiguous states, attending state society annual meetings. He also attended the AMA National Advocacy Conference in Washington, D.C., and the AMA Annual Meeting in Chicago. Missouri Medicine Editor John Hagan, MD, and MSMA staff continue to work to get the journal published online through PubMed Central, PubMed, and Medline.

SHINE

Mr. Jonathan Smith, Regional Manager – SHINE of Missouri, outlined the many benefits of the health information exchange and shared information on the approximate annual cost to connect. Live, open demonstrations are available online. Mr. Smith encouraged members to invite him to their society meetings or CME events; he will be glad to give a presentation on SHINE.

Medical Economics

Resolution #5 – Creating a Standardized Priority Menu for Physicians Calling in Prescriptions
Missouri State Medical Association will work with the Missouri Pharmacy Association to identify measures to promote speedy and safe communication between physicians and pharmacies. In the State of Missouri, including, but not limited to, seeking to have a physician access number placed very early in the automated queues of as many pharmacies as possible.

CME

Peggy Barjenbruch, MD, thanked Betty Drees, MD, for her work as Chair of the Commission on Continuing Education. Dr. Barjenbruch stated that planning has begun for the 2019 Annual Convention, April 5-7, 2019, at the Westin Crown Center in Kansas City. Actions and Recommendations on Resolutions from the 2018 Annual Meeting are available on MSMA's website under the Annual Convention tab.

Physicians Health Committee

Lisa Thomas, MD, reviewed the MPHP reports and discussed the importance of the MPHP. Hospital realize a great financial benefit when physicians receive assistance

Appointments

- Councilor Advisors for Committees and Commissions are
- David Kuhlmann, MD – Commission on Medical Economics
- Peggy Barjenbruch, MD – Commission on Continuing Education
- George Hubbell, MD – Commission on Public Affairs
- Lisa Thomas, MD – Physicians Health Committee
- Missouri Medicine Editorial Board - Kathy Perryman, MD, will replace Jim Gibbons, MD, for anesthesiology.

District Reports (selected)
District 3

I.J. Singh, MD, reported that the St. Louis Metropolitan Medical Society (SLMMS) hosted its opioid symposium for physicians on Saturday, April 21 and

offered an overview of the results of SLMMS' Second Annual Physician Insurance Survey. Results will appear in the August issue of the St. Louis Metropolitan Medicine magazine. In September, SHINE of Missouri will host a CME program on Quality Matters: The New Data Dilemma.

District 5

Dr. Thomas welcomed Stephen Foutes, MSMA staff, as the new executive director of the Boone County Medical Society. She reported that Donna Corrado and Mary Heimburger are trying to reorganize the BCMS Alliance. Boone Hospital's lease with BJC ends in 2020. BCMS hosted a SHINE dinner on June 25.

District 6

David Kuhlmann, MD, introduced Amanda Turner, MD, as the new District 6 Vice Councilor.

District 7

Lancer Gates, DO, reported that KCMS hosted its summer social for Kansas-based members on June 14, with 11 legislators attending. There are five trainings scheduled over the next three months for the "Stop the Bleed" campaign

District 8

Brian Curtis, MD, reported that KCU-Joplin and KCU-Kansas City graduated over 400 progressive first-year medical students. KCU-Joplin will be seeking full accreditation.

District 9

Lirong Zhu, MD, reported that a physician from Mercy has become the chief medical officer of Phelps County Regional Medical Center, and they are looking forward to greater collaboration between the two organizations.

District 10

Sharon Wallace, MD, introduced Douglas Wallace, MD, as the new District 10 Vice Councilor.

Medical Student Section

Scott Berndt reported that UMC-MSS will be hosting a Residency Directors' dinner in October. He encouraged members to reach out to medical students to assist with writing resolutions.

Resident and Fellow Section

Joanne Loethen, MD, reported that membership and engagement continue to be a top priority. They will be encouraging participation in White Coat Day.

Organized Medical Staff Section

Peggy Barjenbruch, MD, reported that about 100 representatives had met in Chicago. Eight resolutions were presented, and she discussed in particular Resolution 717 regarding the independence of medical staff.

AMA Report

Edmond Cabbabe, MD, reported on the delegation's experience at the AMA meeting in Chicago. The AMA Foundation Missouri Honor Fund grant of $40,000 (combined with AMA Foundation grant) was presented to a St. Louis clinic that serves the immigrant population. The AMA interim meeting will be held November 10-13, in National Harbor, Maryland.

Meeting of October 14, 2018 - Jefferson City

Medicine gained a significant tort reform victory in the recent Missouri Supreme Court decision (Shallow v. Follwell), MSMA Council heard at your Association's October Council Meeting in Jefferson City.

Ravi Johar, MD, reported that MSMA is participating in TCD (Time-Critical Diagnosis) Task Force meetings. Issues for the upcoming 2019 legislative session include PDMP, APRN licensure, and prior authorization reforms. Dr. Johar encouraged members to sign up as Physician of the Day at the Capitol, and invited everyone to the "White Coat Rally" lobbying day scheduled for March 5, 2019.

MSMA and statewide medical school deans are in partnership to make physicians and physicians-in-training aware of the benefits of organized medicine.Utilize the recruitment tools at www.msma.org/engage.

SHINE

The Show-Me Health Information Network (SHINE) will host an upcoming CME event in Hannibal. SHINE offers a positive cost benefit versus plans that charge for individual features (EHR, patient portal, etc.) Other positive aspects include a discount for early-adopters, billing after one year, and the ability to disconnect with a five-day notice if not satisfied.

Annual Convention

Physicians are invited to MSMA's 161st Annual Convention, where six General Sessions will be offered

and free CME to members. Program, registration, lodging, exhibit information, House of Delegates, and disposition of 2018 resolutions can be found at www.msma.org/annual-convention.

Membership

Warren Lovinger, Jr., MD, reported that MSMA staff will be traveling more extensively to reach out to new and existing members. The Council also heard more information on the MSMA Ambassador membership program and fund-raising for the Missouri State Medical Foundation scholarship program, which currently provides $180,000 in scholarships to students at the six Missouri medical schools.

Public Affairs

George Hubbell, MD, discussed Resolution #10/ Breastfeeding which was adopted by the MSMA House of Delegates at the 2018 Annual Convention. Since resources exist for collecting breastfeeding data, the Commission recommended an article be published in Progress Notes encouraging physicians to distribute data to increase Missouri breastfeeding rates. Craig Yugawa, Medical Student Section Councilor, stated the resolution was sponsored by the MSS, and offered to contribute to the article.

District Reports (selected)

District 3

Inderjit Singh, MD, reported the St. Louis Metropolitan Medical Society's second Physician Insurance Survey results are on the SLMMS website, www.slmms.org. The Annual Hippocrates Lecture featured Steve Miller, MD, of Express Scripts: "Drug Pricing Transparency: What Doctors Need to Know to Provide Care in a Murky World."

District 5

Lisa Thomas, MD, reported that Boone County Medical Society's annual gala is February 2, 2019, at The Club at Old Hawthorne. Members met in November for a program on identity theft and human trafficking. BCMS is supporting its Alliance in its reorganization efforts; the Alliance will be sponsoring family-focused events.

District 7

Michael O'Dell, MD, reported that KCMS will hold its annual meeting November 28 at the Overland Park Convention Center.

District 8

Jim Blaine, MD, organized the Greene County Medical Society Opioid Committee to coordinate physician activity and input with local Greene County governmental, judicial, and law enforcement officials as well as the Mental Health Substance Abuse and Behavioral Disorder Task Force and addiction center physicians. Alexander Hover, MD, stated that he and Matthew Stinson, MD, had participated in an Opioid Advisory Council in May. He encouraged collaboration with Alliances, and reported that the GCMS Alliance is developing AMA-approved materials on opioid abuse for distribution.

District 10

Douglas Wallace, MD, reported that the Cape Girardeau Area Medical Society hosted a Cancer Symposium in October.

Resident and Fellow Section

Nathaniel Barbe, DO, reported the RFS is promoting the White Coat Rally event, and encouraging Medical Student Section members to continue their membership after transitioning to Resident and Fellows.

AMA Report

Edmond Cabbabe, MD, reported the AMA delegation will represent Missouri physicians at the 2018 AMA Interim meeting in Maryland in November. Charles Van Way III, MD, authored the recap in the upcoming Missouri Medicine. The recipient of the Missouri Honor Fund/AMA Foundation $41,000 grant was an urban clinic in St. Louis that focuses on diabetes prevention. The grant can be applied for online on the AMA Foundation website. Barbara McAneny, MD, President of the American Medical Association, will speak at the second House of Delegates' April 7, during the 2019 MSMA Annual Convention.

Alliance

The Alliance encouraged participation in the Alliance's Holiday Sharing card campaign. The Alliance presented a ceremonial check for $1,000 to Lisa Thomas, MD, of the Missouri Physicians Health Program, in honor of Marsha Conant's 2017 term as Alliance President.

Meeting of January 2019 - Jefferson City

MSMA Council met via conference call for its January Council Meeting due to inclement weather. Following are the highlights.



Twenty-three physicians received their 50-Year Physician Pin in 2019. Those in attendance who received their Pin during the Presidential Inauguration were, from left: Drs. Michael Clarke John Hagan, Christopher Jung, Mary Case, MSMA President Joe Corrado (presenting), Kenneth Azan, and Krikor Partamian.

Advocacy

MSMA President Joseph Corrado, MD, is representing MSMA around the state, visiting nearly all county medical society meetings. He reminded members to attend the White Coat Rally Day on March 5. You can sign up at www.msma.org/white-coat-rally. MSMA intervention helped end Medicaid's Opioid Policy Advisory Council (OPAC) program on Opioid Prescription Intervention and its mass letter campaign. Opioid letters have now stopped, thanks to the involvement of MSMA at the committee meetings in Jefferson City. MSMA has thanked Governor Parson for his approach in holding opioid prescribing committee meetings in lieu of the letters. MSMA will remain involved and work with OPAC.

Annual Convention

MSMA's 161st Annual Convention registration is open and participants need to make hotel reservations by March 4. Six General Sessions will feature topics on Near-Death Experiences, Non-Opioid Pain Medicine, Physician Suicide, Alcoholism, Generational Differences, and Physician Employment Negotiations. Visit www.msma.org/annual-convention for more information.

SHINE

Show-Me Health Information Network (SHINE) is growing throughout Missouri. A Kansas City health system, Prime Health, which includes St. Joseph Health Center, St. Mary's-Blue Springs, and the three hospitals on the Kansas side, has signed up to utilize the HIE. This is the second health system in Kansas City, with St. Luke's already being on board. There are a number of independent physicians in Joplin who are expressing interest.

Association Health Plan

MSMA has joined other state medical associations in forming a nationwide Association Health Plan (AHP) to benefit members. Active MSMA members who are interested in learning more about participating in the AHP, visit www.msma.org/AHP for more information.

Resolutions

Resolution #6 – Medical Records Custodial Storage Because there are vendors who handle medical records and storage, the resolution was not adopted. MSMA will publicize information regarding the storage of medical records upon retirement or relocation in Progress Notes and on www.msma.org.

Alliance

MSMA Alliance President Gillian Waltman thanked all who participated in the Holiday Sharing Card campaign, and reported that more than $3,000 was raised among 38 participants. The Show-Me Alliance News and Missouri Medicine listed those who contributed. During MSMA's Annual Convention, the Alliance will host a fundraiser with the theme "The British Invasion" on Friday night. Tickets may be purchased in advance, and funds raised would benefit MSMF.

Reports

The Council approved the following reports: Commission on Continuing Education, Physicians Health Committee, Publications Committee and Editorial Board, Actions and Recommendations on Resolutions from the 2018 Annual Meeting, and the AMA Report. **MM**

Reports of the Delegate Handbook: 2018-2019

Secretary

The Missouri State Medical Association had 3,731 members as of December 2018. This was a net loss of 227 members from our membership of 3,598 as of December 2017. Following is a breakdown according to classification.

Year	Students	Residents	Active	Honor	Total
2017	790	173	2,585	410	3,958
2018	835	112	2,381	403	3,731
	+45	-61	-204	-7	-227

The number of member deaths reported during 2018 totaled 15.

The Committee on Nominations, which is appointed by the President, from the House of Delegates, must submit nominations for the following offices:

Three Vice Presidents to fill the expired terms of Michael Bukstein, MD, Hannibal; William Huffaker, MD, St. Louis; and Robert Gibbons, Jr., MD, Prairie Village, Kansas.

Speaker and Vice Speaker to fill the expired terms of Lancer Gates, DO, Kansas City, Speaker, and Sam Page, MD, Creve Coeur, Vice Speaker.

Three Delegates and One Alternate Delegate to the AMA to fill the vacancies created by the expiration at the conclusion of the 2019 Annual Convention of the terms of Delegates: Elie Azrak, MD, St. Louis; Rebecca Hierholzer, MD, Leawood, Kansas; James Conant, MD, St. Joseph; and Alternate Delegate: Shannon Tai, Lisle, Illinois. The new two-year terms will begin at the conclusion of the 2019 MSMA Annual Convention and end at the conclusion of the 2021 MSMA Annual Convention.

The terms of the following Councilors will expire in 2019: 1st District – Robert Corder, MD, St. Joseph; 2nd District – John Memken, MD, Hannibal; 3rd District – Robert Brennan, Jr., MD, St. Louis; Inderjit Singh, MD, St. Louis; 4th District – Kevin Weikart, MD, Lake St. Louis; 6th District – David Kuhlmann, MD, Sedalia; 7th District – Betty Drees, MD, Kansas City; 8th District – Alexander Hover, MD, Ozark; 10th District – Sharon Wallace, MD, Cape Girardeau; Organized Medical Staff Section – Peggy Barjenbruch, MD, Mexico; Young Physician Section – Ramona Behshad, MD, St. Louis; Resident and Fellow Section – Nathaniel Barbe, DO, Jefferson City; Medical Student Section – Craig Yugawa, St. Louis.

The terms of the following Vice Councilors will expire in 2019: 1st District – Robert T. Weigand, MD, St. Joseph; 2nd District- Sandra Ahlum, MD, Hannibal; 4th District – Keith Ratcliff, MD, Washington; 6th District – Amanda Turner, MD, Nevada; 8th District – Brian Curtis, MD, Joplin; 10th District – Douglas Wallace, MD, Cape Girardeau; Organized Medical Staff Section – James Conant, MD, St. Joseph; Young Physician Section – Sarah Florio, MD, Lee's Summit; Resident and Fellow Section – Daniel Young, MD, St. Louis; Medical Student Section – Scott Berndt, Kansas City.

Delegates shall meet during the Annual Convention to elect the Councilors and Vice-Councilors for their respective districts and sections. The election shall be certified to the House of Delegates on the prescribed form which will be furnished.

The entire session will be held at the Westin Kansas City at Crown Center Hotel, Kansas City, Missouri. The House of Delegates will hold its First Session on Friday, April 5, 2019, at 8:00 a.m. and the Second Session on Sunday, April 7, 2019, at 8:15 a.m.

Registration facilities will be open on Thursday, April 4, at 3:30 p.m.; Friday, April 5, at 6:30 a.m. and Saturday, April 6, at 6:30 a.m. Registration will be in the Century Foyer.

Alliance

The Alliance year began in March 2018 during the MSMA convention in St Louis when the 2018-2019 Alliance officers were installed. Mary Shuman from St. Joseph was the installing officer. Gill Waltman was installed as president, and Diana Corzine as president-elect. Also installed were vice presidents Kelly O'Leary (Health), Kirk Doan (Legislation), Shweta Agarwal (Membership), Sana Saleh (Recording Secretary) and Debora Snyder (Treasurer.)

Look on the Bright Side was the theme selected by Mrs. Waltman (a quote from Monty Python, for any British humor enthusiasts!). Those who know her will confirm she's always been an optimist. It appealed to her as a theme because there are many reasons for people to feel depressed or unhappy, from economic problems, natural disasters, the political climate, health-related issues including the opioid crisis and - within our own ranks - the wearing down of the medical profession from all sides creating the need to defend medicine and patients from public opinion, invasive hospital and insurance influences, and scope-of-practice usurpers.

Mrs. Waltman presided over an Alliance executive board meeting on May 16 in Columbia. Additional officers were appointed to the board and all members presented their plans for the year. Kathy Weigand was appointed as the vice president for Foundations after the elected officer resigned.

At the AMA Alliance annual meeting in Chicago in June, MSMA Alliance Past President Sue Ann Greco was sworn in as the national Board Secretary, along with President Cami Pond and her new officers. Missouri had excellent representation at the meeting.

An AMA Alliance initiative to promote happy families and combat physician burnout established, with the support of the AMA, a Physician Family Day on Saturday, August 25, 2018. Many counties planned family outings or events on that date for local physician communities. Plans are to hold this event annually on the last Saturday in August.

The Alliance Fall Conference was held Oct 10-11 at Westminster College in Fulton. Donna Corrado was appointed as conference coordinator. We received a warm welcome from Dr. David Roebuck, the Dean of Academic Affairs. There was an enthusiastic attendance comprised of Alliance members and undergraduate students, many of whom were pre-med.

Tuesday's program focused on the opioid epidemic and comprised two different sessions. Identifying the Challenges Facing Missouri's Criminal Justice System and The Addiction Epidemic: A Community Problem with a Community Solution. Speakers included the Director of the Re-Entry program at the Missouri Department of Corrections in Jefferson City, and a licensed professional counselor in addiction counseling from St. Louis. Health vice president Kelly O'Leary joined the other speakers for an animated panel discussion with great audience interaction, especially from the students. This was followed by a private tour of the Marylebone Church and Churchill Museum and an evening Dutch treat event at the Buckshot Saloon in Kingdom City. MSMA President Dr. Joe Corrado gave an update on problems facing organized medicine from his visits to medical societies within Missouri and the contiguous states.

At the October MSMA Council meeting a token check was presented by the Alliance to Dr. Lisa Thomas of Missouri Physicians Health Program. Donations amounting to $1000 were received from individual Alliance board members to recognize Marsha Conant for her year of service as Alliance President.

The Alliance Holiday Sharing Card was published with donor names in December in Show Me Alliance News, Missouri Medicine, and on the MSMA website. Proceeds from donations amounted to more than $3,000 to benefit the Foundations. Thanks to all who participated.

The Alliance hosted many charity and fundraising events over the holidays to provide support for local food banks, a mobile food drive, shelters, school programs and local charities.

The Alliance Day at the Legislature was held February 20 in Jefferson City following the winter board meeting the previous day. Legislative Vice President Kirk Doan organized the event, coordinating his efforts with the staff at MSMA. Sen. Bob Onder volunteered his office at the Capitol as the base of operations. Speaking as a physician and legislator, he discussed the various issues affecting medicine before leaving for his busy day. Alliance members visited many legislators, requesting support for the Prior Authorization Reform bill [HB 751; SB 298] and the Prescription Drug Monitoring Program [HB 188]. Attendance at the senate hearing for SB 298 with Sen. Onder presiding was most informative.

The MSMA Alliance Annual Meeting will be held in conjunction with the MSMA convention in Kansas City April 4-6. The Alliance Foundation Fundraiser Dinner will be held on Friday April 5 at the Westin. In honor of Mrs. Waltman's theme for this year Look on the Bright Side, it is called The British Invasion! Kathy Weigand is chairing the event.

Current Alliance Issues: Pertinent issues discussed at board meetings this year included maintaining membership numbers and also identifying current members to take on leadership positions. The Alliance is working to increase membership, round up former members and recruit new ones and hopes to produce an updated directory. Efforts are being made to retain the dissolved Boone County Medical Association Alliance members, at least as direct members of the MSMA Alliance, and to re-form a local Alliance. The main reason for the Boone demise was not lack of member numbers but lack of volunteers to step up to leadership positions.

Sympathies were sent to Millie Bever on the loss of her husband Grant Bever, MD, who passed away in June after a long illness. And we mourn the loss of Carol Jean DeFeo, a past state Alliance president and stalwart Alliance member, a mentor, treasure, and friend to so many.

Continuing Medical Education

The Commission reviewed and approved the following accreditation actions:

- Greene County Medical Society-Springfield, MO
- Lake Regional Health System-Osage Beach, MO
- North Kansas City Hospital-Kansas City, MO
- Cape Girardeau County Area Medical Society-Cape
- Girardeau, MOCapeCGirardeau, MO

The following entities submitted Progress Reports that were approved by the Commission:

- Esse Health-St. Louis, MO
- St. Francis Medical Center-Cape Girardeau, MO

The MSMA sent a letter to the CEOs of MSMA-accredited providers requesting nominations for the CME commission. The letter was a great tool to secure new Commission members and recruit new MSMA members. As a result of the letter, four new members joined the MSMA. Additionally, the four new members were appointed to the CME Commission.

The Commission planned and approved the 2018 Annual Convention CME Program approved for 14.00 hours of AMA PRA Category 1 Credits™. Additionally, the program was approved for 9 American Board of Internal Medicine Maintenance of Certification Points.

Following the Annual Convention, attendees were able to participate in an online survey that measured outcomes based on questions designed by the Commission.

In 2018 the following entities withdrew from accreditation:

- Kansas City Ophthalmology and Otolaryngology Society
- St. Louis Metropolitan Medical Society
- SSM St. Mary's Jefferson City

The Missouri State Medical Association currently accredits twenty-four entities statewide. MSMA staff conducted a spring and fall new staff training at MSMA headquarters. The Commission approved an increase in the accredited provider Annual Maintenance Fee from $1600 to $2500 beginning in 2020 in an effort to make the CME recognition program self-sufficient.

MSMA staff attended the state medical society meeting sponsored by the ACCME April 16-19, 2018 in Chicago, ACCME's Annual Conference where attendees discussed issues and trends relevant to CME. Dr. Joan Shaffer and MSMA staff also attended the 2018 ACCME SMS Meeting in Chicago, IL, December 6-7, 2018. Additionally, staff participated in the ACCME's monthly noon conference calls.

Membership

MSMA closed out the 2018 membership year with 2,381 active physician members, 835 medical student members, 112 resident/fellow members and 403 retired physician members. AMA reports a total of 2,198 active members from Missouri in 2018. On the state level, MSMA recruited 178 new members in 2018, 55 of whom took advantage of the mid-year, half-price offer.

Membership requires all-hands-on-deck. Staff has worked to implement new and different ways to boost membership, with an approach focused on awareness, engagement, recruitment, and retention. We are making every effort to put our leadership in contact with new members, prospects, and those who aren't renewing their membership annually. A Councilor Engagement Plan was introduced in July; and we launched a new landing page with physician recruitment tips and tools at www.msma.org/engage.

MSMA leaders have been signing customized letters in conjunction with each Council meeting; which MSMA staff then mails the letters to lapsed members and non-members within each Councilor's district. We are excited to be coordinating small group sessions among leaders and non-members in the coming year as well.

In addition to the long-standing benefits and resources MSMA provides to our members, having the Show-Me Health Information Network (SHINE of Missouri) available to members at a discount proves to be a great asset in promoting MSMA membership.

Educational sessions are being offered during Convention specifically appealing to young physicians, residents, and medical students. Moneta Group, an MSMA preferred partner, also presented to residents at Truman Medical Center on debt management last summer.

The local component medical societies statewide have appreciated their visits from MSMA President Joe Corrado, MD, this past year. MSMA staff has coordinated with members from inactive local component medical societies who want to revitalize their societies.

MSMA's social media is growing across the various platforms (Facebook, Instagram, YouTube, and LinkedIn). Video posts featuring members are performing well.

Tune in to our Facebook page at www.facebook.com/momedical, follow us on LinkedIn, check us out on Instagram, tweet with us @MOMedicalAssn, and watch MSMA on YouTube.

MSMA is proud to have such amazing leadership and members. Please read about them as we acknowledge their accomplishments in each issue of *Missouri Medicine.* Share

MSMA and organized medicine's successes with your non-member colleagues as often as you can. Thank you for your help in making MSMA the one membership every physician needs.

Missouri Physicians Health Foundation

This has been a busy year as indicated by the number of referrals and the numerous Missouri physicians that were assisted. The MPHP provides a variety of services. This includes consultation, intervention, referral for treatment, monitoring and advocacy. The consultive service is especially active. Hospital administrators, physicians, colleagues and family members call the Program Coordinator or Clinical Coordinator to make a referral, discuss a potential referral or brainstorm about the necessity of making a referral. Information is often requested about how to identify problems, what services are available and how to handle issues of impairment should they occur. Many hours are required to meet their needs. The MPHP provides a safe and knowledgeable venue for any question or concern about physician health.

Missouri State Medical Foundation

The Foundation is in good health and doing excellent work. It made over 3,000 medical school student loans since 1961 totaling almost $12 million. Although the Foundation is no longer making medical school student loans, the scholarship program has benefited hundreds of Missouri medical students. Your Missouri State Medical Foundation has spent $1,145,000 on scholarships and scholarship fund matching grants since 2001.

MSMA regularly publishes pictures in *Progress Notes* with medical students receiving MSMA Scholarships. The Foundation funds the $3,000 MSMA Scholarships awarded to ten Missouri medical students at each of the six medical schools. We are budgeting $180,000 this year for 60 MSMA Scholarships.

The MSMA Alliance is an important partner to the Foundation through its annual fund-raising activities.

MSMA Insurance Agency

Your MSMA Insurance Agency is an independent insurance agency that offers professional insurance consultation to all Missouri physicians. The Agency offers policies primarily for professional liability and health, but also covers workers compensation, business office coverage, disability, and life.

Agency staff has been instrumental in assisting numerous state medical associations in studying and forming an Association Health Plan which it is preparing to launch in 2019.

The board of the Insurance Agency reviews the budget and financial statements at each quarterly meeting. Agency financial statements are audited and consolidated into the MSMA financial statements.

The board is supportive of the Agency and encourages all MSMA members to contact the Agency for a competitive health insurance or professional liability insurance bid.

Committee on Public Affairs

The Public Affairs Commission was assigned Resolution #10 as directed by the MSMA House of Delegates: Collection of Breastfeeding Data at Well-Baby Visits in First Year of Life. 2018 House of Delegates amended and adopted: Resolved, that our MSMA explore the feasibility of a study on the collection of breastfeeding data with state Practice Based Research Networks and relevant specialty medical associations.

The Commission suggests increasing the breastfeeding rates in Missouri through distribution of specific data through its communications and encouraging the effective specialty groups to take on and share in this challenge statewide. The Commission also recommended that MSMA add the above resources to our website under Public Health for use by members and the general public.

Young Physician Section Report

The Young Physician Section (YPS) of MSMA will have a business meeting during the 2019 Annual Convention. The business meeting begins at 10:45 a.m. and is followed by a joint program, focusing on financial planning, for YPS, RFS and MSS members.

At the 2018 meeting, the section elected its officers for 2019. They were: Chair, Albert Hsu, MD; Vice-Chair, Kirsten Dunn, MD; Secretary, Fola Fasuyi, MD; and Treasurer, Ramona Behshad, MD. Dr. Dunn was named the YPS delegate. Dr. Behshad continues to serve as YPS councilor; Sarah Lovinger Florio, MD, serves as vice councilor. They were elected at the 2017 Annual Convention and their terms expire at the close of the 2019 Annual Convention.

During the 2018 Convention, YPS members heard a presentation on malpractice lawsuits from attorneys at Williams Venker and Sanders LLC, based in St. Louis.

Throughout 2018, Dr. Hsu and fellow YPS member Nita Kohli, MD, MPH, posted articles/updates on the MSMA website about attending AMA meetings and actions taken by the AMA-YPS.



The MSMA Resident and Fellow Section introduced a resolution creating a Women Physicians Section within the MSMA. Review the new section guidelines at www.msma.org/msma-constitution-bylaws.

Dr. Hsu was appointed to serve on the Editorial Board of Missouri Medicine, and YPS member Jessica Bauerle, MD, was appointed to the newly created position of Young Physician Contributing Editor to Missouri Medicine. Dr. Bauerle's three-year term began Jan. 1, 2019.

International Medical Graduate Section

Last year has been quiet for the IMG section of the MSMA. We had the annual convention during which Louis DelCampo, MD, has come forward to serve as the Vice Councilor. He is an Anesthesiologist with Pain Management subspecialty practicing in Southwest Missouri region.

The Indian Medical Council has been dissolved locally and physicians of Indian origin now belong to AAPI (American Association of Physicians of Indian Origin) which is a national organization. Activities in St. Louis include meeting for social events a few times a year. The focus of this group is to facilitate J1 visa waivers to physicians so that they can stay longer to pursue employment that allows them to stay in the US. This group has been meeting with local politicians to help this process.

Physicians of Pakistani origin also now belong to a national association called APPNA (Association of Physicians of Pakistani Descent of North America) which has chapters in many states, however does not have one in Missouri since last year. No activity is reported locally due to that.

Edmond Cabbabe, MD, who had served as the past president of NAAMA (National Arab American Medical Association) has been awarded the highest award by St Louis Metropolitan Medical Society last year, the Robert E. Schlueter Leadership Award. He is the 20th recipient of this award, which is given to a person for long-standing contribution to medicine in the areas of leadership, scientific orientation, advocacy and community service. Dr. Cabbabe has served as the past president of SLMMS, MSMA, Missouri Association of Plastic Surgeons and currently serves as a delegate to the AMA since 2009, including being on the board of the AMA Foundation, a charitable branch.

Resident and Fellow Section

The MSMA Resident and Fellow Section (RFS) held a steady course over the 2018-2019 year. Primary objectives have been to continue to enhance RFS presence within the MSMA, improve RFS membership, develop sustainable strategies for ongoing membership recruitment, and grow networks with other MSMA sections - specifically the Young Physician Section (YPS) and the Medical Student Section (MSS). Through our efforts to pursue these goals, the RFS continues to show growth at both the state and national level.

At the 2018 MSMA Annual Convention, our governing council positions were restructured to better reflect duties unique to our section. Additionally, collaborative experiences with both the YPS and MSS were launched in an effort to bridge the membership transition through each phase of physician development. Again at this year's Annual Convention, our three sections will join in shared programming and networking opportunities. At the state capitol, multiple RFS members have volunteered as Physician of the Day and many participated in MSMA's 2019 White Coat Rally. Regarding our membership efforts, our section continues to work with the MSMA Membership Committee on ways to boost membership among post-graduate trainees. As part of this effort, the RFS continues to grow its Resident Ambassador Program which was launched in early 2018. We now have multiple ambassadors within each metro area. Each ambassador serves as a local liaison of the MSMA mission to her or his respective training program and institution.

At the national level, MSMA-RFS continued to have strong representation at AMA Annual and Interim meetings. Currently, we have representation within multiple standing committees of the AMA including the Committee on Membership and the Committee on Public Health. As a state section, we continue to have regular representation at AMA-RFS meetings as we bring the voices of Missouri residents and fellows to the national stage.

Medical Student Section

A.T. Still University – KCOM

The A.T. Still University-Kirksville College of Osteopathic Medicine (KCOM) AMA/MSMA-MSS Chapter held two successful recruitment efforts this year. We held our annual recruitment event at the Taste of Kirksville, where students learn about and join student organizations while local food vendors bring samples from their various restaurants. During our second recruitment event, we brought in plastic surgeon Dr. Schuyler Metlis from Hannibal Regional Medical Group who showed students how to work together as DOs and MDs in organized medicine.

We were very excited to host AMA Immediate Past President David Barbe, MD, at a campus- wide event in spring 2018. He discussed the importance of AMA, advantages of becoming members as medical students, the impact of the Medical Student Section on HOD Policy, and practicing in rural medicine.

Our main service projects each year are bi-annual blood drives with the Red Cross. We are happy to announce we maintained our Premier Blood Partner status with the Red Cross this year. Additionally, we hosted a historic blood drive in December 2018. Our blood drive received an exceptional 75 total units of blood from students, faculty, staff, and community members. This was the highest amount in our MSS chapter's history with the Red Cross, and the second-highest total at our institution. Seventy-six total units is the record on campus, so we were very close. Our spring blood drive is just around the corner and the Red Cross is increasing our appointment allotments to account for our continued success.

Last year, our previous MSS President, Lauren Drake, discussed us working on planning an Opioid/Naloxone Workshop. As of this update, we are holding a 2-hour Opioid Overdose and Training Workshop with the MO-HOPE organization from St. Louis. We have combined our efforts and resources with the SOMA and MAOPS organizations on campus to hold as large of an event as possible for our first- and second-year members and non-members. We will continue to be a state and national voice and look forward to another year with the incoming class.

Kansas City University of Medicine and Biosciences

The Kansas City University of Medicine and Biosciences (KCU) MSMA-AMA Chapter started this academic year by continuing the highly-successful "How To Survive Medical School" event for the incoming Class of 2022, which included tips on how to survive medical school and a short introduction to MSMA/AMA. We followed this up with a second recruitment event with MSMA President Elect James DiRenna, DO, who spoke about his involvement within the MSMA. Between these two recruitment events, we brought our first- and second-year member total to 70+.

Throughout the year, the executive board planned a variety of events. Schoen Kruse, PhD, a professor at KCU, hosted a talk about his own wellness journey and gave advice on how medical students should focus on themselves. Additionally, we hosted a Picmonic presentation where students could learn more about this learning service and discount codes for cheaper access. After AMA's Interim meeting, my fellow delegate and I gave a presentation explaining how policy is written, revised, and voted upon. Following that, we hosted a Heart Health Day event for Heart Health month where we organized an exercise class, led by fellow students, with another club on campus and provided healthy snacks to students and faculty. However, the most important event all year was the Opioid Overdose Informational Session and Training. We hosted Kamile Johnson, PharmD, and Neann Wedgeworth from the local KC Care Clinic, who presented facts about the opioid crisis and how to use Narcan, and the talk was given to almost 100 faculty and students.

The chapter at KCU is also very intent on helping the community around us. We have volunteered at Hope Lodge, Kansas City Community Kitchen, and the Ronald McDonald House. We try to schedule at least one event a month so we can provide opportunities for about 20 members a month to give back. Coming up, we are looking forward to transitioning the class of 2022 into leadership roles, coordinating upcoming speakers, and attending MSMA's state convention as well as Annual AMA in June. The chapter at KCU is excited to keep working in the coming year.

Saint Louis University

The Saint Louis University Chapter welcomed the Class of 2022 during orientation week with a chapter lunch presentation on AMA, MSMA and SLMMS. At that time, MSMA Past President Ravi Johar, MD, spoke to us about the role of organized medicine in health policy and his experiences with MSMA. We again introduced students to MSMA with tables at the Student Interest Group Fair during the first few weeks of school.

This year our chapter continued its strong commitment to serve the St. Louis community. Chapter leaders Amin Karadaghy MS2 and Amy Tian MS2 coordinated student involvement in the Health Protection and Education Services Clinic at the University City Public Library, providing free screenings to 50 patients on the third Saturday of each month. The new addition of a bone mineral density screening machine has made a large impact on the identification of osteoporosis in the St. Louis community.

Beyond SLU, our chapter participated in the larger SLMMS, MSMA and AMA organizations. George Kung MS2 worked to more closely integrate SLMMS with the AMA/MSMA presence on campus. Monica Ou MS1 was recently appointed as the SLMMS Student Board Member for 2019. Three of our members attended the 2018 MSMA Annual Convention in St. Louis. Nationally, our chapter sent three members to AMA Annual in June in Chicago.

We are dedicated to changing healthcare policy for the better. Shannon Tai MS3 worked with the MSMA-MSS board to submit a resolution through SLMMS addressing the needs of foster children in the healthcare system. Dr. Johar and Edmond Cabbabe, MD, were kind enough to invite interested students to the SLMMS resolution meeting to discuss considered resolutions and develop ideas for potential resolutions to be written. We hope to produce resolutions and further involve students in the writing process in the future.

Emergency medicine physician Tina Chen, MD, presented on the acute management of opioid patients and reflected upon her experience with the crisis firsthand at SLU. The 2018 SLMMS President Chris Swingle, DO, spoke to SLU students about the importance of SLMMS and participation in organized medicine on a local level, as well as state and national levels. We are grateful for last year's success and hopeful of our chapter going forward.

University of Missouri - Columbia

The MSMA-MSS at University of Missouri-Columbia started off the year strong with a table at the orientation activities fair for M1s and a luncheon meeting to provide information on the benefits of organized medicine. We recruited 49 new M1s to join and get excited about opportunities within the MSMA and AMA.

In August, we hosted our first "Pints and Policy" event of the year, where students discussed the debate around scope of practice legislation for mid-level providers. In September, Heidi Geisbuhler, Director of Legislative Affairs for MSMA, came to speak to us about the legislative process, MSMA lobbying, and how students can get involved.

In October, we partnered with the Boone County Medical Society (BCMS) to co-host a Mizzou Residency Directors Forum at The Roof in Columbia, MO for all third-year medical students. We also had our annual Halloween party fundraiser, where we raised $1,079 for MedZou, the free student-run community clinic at Mizzou.

We were awarded a Section Involvement Grant from the AMA, which helped fund a MedZou event, Project Homeless Connect, helping connect the homeless population of Columbia with health resources around the city.

During our Advocacy Week in November, Mizzou focused on raising awareness about the national opioid epidemic. We hosted a documentary screening of the film Heroin followed by a discussion, which was well-attended and very successful.

In January, we held a Resolution Writing Workshop where Albert Hsu, MD, and Jared Lammert, MD, discussed the process of writing a resolution, and students spent time brainstorming and beginning to write resolutions for the upcoming MSMA meeting in April.

As in the past, Mizzou has continued to have strong attendance at national conferences and representation in state leadership. In November, at the AMA Interim Meeting, Calli Morris and Nikki Kagan represented Mizzou at the Medical Student Section Meeting, with Nikki Kagan also serving on the Region 2 Board. Six additional students also attended the Interim meeting. Nikki Kagan also attended the Region 2 conference held in Chicago. For the State MSS, Scott Berndt is currently serving as Vice-Councilor and Calli Morris is serving as Chair.

University of Missouri – Kansas City

This has been an excellent year for the UMKC chapter of the MSMA-MSS. We started with great recruiting in August for our Year 1 and 2 students in our 6-year med program. Afterwards we had great questions and interest. We were able to register a lot of people into our chapter, of which we are very proud!

We usually have one meeting a month, where we talk about policy and what we can do to improve advocacy and legislation in the medical community. We had a fun national advocacy week, and Nick Yeisley helped arrange a successful guest lecture from Betty Drees, MD; an opioid training event; and a visit to our local legislative offices. We also led a Med-Out-The-Vote campaign for the midterm elections in our area.

We had another recruitment event for the Year 3-Year 6 students in the medical school and we look forward to continuing our UMKC events with a Differential Diagnosis event and another community service event that we are still planning.

Outside of UMKC, our chapter members continue to be involved on the regional and national Level. Manna Varghese is a part of the governing council of the AMA and has been going to regional meetings across the country. Nick Yeisley is a member of the AMA-MSS Minority Issues Committee. Akash Jani, our president, serves on the regional board. Priya Jain, Connor King, and Andrew Williams are all involved in Region 2 subcommittees. We have had good UMKC representation at national conferences (Interim, MARC, and



The MSMA Medical Student Section was well represented by six schools of medicine from around the state: A.T. Still University Kirksville College of Osteopathic Medicine, Kansas City University, Saint Louis University, University of Missouri -Columbia, University of Missouri - Kansas City, and Washington University.

Annual) in recent years, and we look forward to continuing that in the coming year. We are extremely grateful to the MSMA for all of their assistance in helping us travel to these conferences, which are often far (e.g. Hawaii, Washington, D.C.), and look forward to another wonderful year.

Washington University

The Washington University chapter continued our success in training physician-advocates and healthcare leaders. Last spring, we hosted the president of the AMA, David Barbe, MD. He gave a well-attended talk, was given a tour of the medical campus, and met with administrators and student-leaders. We began the school year with a very successful recruiting event during the First-Year activities fair. Our first meeting featured an introduction to the AMA, MSMA, and SLMMS. Students were given the opportunity to learn more about organized medicine and SLMMS from SLMMS President Christopher Swingle, DO, and Executive Vice President Dave Nowak.

We started a new program this year called Pints & Policy. During each session, medical students meet with a policy leader to discuss current legislation and ways students can get involved early in their career with advocacy. Leaders of the sessions have included Ed Weisbart, MD; Ilana Rosman, MD; and Ravi Johar, MD. The sessions have been well-received, and we hope to expand them in the future.

We launched a new elective class this year, which introduced first-year students to the intersection of policy and medicine. The 16 students enrolled in the course received lectures from leading experts in policy, including our faculty advisory Graham Colditz, MD. Other speakers included David Barbe, MD; Sam Page, MD; Samer Cabbabe, MD; Lynn Cornelius, MD; Colleen McNicholas, DO; William Peck, MD; Representative Stacey Newman; Tim McBride, PhD; and Mr. Jeff Howell. Each student also participated in a policy drafting session and presented their proposed policy at the end of the course. Student feedback from the course was excellent. We anticipate more student engagement with health policy in the future.

We have continued to focus on giving future physicians the skills to advocate for their patients. Our advocacy chairs organized a letter-writing day in the Spring. We also sent 10 students to the MSMA Lobby Day in Jefferson City and will attend the 2019 White Coat Rally. We led a large voter registration drive this fall and hosted a "Meet Your Ballot" event to familiarize students with issues and candidates. We are hosting an Advocacy Workshop this spring to introduce students to the Missouri legislature and ways to engage in policy. We will send students to the annual AMA Medical Student Advocacy and Regional Conference in Washington D.C., as well.

Individual student leaders are continuing their involvement. WUSM sent seven students to the AMA Annual meeting and three students to the AMA Interim Meeting. At Interim, two students, Jane Hayes and Samantha Lund, authored resolutions that were well received and passed through the Medical Student Session. Several WUSM members continue to serve on AMA committees, Region 2 Leadership, the MSMA-MSS Council, and the SLMMS Council. As we transition our leadership roles to the next class of medical students, we are excited to continue working to improve healthcare on a local, state, and national basis in 2019. **MM**

Missouri State Medical Association

Statement of Financial Position
December 31, 2018

ASSETS

	2018	2017
CURRENT ASSETS:		
Cash and Cash Equivalents	$ 650,880	$ 676,120
Current Investments	10,003,098	11,238,775
Interest Receivable	47,913	-
Accounts Receivable	28,197	23,974
Taxes Receivable	-	5,426
Prepaid Taxes	-	4,050
Prepaid Expenses	29,116	5,568
Total Current Assets	10,759,204	11,953,913
FIXED ASSETS:		
Land	83,000	83,000
Building and Improvements	605,078	605,078
Organization Costs	1,430	1,430
Furniture and Equipment	311,536	312,318
Less: Accumulated Depreciation	(888,883)	(885,691)
Total Net Fixed Assets	112,161	116,135
NON-CURRENT ASSETS:		
Deferred Tax Asset	33,357	41,892
Non-Current Investments	2,639,020	2,627,650
Total Non-Current Assets	2,672,377	2,669,542
TOTAL ASSETS	$ 13,543,742	$ 14,739,590

LIABILITIES AND NET ASSETS

	2018	2017
CURRENT LIABILITIES:		
Accounts Payable and Accrued Expenses	$ 17,735	$ 11,542
Producer Commissions Payable	14,099	11,097
Income Taxes Payable	2,262	-
Funds Held for Others	18,977	18,709
Accrued Vacation	82,410	94,741
Deferred Revenue	34,443	31,904
Deferred Dues	606,311	629,981
Total Current Liabilities	776,237	797,974
NON-CURRENT LIABILITIES:		
Deferred Compensation Agreement	484,863	560,128
Pension Benefit Liability	3,401,270	4,698,677
Total Non-Current Liabilities	3,886,133	5,258,805
Total Liabilities	4,662,370	6,056,779
NET ASSETS:		
Without Donor Restrictions	8,881,372	8,682,811
Total Net Assets	8,881,372	8,682,811
TOTAL LIABILITIES AND NET ASSETS	$ 13,543,742	$ 14,739,590

Missouri State Medical Foundation

Statement of Financial Position
December 31, 2018

ASSETS

	2018	2017
CURRENT ASSETS:		
Cash	$ 596,484	$ 492,743
Investments	3,480,006	294,977
Notes Receivable - Current	273,230	322,345
Accrued Interest	69,223	101,209
Total Current Assets	4,418,943	1,211,274
EQUIPMENT:		
Office Equipment	1,091	1,091
Software	10,692	10,692
Less: Accumulated Depreciation	(11,710)	(11,492)
Total Net Fixed Assets	73	291
NON-CURRENT ASSETS:		
Investments	1,073,553	4,555,069
Notes Receivable - Long Term	1,093,917	1,317,503
Allowance for Doubtful Accounts	(218,880)	(218,880)
Notes Receivable - Long Term (Net)	875,037	1,098,623
Total Non-Current Assets	1,948,590	5,653,692
TOTAL ASSETS	$ 6,367,605	$ 6,865,257

LIABILITIES AND NET ASSETS

LIABILITIES:		
Funds Held for Others	$ 208,891	$ 200,469
TOTAL LIABILITIES	208,891	200,469
NET ASSETS:		
Without Donor Restriction	6,158,714	6,664,788
TOTAL LIABILITIES AND NET ASSETS	$ 6,367,605	$ 6,865,257

Missouri Physicians Health Program

Statement of Financial Position
December 31, 2018

ASSETS

	2018	2017
CURRENT ASSETS:		
Cash and Cash Equivalents		
Cash - Checking	$ 62,624	$ 86,177
Cash - McIntosh Fund	77,045	67,972
Mutual Funds - McIntosh Fund	12,639	15,467
Certificates of Deposit	240,000	135,000
Accounts Receivable	154,708	179,131
Allowance for Doubtful Accounts	(34,071)	(10,200)
Accrued Interest	37	37
Total Current Assets	512,982	473,584
NON-CURRENT ASSETS:		
Investments - McIntosh Fund	12,006	8,112
Property and Equipment		
Office Furniture and Equipment	43,370	48,077
Less: Accumulated Depreciation	(37,267)	(42,453)
Net Property and Equipment	6,103	5,624
Total Non-Current Assets	18,109	13,736
TOTAL ASSETS	$ 531,091	$ 487,320

LIABILITIES AND NET ASSETS

CURRENT LIABILITIES:		
Accounts Payable	$ 5,472	$ 6,649
Accrued Payroll Tax	166	-
Accured Vacation	31,324	21,884
Total Current Liabilities	36,962	28,533
NET ASSETS:		
Without donor restrictions	494,129	458,787
Total Liabilities and Net Assets	$ 531,091	$ 487,320

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2019 Annual Convention Attendance

Delegates	*88*
Members	*96*
Exhibitors	*45*
Staff	*16*
Guests	*71*
Officers	*8*
Councilors/Vice	*34*
Alliance	*20*
Total	*378*

(Actual numbers will not balance due to overlaps in positions served.)

Officers
Brian Biggers, MD
Michael Bukstein, MD
Joseph Corrado, MD
James DiRenna, Jr., DO
Ravi Johar, MD
Warren Lovinger, Jr., MD
Sam Page, MD
David Pohl, MD

Councilors
Elie Azrak, MD
Peggy Barjenbruch, MD
Ramona Behshad, MD
Robert Brennan, Jr., MD
Robert Corder, MD
Betty Drees, MD
Lancer Gates, DO
Alexander Hover, MD
George Hruza, MD
George Hubbell, MD
Sri Devi Kolli, MD
David Kuhlmann, MD
John Memken, MD
Inderjit Singh, MD
Matthew Stinson, MD
Marc Taormina, MD
Lisa Thomas, MD
Sharon Wallace, MD
Kevin Weikart, MD
Craig Yugawa
Lirong Zhu, MD

Vice Councilors
Sandra Ahlum, MD
Clark Andelin, MD
Scott Berndt
James Conant, MD
Louis DelCampo, MD
Omofolarin (Fola) Fasuyi, MD
Sarah Florio, MD
Michael O'Dell, MD
Keith Ratcliff, MD
Amanda Turner, MD
Douglas Wallace, MD
Robert Weigand, MD
Daniel Young, MD

Delegates
District 1
Buchanan County Medical Society
James Conant, MD
James Reynolds, MD
Robert Weigand, MD

District 2
Northeast Missouri Medical Society
Sandra Ahlum, MD
Hossein Behniaye, MD
Michael Bukstein, MD
Lent Johnson, MD

District 3
St. Louis Metropolitan Medical Society
David Butler, MD
Edmond Cabbabe, MD
Erin Gardner, MD
Karen Goodhope, MD
Thomas Greco, MD
Ravi Johar, MD
Sam Page, MD
Jennifer Page, MD
David Pohl, MD
Jo-Ellen Ryall, MD
Stephen Smith, MD
Christopher Swingle, DO
Jeffrey Thomasson, MD
Alan Wild, MD

District 4
St. Charles-Lincoln County Medical Society
Brian Andrews, MD
Jeffrey Copeland, MD
Matthew Meier, DO
William Sill, DO
Thomas Tyree, MD
Martin Willman, MD

Tri-County Medical Society
Christiane Korba, MD
Timothy Long, MD
Keith Ratcliff, MD

District 5
Audrain County Medical Society
Joseph Corrado, MD
Diane Jacobi, MD

Boone County Medical Society
Milamari Cunningham, MD
Ted Groshong, MD
Alan Hillard, MD
Jerry Kennett, MD
Hung Winn, MD

District 6
West Central Medical Society
William Haynie, MD
Warren Lovinger, Jr., MD
Amanda Turner, MD
William Turner, MD

District 7
Kansas City Medical Society
Thomas Allen, MD
Barbara Buchanan-McCanse, MD
Richard Butin, MD
James DiRenna, Jr., DO
William Dorzab, MD
John Hagan, III, MD
Frederick Hahn, Jr., MD
Rebecca Hierholzer, MD
Andrew Jurgensmeier, MD
Ann Karty, MD
Thomas Lovinger, MD
Michael O'Dell, MD
John Chris Perryman, MD
Kathy Perryman, MD
Donald Potts, MD
John Stanley, MD
Charles Van Way, III, MD

District 8
Greene County Medical Society
Brian Biggers, MD
Jim Blaine, MD
Michael Clarke, MD
Norman Knowlton, III, MD
William Reynolds, MD
Carlin Ridpath,MD
Tim Swearengin, DO
William Taylor, MD
James Wolfe, MD

District 9
Mid-Missouri Medical Society
Omofolarin(Fola) Fasuyi, MD

District 10
Cape Girardeau County Area Medical Society
George Pjura, MD

Medical Schools
A.T Still Osteopathic School of Medicine
Bryan Roberts

Kansas City University of Medicine
Victoria Gordon
William Hrebec

St. Louis University
John Lee
Monica Ou

University of Missouri-Columbia
Pooja Nair
Abdoulie Njai

University of Missouri-Kansas City
Priya Jain
Andrew Williams

Washington University
Samantha Lund
Adrienne Visani

International Medical Graduate Section
Louis DelCampo, MD

Resident and Fellow Section
Frances Mei Hardin, MD
Brette Harding, MD
Jared Lammert, MD
Joanne Loethen, MD
Nathanial Nolan, MD

Young Physician Section
Sarah Florio, MD

Delegates-At-Large
Past Presidents
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Jeffrey Copeland, MD
William Dorzab, MD
Frederick Hahn, Jr., MD
Ravi Johar, MD
Lent Johnson, MD
Jerry Kennett, MD
Norman Knowlton, III, MD
Warren Lovinger, Jr., MD
Marvin Singleton, MD
John Stanley MD
Jeffrey Thomasson, MD
Charles Van Way, III, MD
James Wolfe, MD

Vice Speaker
Sam Page, MD

Members
Allan Allphin, MD
Clark Andelin, MD
Kenneth Azan, MD
Elie Azrak, MD
Peggy Barjenbruch, MD
Ramona Behshad, MD
Scott Berndt
Meelie Bordoloi
Robert Brennan, Jr., MD
Joe Brunworth, MD
Richard Butin, MD
Sailaja Bysani
Calvin Cajigal, MD
Mary Case, MD
David Chang, MD
Blake Cooper, DO
Robert Corder, MD
David Cort, MD
Tamara Crowell, DO
Arthur Daus, MD
Betty Drees, MD
Catherine Dunn, MD
Karen Edison, MD
Jack Edmisten, MD
Keith Fischer, MD
James Fleming, MD
Christine Franzese, MD
Joe Gardner, MD
Lancer Gates, DO
Mark Gilbert, MD
Peter Greenspan, DO
Dan Hancock, MD
Michael Hoeman, MD
Caleb Holtmeyer
Alexander Hover, MD
George Hruza, MD
George Hubbell, MD
Sherifa Iqbal, MD
Feraas Jabi, MD
Akash Jani
David John, MD
L. Mark Johnson, MD
Christopher Jung, MD
J. Marshall Jung, MD
Amanda Kingston, MD
Sri Devi Kolli, MD
Shannon Kraft, MD
David Kuhlmann, MD
Gregg Laiben, MD
Lauren Lester
James Lin, MD
Clara Liu
Nicholas Madaffer, DO
Carlos Maitz, MD
Jasraj Marjara
David McCormick, MD
Larry McIntire, MD
David McKinsey, MD
Joel McKinsey
John Memken, MD
Neal Meyer
Shelby Meyer
Calli Morris
Carl Myers, MD
Helen Nguyen, MD
Eliot Nissenbaum, DO
Angela Olomon, DO
Krikor Partamian, MD
Jonathan Patterson, MD
Larry Rues, MD
Felix Sabates, MD
Joan Shaffer, MD
Anjum Shariff
Lydia Sharp
Alex Shimony
Inderjit Singh, MD
Larry Stewart, MD
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Nanda Thimmappa
Lisa Thomas, MD
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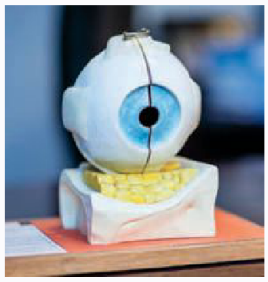
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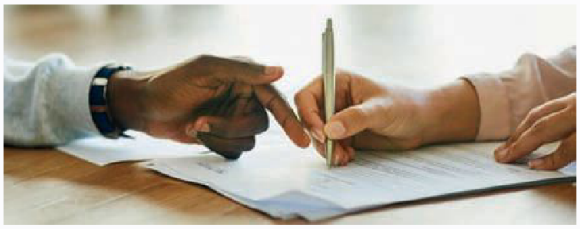
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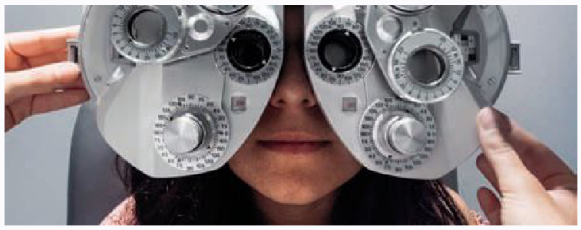




















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