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Missouri Medicine

The Journal of the Missouri State Medical Association - Since 1904

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Bashing Big Pharma*

by Charles W. Van Way, III, MD



*Oklahoma settled its claims against Purdue Pharma and the Sackler family for $270 million in March 2019. More than 1,600 other lawsuits are pending.

I read in the newspapers (remember them?) that Massachusetts is suing the Sackler family. Now, that's a very rich family, whose members have a long history of contributing to good works. These include art museums, civic programs, symphonies, and so forth. Governments don't usually sue rich families, especially civic benefactors. What does the state of Massachusetts have against the Sackler? They own Purdue Pharma, a privately held company which makes OxyContin. Its main ingredient is oxycodone, the most widely prescribed opioid. From selling oxycodone, the Sackler family has made a lot of money.

As we all know, oxycodone has been a major factor – perhaps *the* major factor – in the rise of the opioid epidemic. More people now die from opioids than from motor vehicle crashes. Or firearms. The number continues to rise, fed partly by legally-prescribed drugs, and partly by illegally made drugs on the black market. Physicians have taken our share of the blame for this, and rightfully so. But it's clear that we were not the only cause. And so, the search goes on for who to blame.

Money is a factor in all of this. Governments at all levels have found opioid addiction to be very expensive, not just in direct costs of medical care and law enforcement, but also in terms of lost income. Addicts are very poor taxpayers, and that's a problem for governments. A lot of states, cities, and local governments would very much like to find someone with deep pockets to pay some of the costs.

We've been here before. The obvious example is the tobacco lawsuits. Whether they've done much to curb smoking is uncertain, but they have limited tobacco advertising. Smoking has certainly decreased. Except for vaping. And marijuana. Which have both increased, largely due to increased advertising (vaping) and favorable publicity (marijuana). But even in the drug area, there was the frenzy over rofecoxib and similar COX-2 inhibitor drugs ten or fifteen years ago. The public, and lawyers, discovered that known side effects of these drugs really existed, and sued the companies that made them. Money was extracted from Big Pharma, and the whole thing subsided.[1]

Back to the lawsuits. As civic philanthropists, the Sacklers have had a high profile, especially in New York.



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At the New York Metropolitan Museum of Art, there is a Sackler Wing. But despite this, the *New Yorker* magazine published an "expose" of the family in 2017, entitled "An Empire of Pain."[2] It basically called them the Great Villain in the opioid crisis. And it opened hunting season on the Sacklers personally. A large number of states, counties, and cities across the country had already lined up to sue Purdue Pharmaceuticals. Massachusetts is the first state to sue members of the family by name, but others will surely follow.

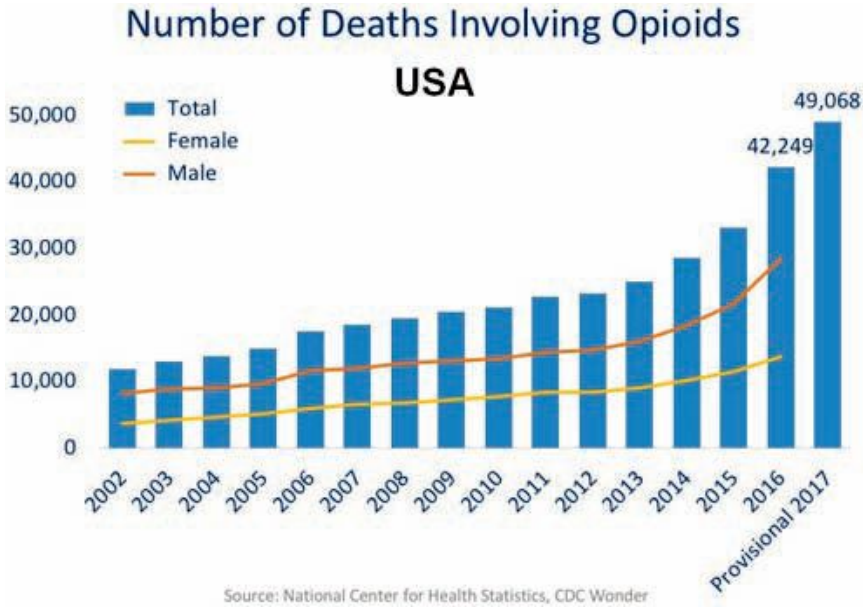


Figure 1. Number of yearly U.S. opioid overdose deaths from all opioid drugs. There were 72,000 drug overdose deaths overall in 2017 in the USA.

Now, Big Pharma was first used about 10-15 years ago to describe the top worldwide companies. Today, it's used more simply to describe the pharmaceutical industry as a whole. Purdue Pharma is mid-sized, by the standards of Big Pharma. Privately held, its revenue is $3 billion or so per year. Given an earnings ratio of 20, that would make it worth $60 billion. It's not for sale, nor is it listed on the markets, so that's not an accurate figure. But it's in the ball park. The top six pharmaceutical companies, the original Big Pharma, have valuations of $100 billion and more.

While Purdue makes a variety of products, its main focus is on pain management. And its best-selling pain medication is OxyContin, a supposedly long-acting form of oxycodone. Introduced in 1996, it was heavily promoted as being relatively safe from abuse, and long-acting. This last meant that it would be useful for chronic pain, with twice-a-day dosage. As we know now, both of these claims were false. Yet, the drug was promoted heavily as if they were true. That's called false advertising, otherwise known as lying to the public. Therefore, the lawsuits.[3]

The marketing of OxyContin (1996) and its predecessor MS Contin (1984) began at an auspicious time. The "no one should suffer pain" movement was ramping up. Organizations such as Kansas City's Center for Practical Bioethics were complaining loudly that doctors were too reluctant to prescribe pain relievers. The "pain is a vital sign" movement had gained traction. Patient satisfaction surveys had begun to circulate, and to be taken very seriously by hospital administrators, news media, and other gullible people. Most importantly, physicians, other health professionals, and hospitals had forgotten that morphine and its derivatives are very dangerous drugs. And so, we have the opioid epidemic today. It's a lot harder to cure addiction than it is to prevent it. We have not yet found a way to put this evil djinn back in the bottle. Figure 1.

Will the lawsuits help? They actually serve two useful purposes. First, they provide a lot of publicity about the problems of opioid over-use and abuse. Warning the public is a Good Thing. And let's face it. Medical journals provide a lot of useful information, but a lot more people read *The New Yorker* and the *Wall Street Journal*. Second, the opioid epidemic has cost a lot, and recouping some of the costs is seen by the general public to be very reasonable.

So, if the company was at fault, why sue the Sacklers? Probably, Massachusetts looked at all of the other 1,600 lawsuits against Purdue, and figured Purdue would simply go under. And so, it has. Purdue Pharma is now preparing to file bankruptcy.[4] That would allow the Sackler family to avoid responsibility. But fair is fair. When a family has become extremely rich while starting a national epidemic of drug use, it serves justice to hold that family responsible for its collective actions.

Lawsuits won't cut the supply of drugs very much, if at all. They might drive Purdue Pharma out of business, and the Sackler family may move down the list of America's richest families (currently #16). Unhappily, the overall

situation won't really change a great deal. Other companies already make opioids. Purdue isn't even the only source for oxycodone. OxyContin is protected by patents, but oxycodone has been around since 1916. It's made around the world by many other companies. It's a generic medicine in the U.S. There's a huge supply worldwide. Is some of that being diverted into illegal channels? The question pretty much answers itself. Oxycodone, fentanyl, and other opioids come into the U.S. by many different routes to supply the underground trade. The heavily-regulated U.S. drug industry doesn't supply much, if any, of that illegal supply.

Lawsuits are a blunt instrument. Still, adverse publicity combined with monetary damages may have a beneficial effect. If nothing else, they will discourage other entrepreneurs from pushing harmful drugs on the public. Or at least, dampen their enthusiasm. Voltaire once said that the English found it good to kill an admiral from time to time, to encourage the others.[5] Our tort system doesn't actually kill anybody, but the overall effect is similar.

If nothing else, all of this publicity means that we as physicians don't have to accept all of the blame for the opioid epidemic. We do have our share of the accountability, to be sure. We were gullible, when we should have been skeptical. Optimistic, when we should have been wary. We should have known better. But… we, too, are part of society. What everyone believes, we come to believe. And we wanted to believe that we could relieve pain, without risks and consequences. We still want to do that. But now, perhaps, we have become more careful.

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Ovarian Cancer and "Tainted Talc": What Treating Physicians Need to Know

by Rachael Casey, PhD & Timothy P. Larkin

Introduction

On July 12, 2018, a St. Louis City jury sent shock waves across the world, awarding 22 plaintiffs $550 million in compensatory damages and $4.14 billion in punitive damages in a lawsuit against Johnson & Johnson over claims its talcum powder products caused ovarian cancer in women who used the company's products for years.[1]

This case signals a change in the litigation surrounding talc product-induced ovarian cancer in Missouri by placing the blame on potential "contaminants" of talc, rather than the talc itself.





Rachael Casey, PhD, (left), an associate attorney in the Chicago office of Husch Blackwell and a former ovarian cancer researcher, and Timothy P. Larkin (right), an associate attorney in the St. Louis office of Husch Blackwell with experience in mass torts, product liability, and talc litigation in Missouri, wrote this article. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are encouraged to consult their own attorney concerning their specific situation and specific legal questions.

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This recent verdict marked a change from previous talcum product cases in St. Louis by focusing on claims that ovarian cancer was caused by exposure to asbestos allegedly found in Johnson & Johnson's talcum powder, compared to claims that the cancer was caused by the talc. Further, the July 2018 verdict was the first multi-plaintiff talcum powder litigation decided in the United States. To date, evidence presented in the state court trials included company documents that suggested Johnson & Johnson may have been aware of the potential link between talcum powder contaminants and ovarian cancer since the 1970s.

The purpose of this article is to give an overview of the current medical knowledge as to the causes of ovarian cancer, outline the current state and strategies of talc-related ovarian cancer litigation in Missouri, and identify practical challenges facing medical professionals as a result of this ongoing litigation.

Ovarian Cancer & Risk Factors

The American Cancer Society predicts that there will be approximately 22,240 new cases of ovarian cancer diagnoses and approximately 14,070 ovarian cancer deaths annually in the United States.[2] The most reliable predictors of ovarian cancer are a familial history of breast or ovarian cancer and mutations in certain *BRCA1* and *BRCA2* genes, suggesting that the disease has a strong genetic component.[3] Increased incidence of ovarian cancer is associated with women who are over 55 years old, have never given birth to children, or have taken hormone replacement therapy for over ten years.[4]

While several factors predicting ovarian cancer risk have been identified, no factors have been proven to cause ovarian cancer, although talc has long been considered a potential causative agent for this disease.[5] However, the scientific and medical communities have not reached an agreement as to whether talc usage does or does not cause ovarian cancer. The U.S. Center for Disease Control and Prevention does not list talc as an ovarian cancer risk,[6] while the International Agency for Research on Cancer, part of the World Health Organization, classifies the genital use of talc-based body powder as "possibly carcinogenic to humans."[7]

There is a body of evidence that talc product use may be associated with an increased incidence of ovarian cancer, but that evidence relies on women's memories about their past use of talc products.[8] In these studies, ovarian cancer patients remembered using talc products more often than ovarian cancer-free women, or more ovarian cancer patients remembered using talc products than ovarian cancer-free women.[9] The scientific rigor of these retrospective studies has been criticized and other research casts doubt on their reliability.[10] These studies often failed to distinguish which type of cosmetic product was used (dusting powder, baby powder, talc, bath talc), the exact composition of the cosmetic product, or the brand of the cosmetic product.[11] Nor did the studies address whether asbestos was a component of the cosmetic product investigated.[12]

Perhaps more telling, there seem to be no experimental studies providing scientific evidence that talc causes ovarian cancer.[13] This less-than-compelling scientific record may be part of the reason for the recent shift in litigation strategy: from blaming ovarian cancer on talcum products to blaming ovarian cancer on a specific compound sometimes found in coexistence with talc—asbestos.[14]

Neither talc nor asbestos has been shown to cause ovarian cancer.[15] However, asbestos is a compound that is well-known to cause lung cancer and mesothelioma.[16] It is known to be a potent carcinogen and in recent litigation, juries have been persuaded that it is carcinogenic enough to cause ovarian carcinoma.[17]

Talc Litigation in Missouri

While the first talc trial was in 2013 in South Dakota,[18] Missouri became a hot spot for such filings after the first verdict by a U.S. jury to award damages over such claims was ordered in the Circuit Court of the City of St. Louis in February 2016.[19] Since the February 2016 verdict, there have been several other high profile talc trials in St. Louis City, most recently with the first multi-plaintiff verdict in July 2018. As of February 2019, Johnson & Johnson is facing roughly 13,000 lawsuits over talc in the United States, most of which have been consolidated in federal court in New Jersey, where the company is headquartered.[20] About 700 of these lawsuits have been filed in St. Louis City.[21] Because of these strategic filings by plaintiffs' counsel, St. Louis City has consistently been ranked as one of the most "plaintiff friendly" venues in the country.[22] The American Tort Reform Foundation complained that plaintiffs' lawyers' ability to "introduce junk science in the city's talc litigation" helped to explain St. Louis city's popularity as a place to file these lawsuits.[23]

Many of the unsuccessful lawsuits against Johnson & Johnson lacked persuasive explanations of the biological mechanisms by which talc is exposed to ovaries and by which talc causes ovarian cancer.[24] In the Ingham case, a new theory prevailed. Here, specific components of Johnson & Johnson's talcum powder products were identified and called out as cancer-causing agents: the talc itself, as well as "other carcinogens, including asbestos, asbestiform fibers, and arsenic."[25] Instead of solely relying on talc as the cancer-causing culprit, the litigants offered the theory that the talc was "tainted" with known carcinogens.

The Food and Drug Administration, which investigates and monitors reports of asbestos contamination in consumer products, commissioned a survey in 2009-2010 to screen for asbestos in raw material talc, commercial talc, baby powders, and talc-containing cosmetics. It reported that no asbestos was detected in any of the samples.[26]

There are allegations that Johnson & Johnson routinely performed certain quality assurance tests on its source talc.[27] An internal memo in 1969 referred to tests reporting that some of their talc samples tested positive for trace amounts of asbestos.[28] Tests performed between 1970-2000 yielded results that indicate that some samples might have contained trace elements.[29] It is unclear whether Johnson & Johnson's testing definitively established that those trace elements were asbestos or some other non-carcinogenic agent.[30] Johnson & Johnson chose not to share the information with the public.[31]

The Ingham court was persuaded that Johnson & Johnson knew or should have known that the talc it purchased to make its baby powder might have been contaminated with carcinogens such as asbestos. This seems to be the first successful ovarian cancer lawsuit that relied on the theory that Johnson & Johnson's source talc material might have been contaminated with traces of asbestos or other cancer-causing compound.[32]

In view of these recent developments, the Department of Justice has subpoenaed Johnson & Johnson for internal company documents about its knowledge of asbestos risks in its talc products.[33] It is hoped that the presence or absence of asbestos in Johnson & Johnson's source talc will be definitively settled. But for now, it simply is unclear whether Johnson & Johnson's talc products may or may not have contained asbestos.

But even if asbestos is confirmed to have been in Johnson & Johnson's source talc, there is still the unresolved question as to whether or not asbestos causes ovarian cancer, and whether asbestos would cause ovarian cancer when present in trace amounts in genital talc products.[34]

The litigation outcomes have been mixed, but the awards have been large enough to induce Imerys Talc America Inc., which supplies talc to Johnson & Johnson, to file for bankruptcy to end the lawsuits alleging that Imerys's talc caused ovarian cancer or mesothelioma.[35] Johnson & Johnson remains committed to fighting the ongoing litigation in Missouri after the Ingham verdict, explaining "every verdict against Johnson & Johnson in this court that has gone through the appeals process has been reversed."[36]

Treating Physicians & Causation Theory

The debate in the scientific and medical community as to whether talc usage may cause ovarian cancer has impacted the litigation strategy and role of expert testimony in talc trials to date. When it was noted in the Ingham lawsuit that, during the course of their patients' treatment, none of the plaintiffs' treating physicians concluded that talcum powder products caused their patients' ovarian cancer, the plaintiffs filed a motion to exclude testimony on causation from plaintiffs' own treating physicians.[37]

Missouri courts now follow the Daubert standard for the admission of expert testimony.[38] Under this standard, a witness who is qualified as an expert by knowledge, skill, experience, training or education may testify in the form of an opinion or otherwise if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principals and methods to the facts of the case.[39]

Following this standard, the Ingham plaintiffs argued that their own treating physicians should be excluded from providing testimony on causation, as plaintiffs' treating physicians either testified they were not experts in the causal relationship between talc and ovarian cancer, or that they did not have an opinion as to whether their patient's cancer was caused by exposure to talcum powder.[40] Plaintiffs further argued that treating physicians who stated that they had no opinion about the cause of their patients' ovarian cancer should be excluded from testifying about topics related to causation, as such testimony would not be helpful to the trier of fact.[41]

In opposition, Johnson & Johnson reasoned that outside of known causes of ovarian cancer such as certain genetic factors, it is not possible to identify the cause of an individual patient's cancer within the present state of scientific knowledge, acknowledging that plaintiffs' treating physicians deposed in Ingham generally testified they had not formed opinions about the specific cause of their patient's ovarian cancer.[42] Johnson & Johnson argued against plaintiffs' attempt to attribute treating physicians' non-position on causation to an alleged lack of expertise, even though understanding the risk factors for and causes of ovarian cancer is part of any treating physician's training, background and experience.[43]

In the end, the physicians who expressed opinions about causation in this case were allowed to testify about that subject at trial, while the physicians who hadn't expressed opinions on causation were not allowed to testify about that subject at trial.[44]

The role of expert testimony was crucial in the outcome, as the Ingham court relied on the paid expert causation testimony of Drs. Dean Felsher and David Egilman, neither board-certified in gynecology or oncology at the time of trial,[45] to conclude plaintiffs' ovarian cancer was a result from plaintiffs' exposure to talcum powder.[46]

Ongoing Liability Issues for Treating Physicians

In future talc litigation, it is likely that treating physicians will be called upon as either an expert witness for litigants or as a fact witness for their patients, or both.

As physicians evaluate patients diagnosed with ovarian cancer, it may be prudent to identify which factors should be assessed as causing or contributing to the disease. It may also be prudent to develop protocols to ensure such factors are uniformly assessed for all affected patients.

As scientific and medical views about the causative factors of ovarian cancer evolve, such protocols can be updated and those revisions documented as needed.

Thus, in the future, when a patient becomes a litigant, she can present to the court facts that were recorded by her treating physician, and the principles and methods her treating physician used to memorialize those facts. Whether the treating physician is asked to supply an opinion or a

factual record, the court is more likely to be satisfied that the physician's record is reliable and suitable for the court's consideration when shown that the record was generated in a manner consistent with Missouri standards for expert testimony.

Conclusion

As attorneys, we have focused on the legal issues relating to talc products as potential causative agents for ovarian cancer, but this litigation will likely affect the medical practices of many physicians.

The ongoing cases may reshape attitudes about what is considered a cancer-causing agent and what isn't, what a physician's best practices are when a common household item is classified as "maybe" containing cancer-causing agents, and how to answer patients' questions when they ask their doctor to assess the risks posed by their past use of certain products.

At the very least, the physicians of ovarian cancer patients should be prepared for patients' questions about causation when the cancer is initially diagnosed, and for lawyers' questions about causation many years later.

For more specific information about the legal ramifications of these practices, you should consult with a licensed attorney who specializes in healthcare-related litigation issues.

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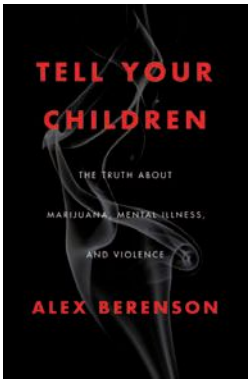
Marijuana Is More Dangerous Than You Think

by Alex Berenson



As legislation spreads, more Americans are becoming heavy users of cannabis despite its links to violence and mental illness.

Over the past 30 years, a shrewd and expensive lobbying campaign has made Americans more tolerant of marijuana. In November 2018, Michigan became the tenth state to legalize recreational cannabis use; New Jersey and others may soon follow. Already, more than 200 million Americans live in states that have legalized marijuana for medical or recreational use. Yet even as marijuana use has become more socially acceptable, psychiatrists and epidemiologists have reached a consensus that it presents more serious risks than most people realize.



Alex Berenson is a former *New York Times* reporter and author of 12 novels. This essay is adapted from his new book, "Tell Your Children: The Truth About Marijuana, Mental Illness and Violence."
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Contrary to the predictions of both advocates and opponents, legalization hasn't led to a huge increase in people using the drug casually. About 15% of Americans used cannabis at least once in 2017, up from 10% in 2006, according to the federal government's National Survey on Drug Use and Health. By contrast, almost 70% of Americans had an alcoholic drink in the past year.

But the number of Americans who use cannabis heavily is soaring. In 2006, about 3 million Americans reported using the drug at least 300 times a year, the standard for daily use. By 2017, that number had increased to 8 million—approaching the 12 million Americans who drank every day. Put another way, only one in 15 drinkers consumed alcohol daily; about one in five marijuana users used cannabis that often.

And they are consuming cannabis that is far more potent than ever before, as measured by the amount of THC it contains. THC, or delta-9-tetrahydrocannabinol, is the chemical responsible for the drug's psychoactive effects.

In the 1970s, most marijuana contained less than 2% THC. Today, marijuana routinely contains 20-25% THC, thanks to sophisticated farming and cloning techniques, and to the demand of users to get a stronger high more quickly. In states where cannabis is legal, many users prefer extracts that are nearly pure THC.

Cannabis advocates often argue that the drug can't be as neurotoxic as studies suggest because otherwise Western countries would have seen population-wide increases in psychosis alongside rising marijuana use. In reality, accurately tracking psychosis cases is impossible in the U.S. The government carefully tracks diseases such as cancer with central registries, but no such system exists for schizophrenia or other severe mental illnesses.

Some population-level data does exist, though. Research from Finland and Denmark, two countries that track mental illness more accurately, shows a significant increase in psychosis since 2000, following an increase in cannabis use. And last September, a large survey found a rise in serious mental illness in the U.S. too. In 2017, 7.5% of young adults met the criteria for serious mental illness, double the rate in 2008.

None of these studies prove that rising cannabis use has caused population-wide increases in psychosis or other mental illness, although they do offer suggestive evidence of a link. What is clear is that, in individual cases, marijuana can cause psychosis, and psychosis is a high risk factor for violence. What's more, much of that violence occurs when psychotic people are using drugs. As long as people with schizophrenia are avoiding recreational drugs, they are only moderately more likely to become violent than healthy people. But when they use drugs, their risk of violence skyrockets. The drug they are most likely to use is cannabis.

The most obvious way that cannabis fuels violence in psychotic people is through its tendency to cause paranoia. Even marijuana advocates acknowledge that the drug can cause paranoia; the risk is so obvious that users joke about it, and dispensaries advertise certain strains as less likely to do so. But for people with psychotic disorders, paranoia can fuel extreme violence. A 2007 paper in the *Medical Journal of Australia* looked at 88 defendants who had committed homicide during psychotic episodes. It found that most of the killers believed they were in danger from the victim, and almost two-thirds reported misusing cannabis—more than alcohol and amphetamines combined.

The link between marijuana and violence doesn't appear limited to people with pre-existing psychosis. Researchers have studied alcohol and violence for generations, proving that alcohol is a risk factor for domestic abuse, assault and even murder. Far less work has been done on marijuana, in part because advocates have stigmatized anyone who raises the issue. Still, there are studies showing that marijuana use is a significant risk factor for violence.

A 2012 paper in the *Journal of Interpersonal Violence*, examining a federal survey of more than 9,000 adolescents, found that marijuana use was associated with a doubling of domestic violence in the U.S. A 2017 paper in the journal *Social Psychiatry and Psychiatric Epidemiology*, examining drivers of violence among 6,000 British and Chinese men, found that drug use was linked to a fivefold increase in violence, and the drug used was nearly always cannabis.

Before states legalized recreational cannabis, advocates predicted that legalization would let police focus on hardened criminals rather than on marijuana smokers, and thus reduce violent crime. Some advocates even claim that legalization has reduced violent crime: In a 2017 speech calling for federal legalization, Sen. Cory Booker (D, NJ) said that "these states are seeing decreases in violent crime."

But Mr. Booker is wrong. The first four states to legalize marijuana for recreational use were Colorado and Washington in 2014 and Alaska and Oregon in 2015. Combined, those four states had about 450 murders and 30,300 aggravated assaults in 2013. In 2017, they had almost 620 murders and 38,000 aggravated assaults—an increase far greater than the national average.

Knowing exactly how much of that increase is related to cannabis is impossible without researching every crime. But for centuries, people all over the world have understood that cannabis causes mental illness and violence—just as they've known that opiates cause addiction and overdose. Hard data on the relationship between marijuana and madness dates back 150 years, to British asylum registers in India.

Yet 20 years ago, the U.S. moved to encourage wider use of cannabis and opiates. In both cases, we decided we could outsmart these drugs—enjoying their benefits without their costs. And in both cases, we were wrong. Opiates are riskier than cannabis, and the overdose deaths they cause are a more imminent crisis, so public and government attention have focused on them. Soon, the mental illness and violence that follow cannabis use also may be too widespread to ignore.

Editor's Note

See "The Cardiovascular Effects of Marijuana: Are the Potential Adverse Effects Worth the High?" on page 146 of this issue.

MM

The Joys and Challenges of Sixty-Five Years in Medicine: A Personal Perspective

by Donald E. Kuenzi, MD

As a child and during adolescence, I had no passion to become a physician. That desire came much later in 1946, during my enrollment at the University of Missouri (MU) in Columbia.

I am now in my 90th year, beginning life as a farm boy during the hardscrabble depression years. Figure 1. With the December 7, 1941, infamous Pearl Harbor bombing, World War II began. I joined the Navy on my 18th birthday, too late to be involved in combat, but I did serve as a radio operator on a mine sweeper staff off southern Japan. I then entered college.

It was during my sophomore year at MU that my physician epiphany occurred. I was living in a rooming house. A fellow MU housemate and I had one of those intimate life-sharing conversations common then, as now, between college students. He was a pre-med student. I was in agriculture school after a brief stint in arts and science. My friend was a charismatic person. He convinced me that medicine was really my calling, not the life of an educated farmer. From that very moment, medicine has been my passion, my career, my muse, my joy. I believe this late-night discussion was providential intervention.



Figure 1. Doctor Don and Martha Kuenzi on receiving the University of Missouri School of Medicine Distinguished Service Award, March 17, 2016.

Donald E. Kuenzi, MD, is a retired general practitioner and MSMA member since 1956. He received the Lifetime Achievement Award of the Kansas City Medical Society and served as President of the Clay County Medical Association, and in many medical organization leadership positions. He and his wife, Martha, have been married 67 years. They have five children, and live in Kansas City, Missouri.
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Using my arts and science courses and swiftly taking pre-med studies, I was soon eligible to apply to the two-year medical school at MU. I was elated when I was accepted. Today when first-year students begin medical studies, they are welcomed warmly into the profession. Special ceremonies are held with their parents, spouses, and family. They are given a white lab coat symbolic of entry into the esteemed profession of medicine.

In the 1950s, when I entered medical school, there was no such ceremony. There was an undercurrent of fear and intimidation. We were told 'you better keep up or you are out.' We wondered if we would pass the difficult 'weed out' courses? As a freshman, anatomy was the pass-fail 'weed out' course. It was taught by Milton Overholser, MD. His class began each day with what we called 'The Rodeo.' Dr. Overholser would ask one of the students to describe the body part to be studied that day – and delivered word for word from Cunningham's Anatomy – in front of the class. Dread was the emotion each day. Would my name be called? Would I be prepared? Usually I was. I passed the course.

As a sophomore, pathology was another high fail course. M. Pinson Neal, MD, was the professor. He began our first day of class with this threat, "I want you boys (there were only two females in the class of 1952) to know that come springtime, some of you will be down in the Ozarks plantin' corn!" Despite these intimidating negatives, learning the basic medical sciences was unbelievably exciting and stimulating.

After successfully completing the first two years of MU medical school, I transferred to the University of Kansas (KU) for my final two years. KU graciously accepted me as part of its junior year class. For this I was most thankful. I mention this because four-year medical schools were under no obligation to offer such acceptance.

In my junior year at KU medical school, 68 years ago, I married my wife Martha, the former Martha Reid of Carrolton, Missouri. Our marriage is the most significant blessing of my life. About two years later we had our first child, a daughter. In 1953 after obtaining an MD degree and

passing the state board exam, I would begin my internship. An intern's salary (if you can call it that) in the Kansas City area was $50/month. Our young family was strapped for cash. If a physician interned at a military hospital, the salary was a then astounding $250/month. Military internships offered excellent post-graduate training. We were off to Oceanside, California, to begin internship at Camp Pendleton Naval Hospital. Figure 2. As my rotating internship developed, I felt it was a very good choice. The teaching staff consisted of specialists from esteemed universities serving their military obligations, all eager to educate interns.



Figure 2 Above, Martha and Don Kuenzi, MD, and baby Anne, Camp Pendleton Naval Hospital, 1955.



Figure 3. Right, Dr. Kuenzi always enjoyed obstetrics, pediatrics and family care during his practice at the Gashland Clinic. Shown 1956 with a one-year well-baby check-up.

As I considered what to do post internship, knowing my inclination was to be a family doctor, I began to look for a place to practice. Family practice residencies were not developed until later. In 1954, family and general practice usually began after a one-year internship. A call came from a Kansas University classmate informing me of a position in family medicine in Gashland, Missouri, a northern suburb of Kansas City. The practice was started by a physician who was called into the Army. I flew back to Kansas City on a four-engine TWA Constellation, surveyed the opportunity, and agreed to take the position when my military obligations were complete.

In 1954, if one graduated from medical school, completed a year of internship, and passed the state board examination, the physician was legally allowed to practice medicine and surgery in that state. Thankfully, today's family practice minimum standards require three years of post-graduate training. I was ill-prepared for my responsibilities. Besides a very busy office, the preceding physician had a sizeable obstetrics practice. A typical day might include hospital rounds, over 50 office patients, several house calls, and perhaps a delivery. Figure 3. In addition to my professional duties, our family steadily expanded to five children. With increasing demand for my time, we added an associate at the Gashland Clinic, and another, and then another. In 2019, the Gashland Clinic has 15 primary care physicians and is one of the largest primary care groups in the Kansas City area.

Initially it was not fun. Office practice was terrifying. Later it became satisfying, eventually joyous. So, where did the joy come in being a family doctor? It began with solid relationships with professional colleagues. Our local group was the Clay County Medical Association. It was a close-knit group, meeting monthly, with a scientific program about a specific disease or a new surgical procedure. A physician starting family practice with a medical degree and one year of internship needed a lot of help. Clay County medical meetings allowed FPs to meet specialists who were willing to answer questions that inevitably arose in my practice. Doctors in the major specialties could be called for advice, and I frequently enlisted their help. For instance, a woman presented with a painful, swollen eyelid. I knew it was a chalazion but didn't know how to care for it. I called an EENT doctor friend thinking he would need to see her. Instead he said, "You can take care of a chalazion," and he outlined what to do. I treated her successfully. Through the ensuing years, I saw many problems that, because of specialists' willingness to share their expertise, I could competently treat. The EENT, a surgeon, a pediatrician, and a pathologist friend were especially helpful in my early years of practice.

By 1970, a national Family Practice Board had been organized and an appropriate board examination created. My goal was to pass the exam and become board certified. By that time my family practice had encompassed about 15



Figure 4. Above, overseas medical missions after his retirement from family practice at age 65, allowed Dr. Kuenzi to continue serving as a physician and seeing many remote areas. He is treating a woman in Nepal, 1999.



Figure 5 Below, Kuenzi children, 2015. Left to right John, Robert, Anne, Frederick, Martha Caroline with Don and Martha Kuenzi.

years. During that time, I was constantly learning by patient experience, reading journals, and absorbing much medical knowledge from my Clay County colleagues. I took two weeks off my medical practice to go to the University of Nebraska Medical School in Omaha to attend an intense review of material likely covered in the FP Board exam. I passed the exam and became certified in the American Board of Family Practice. I will forever be grateful to those generous colleagues who helped prepare me for the exam. To remain certified FPs had to repeat the exam every seven years. Before I retired, I had been successfully re-certified two times. This was a joyous process.

Another joy came in the process of "doctoring." It was satisfying when my treatments were successful, and a learning experience when unsuccessful. I made visits for all my hospitalized patients and was involved in their care. I scrubbed on all their major surgeries. I learned to perform tonsillectomies. If an obstetrics patient required a Caesarian section, I scrubbed in on the procedure and assumed care of the infant. I loved attending the birth of a child. Every delivery was almost a spiritual experience of utmost joy. Many of today's FP no longer see their patients in the hospital, turning their care over to a hospitalist. I found that caring for patients in the hospital made me a better physician. It was also an intense learning experience, expanding my knowledge by being involved in dealing with very sick patients. In my case, doing hospital work was not sound economically, but satisfying professionally.

After practicing nearly 45 years, I retired from Gashland Clinic office practice at age 64. The joy of being a family doctor was amplified by the many retirement letters from patients with whom I had interacted over the years. In many instances, those patients had become great friends. I often cared for several generation members. After that bittersweet change in lifestyle, an association with a Christian Medical-Dental Missionary Group in Tulsa, Oklahoma, allowed me to travel to several countries including Irian Jaya (now West Papua of Indonesia), Cameroon, Africa (three trips with Martha joining me), Myanmar (formerly Burma) with Martha, Sumatra, and Nepal. These trips widened my understanding of the extent of poverty in the world, and the many people who have little or no medical care available. Medical travel deepened my appreciation of the good fortune of having been born in the United States. Figure 4.

Still later in retirement years, I became restive. As a twice-retired veteran of Navy service, I took a part-time position at a local VA Hospital as a compensation-pension examiner. It was a joy to interact and serve the veterans seeking disability benefits. My three days a week job over eight years produced some of the most satisfying experiences of my medical career.

In retrospect, being a physician in family practice for 45 years, after some difficult early years of practice interlaced with fear and trepidation, has been a remarkably satisfying, fulfilling – yes even joyful – experience. Additionally, a committed and supportive wife of 67 years, five healthy and bright children, and a growing Christian faith comprise for me a wonderful life. Figure 5. My hope is that each physician will also feel the same as he or she ends a medical career.

Acknowledgments

Thanks to Noreen Wittwer and Jennifer Nye Johnson for assistance in article preparation. **MM**

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Tutte le cose buone devono finire....
"All Good Things Must Come to an End"

by Joseph A. Corrado, MD

As my year as your MSMA President winds down, please allow me to tell you what's been going on throughout my travels, and what's been on my mind since our last visit in *Missouri Medicine*.

Donna and I had the privilege of attending the Boone County Medical Society's Gala held at the Old Hawthorne Country Club in Columbia on Feb. 2. We were cordially received as the oath of office was administered to Josh Hamann, MD, a Columbia orthopedist, and President Elect Alan Hillard, MD, and several other officers. Many familiar faces greeted us including Drs. Ted Groshong and Jerry Murrell, and George Hubbell as we recognized Beverly Wilcox as past executive director of BCMS and celebrated with John Pardalos, MD, as he received the Distinguished Physician Award. I felt I was coming full circle, after representing District #5 on the MSMA Council for more than a quarter of a century, my last official county installation would be here ... most fitting indeed.

It was off to MSMA's White Coat Rally day on March 5, where dozens of physicians and students in their white coats descended on the Capitol and met with their legislators. Our two pressing issues were bills regarding prior authorization and the PDMP. Just as the legislature is at its halfway point, we hope we can score victories, and it seems that both bills are advancing. Naturally, we always are watching those bills regarding APRN licensure and scope of practice closely.



Joseph A. Corrado, MD, FACS, a surgeon from Mexico, Mo., and MSMA member since 1982, is MSMA President for 2018-2019.
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Last month, during their medical society meeting the Boone Medical Society had an excellent presentation by the leaders of the PDMP from St. Charles County. They did an amazing job explaining and educating the members on their excellent program, and how anyone willing could participate in it. Cost-free, voluntary, and immediately available were the messages they brought.

As you may recall, I am a general surgeon who practices in a small town, and I am very involved in rural surgery's plight and the struggles of our rural hospitals in general. I have been an advocate with the American College of Surgeons in this regard.

What you may not know, is about seven years ago, while attending the Second Annual Rural Surgeon's dinner at the Clinical Congress in San Francisco, I invited our daughter, Meredith, to come up from Los Angeles and join her mom and me. Little did I know how important that trip would become.

There, enveloped in the atmosphere of camaraderie and absorbing the content, she remarked, "Dad, I'd like to make a documentary on rural surgery in the United States. They are all just like you, saying the same things, and all having the same concerns!" Once I knew she was serious, I introduced her to several surgeons from across the country. Traveling with a film crew throughout the country from New York to Oregon, her 200 hours of interviews and research came to fruition and she was finally proud to have her documentary, "Code Blue - Resuscitating Rural Surgery," premier as a red-carpet event in her home town of Mexico at the Presser Performing Arts Center.

Missouri physicians were well represented as Drs. Mike Bukstein, Patricia Hirner, Clark Andelin, Charles Van Way, Jeff Coughanhauer, and I were all captured on film. Many more were interviewed and referenced, but it is only 70 minutes, and jam-packed. There were dignitaries at the premier, including Representative Kent Haden, DVM; Vice president of the American College of Surgeons Phil Caropreso, MD; Karen Deveney, MD, of the American College of Surgeons and the University of Oregon Health Center; and Mike Borgstrom, MD, representing rural surgeons as the former director of the Mittendorf Rural Surgery Center in New York. It was an overwhelming

success, and through this vehicle the College has already used part of the documentary to educate and recruit.

The documentary talked about the struggles to find and keep surgeons, and for that matter, all physicians, in small towns, how important they are to hospitals, and the importance of hospitals to rural economy. Statistics show that the economic worth of a general surgeon to a hospital is between 1.05-2.07 million dollars/year, and that as much as 40% of a small hospital's operating revenue is based on revenues generated by a general surgeon. General surgeons generate about 4.4 million in payroll and creates 26 jobs, including office staff, nurses, lab, and radiology, etc. In fact, many small hospitals are in danger of closing unless they recruit and retain a general surgeon.

But little did I know how soon this would affect me. In my recent research, I have found that 93 rural hospitals have closed between January 1, 2010 and December 17, 2018 as tracked by the North Carolina Rural Health Research Program. By definition, those are hospitals who have ceased providing inpatient services, including six in Missouri alone, and I'm sure we will see more and more to come.

Certainly, times are changing, I understand, but not all for the better. As you may have heard, mid-Missouri is also facing many changes in hospital affiliations and the medical care model. And as I speak, with mergers and system acquisitions abounding, usually "he who pays makes the rules."

I would never have imagined that my own hospital, after celebrating its centennial anniversary would also be affected. We are in the process of hopefully being sold. As of last month, without any discussion or warning, decisions were made to close both our obstetric and pediatric services at SSM-St Mary's Audrain, and subsequently to restrict our anesthesia coverage to the daylight hours Monday through Friday, no nights, weekends, or holidays. That really restricts what an acute care general surgeon, like myself, can safely do. I have given nearly 37 years of my career and my heart to this place.

SSM-St. Mary's Audrain is in the process of negotiations with the University of Missouri Health System and hope this goes through without any glitches; we will see how this will all play out in the end. It certainly will affect our community and all physicians practicing in this area. Our hospital is the number one employer in our county.

There was a study by Finlayson regarding rural hospitals. It produced interesting results, asking residents





Above, "Code Blue - Resuscitating Rural Surgery," premiered as a red-carpet event in Mexico, Missouri, at the Presser Performing Arts Center.

Bottom, Dr. Corrado on the red carpet at the "Code Blue" premiere with spouse, Donna.

where they wanted their care. One hundred percent of those responding would seek care closer to home if the risk at local vs. a remote hospital was equivalent. However, 45% of patients would still seek local care even if local mortality risks were double that of the remote hospital. Astonishingly, 23% of respondents would still stay at their local hospital with a fourfold increase risk of dying. That speaks volumes on where patients would like their care.

So, it is imperative that WE continue to support our local rural hospitals, the economic lifeblood of many communities.

And with that, if you are reading this now, I will have seen you all at the 161st MSMA Annual Convention at the Westin Crown Center in Kansas City, where I handed over my gavel to James DiRenna, DO, the first osteopathic physician to lead the Missouri State Medical Association. I wish him the best of luck and far travels as he visits the good physicians of the state of Missouri.

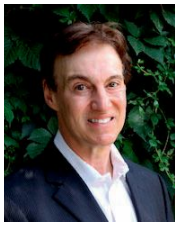
Ciao e dio vi benedica…Bye and God bless. **MM**

Missouri Medicine in the News

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



Ramona Behshad, MD, has been honored by the St. Louis Business Journal as a 40 Under 40 Young Business Leader. Dr. Behshad, an MSMA member since 2012, serves as Councilor to the MSMA Young Physician Section and also as President of the Saint Louis Metropolitan Medical Society (SLMMS).

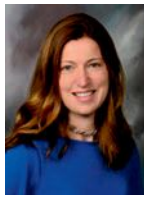


Nicholas Comninellis, MD, MPH, DIMPH, MSMA member since 2019, was honored by the Kansas City Medical Society with the 2018 Patient and Community Advocate Award. Dr. Comninellis in 2004 formed the Kansas City-based Institute for International Medicine (INMED), which prepares physicians and other health professionals in the unique aspects of international mission health care serving the world's most marginalized people.



Christopher Carpenter, MD, MSMA member since 2016, was installed as Professor of Emergency Medicine at Washington University in St. Louis. He is only fourth such Professor in the University's history to be earn this honor. Dr. Carpenter is the *Missouri Medicine* Editorial Board member for Statistics and Methodology.

MSMA wishes to commend Jennifer Conley, MD (left); Amanda Turner, MD (middle); and Benjamin Wilson, MD (right), for serving in a new hospitalist program at Nevada Regional Medical Center to ensure complete coverage is provided within the community. Combined, they represent more than 30 years of MSMA membership support.

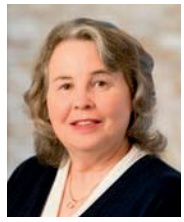








James P. Crane, MD, MSMA member since 1992, Washington University School of Medicine, is a recipient of the 2018 Award of Merit by SLMMS, for his distinguished service to scientific medicine in the St. Louis community.



Congratulations to Betty Drees, MD, *Missouri Medicine* Contributing Editor, on being named a 2019 Icon of Education by Ingram's magazine. Dr. Drees in 2018 became president of the Graduate School of the Stowers Institute for Medical Research. She also is Dean Emerita and a professor at the University of Missouri-Kansas City School of Medicine, where she served as dean for 13 years. An endocrinologist, Dr. Drees is president-elect of the Kansas City Medical Society.



The SLMMS Alliance honored Arthur Gale, MD, as their 2019 Doctor of the Year on Feb. 8. Dr. Gale joined MSMA in 1976, is *Missouri Medicine* Contributing Editor, and has been a steadfast supporter of his patients and profession throughout his career. Sue Ann Greco, SLMMS Alliance President, presented the award.



The 2019 Kansas City Society of Ophthalmology and Otolaryngology presented the Hal Foster Award to John Hagan, MD, *Missouri Medicine* Editor, MSMA member since 1977, at their annual conference on February 8, 2019. The Hal Foster Award is given annually to one ophthalmologist and one otolaryngologist who promotes professionalism and the ideals of Hal Foster, MD, founder of the American Academy of Ophthalmology and Otolaryngology. John Doane, MD, KCOO President, presented the award.



MSMA wishes to congratulate Myrna Gover-Havener, MD, MSMA member since 2011, on joining Compass Health Network in Union.



George J. Hruza, MD, MBA, has assumed the Presidency of the American Academy of Dermatology. Dr. Hruza has been an MSMA member since 1989 and currently serves as MSMA Council Chair.



Laurence Kinsella, MD, was featured in an online article of Bicycling on Jan. 30, 2019, titled "Why This Neurologist 'Spin Doctor' Wants You to Keep Riding." We appreciate Dr. Kinsella's membership support since 2003.



MSMA couldn't be prouder of our Immediate Past President Warren Lovinger, MD, and member since 1979, for the work he is doing in his community to develop support for health care services in Nevada, Mo., through a group called Citizens United to Strengthen Our Hospital.

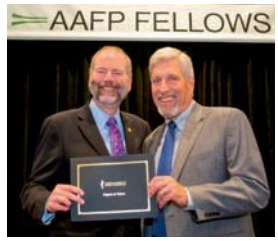


Henry Nasrallah, MD, chair of the St. Louis University Department of Psychiatry, and his wife, Amelia, a research psychologist, have established The Henry and Amelia Nasrallah Center for Neuroscience at Saint Louis University. Dr. Nasrallah is a new member of MSMA.



An MSMA member since 2008, Justin Puckett, DO, FACOFP, (right) has been awarded the 2019 Osteopathic Family Physician of the Year Award by the Missouri Society of the American College of Osteopathic Family Physicians.

Debbie Royce, MD, was selected as the 2018 Citizen of the Year by the Sarcoxie Chamber of Commerce. MSMA appreciates having Dr. Royce as a dedicated member since 2016.



Congratulations to Robert Dwight Shaw Jr., MD, FAAFP, (right) MSMA member since 1980, for achieving the Degree of Fellow of the AAFP!



Caleb Steffen, MD, has been involved in organized medicine ever since attending medical school. MSMA is proud to congratulate him on beginning his new practice with the Jefferson City Medical Group and as an affiliate to Capital Region Medical Center.



Congratulations to loyal MSMA member Kelvin Walls, MD, since 1986 for expanding his practice to include seeing patients at Harrisonville Medical Clinic.



Robert C. Wetzel, MD, has joined the team at Golden Valley Medical in Clinton. MSMA is proud to call Dr. Wetzel an MSMA member since 1994.



Richard L. Wirtz, DO, has been an MSMA member since 2017 and recently joined the team at Saint Francis Healthcare System. Congrats!

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

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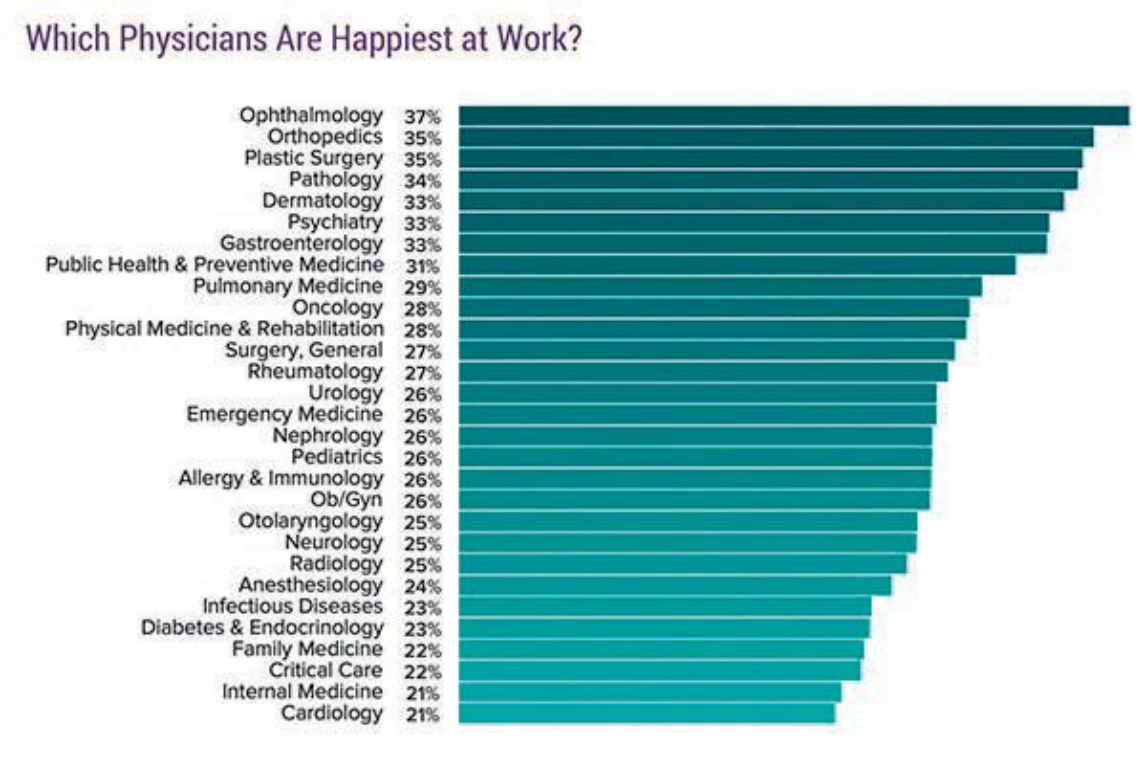
To the MSMA Executive Vice President, Patrick Mills:

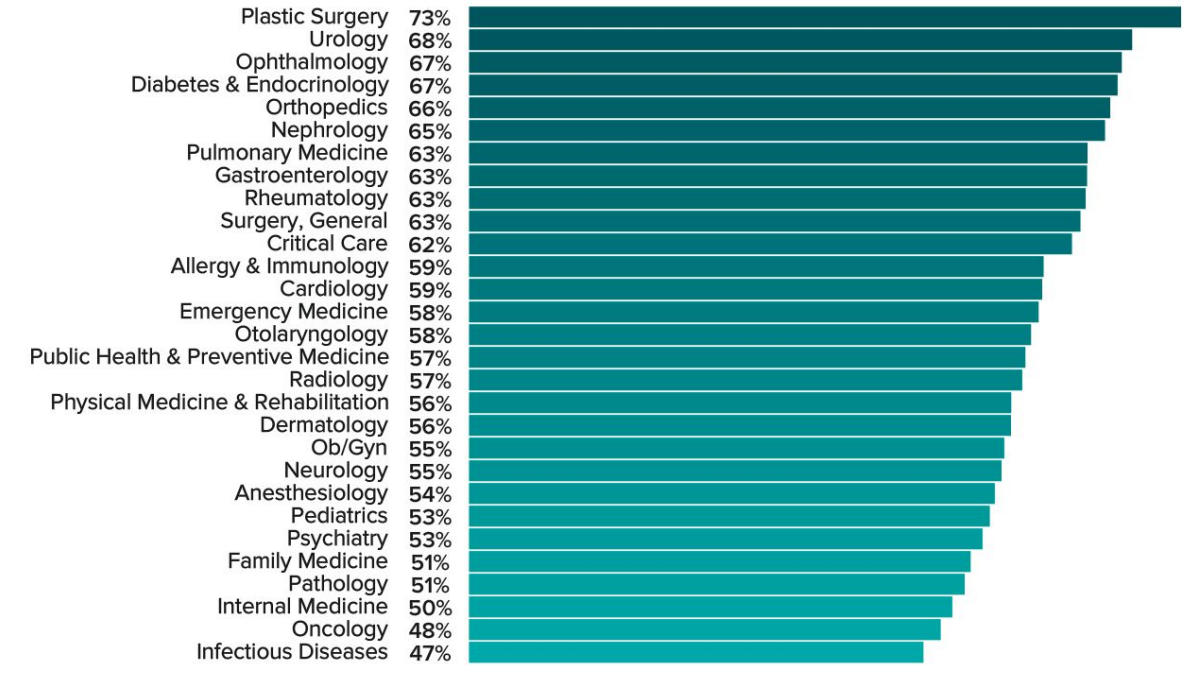
I have been a regular reader of many journals for years. The *Missouri Medicine* journal is truly outstanding especially in the pertinence for current medical practice and the true quality of the writing. A physician can keep up with a lot of modern medical thought by reading this journal. I have previously sent emails to Dr. John Hagan complimenting his editor role. Missouri physicians should really appreciate *Missouri Medicine*.

Richard Whiting, MD, MACP
MSMA member since 1989

MM

1 Picture = 1,000 Words





Source: Medscape

Legislature, Match Day, and Annual Meeting Fill Alliance Calendar

by Gill Waltman

The Alliance Winter Board Meeting and Day at the Legislature were held February 19-20 in Jefferson City in icy conditions. Our board meeting took place the first day at the Baymont Inn. Due to many cancellations, the meeting was conducted partly in person and partly by teleconference. It was most effective.

The following day at the Capitol was organized by our legislative Vice President Kirk Doan. Members were hosted by Sen. Bob Onder, currently the only physician in the Senate. We were briefed by Jeff Howell and Heidi Geisbuhler; Liz Fleenor circulated the materials needed for our visits. Alliance members visited many legislators, requesting support for the Prior Authorization Reform bill (HB 751; SB 298) sponsored by Sen. Bill White and the Prescription Drug Monitoring Program (HB 188) sponsored by Sen. Onder. Attendance at the Senate hearing for SB 298 with Sen. Onder presiding was most informative.

Excellent Match Day events were organized at medical schools across the state the week of March 11-15 as the medical students learned where they will be spending the next three to four years. Many thanks to Millie Bever and Angela Zylka for organizing these events and for the cooperation of the MSMA and medical school staff, and in the case of Columbia, the U.S. Army! Local Alliance members participated in Columbia (Donna Corrado, Mary Catherine Heimburger, Debora Snyder), Kansas City (Marsha and Dr. Jim Conant, Diana Corzine, Sana Saleh, Allene Wright and Lissa Young), and in St. Louis (Millie Bever, Sue Ann Greco, JoEllen McDonald, Sandra Murdock, Kelly O'Leary, Dr. Jo-Ellyn Ryall,and Angela Zylka.)

We are delighted with Boone County Medical Association's recent decision to reinstate and help re-form the formerly dissolved county Alliance. Members Donna Corrado and Mary Catherine Heimburger, with the help of MSMA's Steven Foutes, have worked diligently to present the case on behalf of the Alliance. They are now attempting to increase membership by rounding up former members and recruiting new ones.

The MSMA Alliance Annual Meeting was held in conjunction with the MSMA Convention in Kansas City April 4-6 at the Westin Crown Center. We'll report more on that in the upcoming editions of the *Show-Me Alliance News* and *Missouri Medicine*. **MM**



Alliance members were hosted by Sen. Bob Onder. From left: Donna Corrado, Mary Catherine Heimburger, Kirk Doan, Kelly O'Leary, Angela Zylka, Sen. Onder, Alliance President Gill Waltman, Sue Ann Greco, Sandra Murdock, Sana Saleh.



Alliance members support Match Day events at UMKC (top)and SLU (bottom).





Gill Waltman is the 2018-2019 MSMA Alliance President and Professor, Ophthalmology, Saint Louis University, St. Louis, Missouri.
Contact: gillian.waltman@gmail.com

School of Medicine
University of Missouri Health

One Medical School - Two Campuses

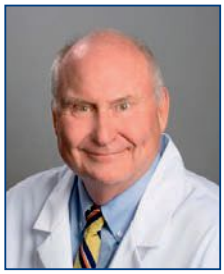
by C. Mark Costley, MD

The University of Missouri School of Medicine produces more of the state's practicing doctors than any other medical school. But for many Missourians, particularly those in rural areas, access to primary care physicians remains a significant problem. To address that issue, the MU School of Medicine launched its class-expansion project. The creation of the Springfield Clinical Campus was a key part of that plan.

The SCC opened in 2016 as a collaboration between MU and CoxHealth and Mercy hospitals. The early returns have been positive for students, attending physicians and patients. The long-term results could benefit the people of Missouri generally and Southwest Missouri specifically as more well-trained physicians with connections to the area are developed.

"I am very impressed with the quality of students coming through the program," said William Moore, MD, who practices internal medicine at CoxHealth. "They are very bright and have the talent and skills needed to be outstanding physicians in the future. They have helped me with the most recent and cutting-edge information in my practice, and my patients appreciate their input in their care.

"My hope is that by introducing them to the community and the health care environment in Southwest Missouri, they will make plans to become permanent members of our health care team. I think this is the ultimate goal for students here in Springfield."



C. Mark Costley, MD, Family Physician, is the Interim Associate Dean for Springfield Clinical Campus of the University of Missouri - Columbia School of Medicine, Springfield, Missouri.
Contact: C.Mark.Costley@coxhealth.com

MU's class-expansion project is designed to increase entering class sizes from 96 to 128. All medical students spend their first two years on the Columbia campus learning basic science from real cases through the patient-based learning curriculum. Students have the option of spending their third and fourth years gaining clinical experience in either Columbia or Springfield.

All seven basic clerkships are available in Springfield. There are two associate directors for each clerkship — one from CoxHealth and one from Mercy — and students can rotate between health systems, even in the same block.

SCC's founding associate dean, Andy Evans, MD, provided a solid foundation. In 2018, he returned to private practice, and C. Mark Costley, MD, a longtime physician in nearby Monett, took over as interim associate dean. Costley continues to recruit physician faculty and build local partnerships to expand and grow MU's Springfield Clinical Campus program.

The Springfield Clinical Campus collaboration actually goes beyond MU, CoxHealth and Mercy. The Springfield Chamber of Commerce, Burrell Behavioral Health, the Federal Medical Center for Prisoners and the Jordan Valley Community Health Center also offer support. Missouri State University provides access to its Student Health Services, IT department, library and recreation center.

The medical students have become a part of the communities of Southwest Missouri. They have completed clinical rotations in Aurora, Monett, Nixa and Strafford. They've provided hundreds of volunteer hours with local organizations such as the Springfield Area Chamber of Commerce's GO CAPS program that gives high school students a chance to explore career options, the Child Advocacy Center that helps victims of abuse, the Convoy of Hope disaster relief charity and the Ronald McDonald House.

"The creation of our Springfield clinical campus in partnership with CoxHealth and Mercy is a great example of a true collaboration that will have a lasting impact on increasing the number of well-trained physicians for our state," said Patrick Delafontaine, MD, the Hugh E. and Sarah D. Stephenson Dean of the MU School of Medicine. "We are very grateful for the support of the university, legislature and the community in Springfield and beyond."





Above, The inaugural class of medical students at the Springfield Clinical Campus, University of Missouri - Columbia, and below, the campus building.

The first group of nine Springfield students began in August 2016. All nine students graduated with Step 2 scores comparable to their Columbia peers, and all matched in their chosen specialties for their residencies. One of the benefits for Springfield students is the one-on-one attention they receive from attending physicians.

"I've gotten to do a lot more than other students across the whole U.S.," said Jakob Allen, MD, a 2018 graduate now serving a plastic surgery residency at the University of Tennessee-Memphis. "This is a unique situation and something all my interviewers wanted to ask me about. I have a lot of examples of being in surgeries and telling them some of those basic fundamental skills that first-year residents or second-year residents would usually do."

Subsequent incoming Springfield classes had 11 students in 2017 and 10 in 2018. A big jump will be made in 2019 when 29 students are slated to arrive.

MU medical students are a select and mostly home-grown group. For example, the entering M1 class of 2018 was culled from a record 2,671 applicants. The 112 who were admitted carried an undergraduate GPA of 3.73 and an average MCAT score of 77 percent. The group has roots in the state, as 85 percent of the M1s are Missouri residents.

As the class sizes grow, the hope is that more students will provide a vital service to the health of their state as practicing physicians.

"From a physician's perspective, teaching these students has inspired me to stay sharp and abreast of new medical developments and be better prepared and has brought new energy to my daily practice," said Bradley Wyrsch, MD, an orthopedic surgeon at Mercy Springfield. "Many of my colleagues have expressed similar experiences. My patients have been very willing to allow student involvement and evaluation in the clinic and seem to be aware of the importance they provide to medical education.

"Having these outstanding young men and women in our community will benefit our medical facilities in regards to recruiting and attracting young physicians to practice in Southwest Missouri. These future physicians will be providing excellent care to the people of our community for years to come." **MM**

Continuing Progress at Saint Louis University School of Medicine

by Robert W. Wilmott, MD

As the Acting Dean of Saint Louis University School of Medicine (SLUSOM) and the Acting Vice President for Medical Affairs, I am pleased to provide an update on the work that we are doing at Saint Louis University School of Medicine. We have been continuing the innovative and transformational work that was begun by my predecessor. Specifically, we have continued the strategic process called, Transformative Excellence in Academic Medicine or TEAM. This is a process whereby we seek to establish a culture that sets an accountability that will lead to quality and growth in everything we do. We have concentrated our work in six areas: delivery of high-value care, patient access, research and education, integration of our missions, support of infrastructure and strategic direction. We have made significant progress since commencing this initiative in January 2017.

In this article, I will summarize some of the highlights of the progress that has been made.

I am delighted to say that we had a very successful reaccreditation site survey by the LCME in June 2018 and our school is better than ever. The changes that we have made in our program have significantly strengthened all our educational programs leading to an increase in the quality of education that our students receive. We are proud of the outcome, and I want to congratulate the large number of people who were engaged with the work.

Turning to Graduate Medical Education, I want to follow up on January 2018 when our GME program received a status of full continuous accreditation, the highest status available. We are very pleased that all our GME programs are in good standing. We have continued to receive site visits for specific programs, and the outcomes have been universally positive. Our residents and fellows work industriously under the supervision of our faculty to deliver the highest health and quality care. We are proud of their achievements and the wonderful positions they go on to occupy as they graduate.

In 2015, Saint Louis University School of Medicine and SLUCare went into a new partnership with SSM Health St. Louis, focused on our three academic hospitals: Saint Louis University Hospital, Cardinal Glennon Children's Hospital, and St. Mary's Hospital. We are now four years into this partnership and making excellent progress. A "concrete" example of the progress that is being made is our new $550 million Saint Louis University Hospital facility on Grand Boulevard.

In addition to this new 316-bed hospital, there will be a new ambulatory care center and new facilities for faculty and staff offices. The new hospital will offer excellent modern facilities for the care of our patients, and it was designed with education in mind, so that it will have the space to accommodate teaching rounds and private discussions with learners. The adjacent ambulatory care center (ACC) will be modern, easily



Robert W. Wilmott, MD, and IMMUNO Professor, MSMA member since 2007, is a pediatric pulmonologist, Professor, Acting Dean, and Vice President for Medical Affairs, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: robert.wilmott@health.slu.edu

accessible and will be staffed exclusively by SLUCare physicians. Both buildings are well underway with the glass exterior in place and protected from the elements so that the contractors were able to continue work throughout the winter. In fact, they are ahead of schedule.



Overview of construction on new Saint Louis University Hospital, opening in September 2020.

We are excited about all the development going on in Midtown St. Louis where several billion dollars of construction are underway, including the Armory Project, the Foundry Project and the new mixed-use development at Chouteau and Grand. This opportunity was created by a 353 Redevelopment Project approved by the City of St. Louis and granted to Saint Louis University. The hospital and ACC will be opening in September 2020, and the other projects will not be far behind. Within a few years the landscape of our part of Midtown will be significantly different.

In addition to the physical evidence of our growing partnership with SSM Health, we are collaborating with them in many other ways including the development of an integrated delivery network, clinical research, provision of high-quality specialty services, and a focus on nursing and allied health education, as well as medical education. This partnership, which was piloted for many years by the pre-existing partnership with SSM Health at Cardinal Glennon Children's Hospital, has been a natural one for the two organizations. Having been the Chair of Pediatrics at SSM Cardinal Glennon Children's Hospital for the last 17 years, I am very excited about the quality of this partnership and its future potential.

This article would not be complete without mention of the research that is underway at Saint Louis University. With all the scares about Avian Flu, Zika, and other infectious diseases, we are proud to have the opportunity to improve vaccines and treatment of infectious diseases through our Saint Louis University Vaccine Center led by Daniel Hoft, MD. It is one of nine federally funded vaccine centers in the country. Ours is one of the largest centers, and we are particularly excited about the Influenza Trials Unit at the Salus Center. This is an innovative clinical trials unit, which we call colloquially "Hotel Influenza." We have a grant currently undergoing review for funding of the trials required to develop a universal flu vaccine, which is a top priority for the National Institutes of Allergy and Infectious Disease. This is just one of many vaccine initiatives being developed under the leadership of Dr. Hoft.

Saint Louis University Liver Center is also a major national center. Drs. Bruce Bacon, Adrian Di Bisceglie, Brent Tetri, and team have led important research into hepatology and, specifically, hepatitis B and C, and non-alcoholic steatohepatitis (NASH) (fatty liver disease). This team's work played an



Cullinan Properties Ltd. is planning an 850,000-square-foot, dense, mixed-use development on the 14-acre property at Grand Boulevard and Chouteau Avenue.

integral role in the recent treatments that led to curing hepatitis C. Our pediatric hepatology team, an integral part of the Saint Louis University Liver Center, continues to receive national accolades. Jeff Teckman, MD, is a national leader into research exploring pathogenesis, diagnostics and therapeutics for alpha-1 antitrypsin liver disease. He also participates in national treatment studies of Hepatitis B, Hepatitis C and other liver conditions. Ajay Jain, MD, has received national awards and grants to broaden our understanding of ways to minimize liver injury and help intestinal growth - critical for babies unable to eat and thus dependent on intravenous nutrition. The SLU Liver Center is one of only three research liver units in the U.S. able to utilize large animal models of disease, such as pigs, to answer critical questions about human nutrition. Dr. Jain is also exploring novel blood tests for detection of liver injury in transplant recipients and leads research into pediatric obesity and fatty liver disease.

Unfortunately, the current opioid epidemic has led to a significant increase in opiate-related mortality in the United States. There are many opportunities to initiate programs in this area. SLUSOM is playing an important part by developing non-opiate alternatives to manage chronic pain. Our director of the SLUSOM Neurosciences Institute, Daniella Salvemini, MD, is a senior investigator who has published extensively in this area and has discovered several non-opiate compounds that alleviate pain in experimental models and these will be moving into human trials. We also seek to create a center for the treatment of opiate addiction and to start a fellowship program in addiction medicine, which will be led by Fred Rottnek, MD, in Family and Community Medicine.

Finally, I am proud to present this report and to have the opportunity to be leading Saint Louis University School of Medicine. We have been going through a difficult time in healthcare with increasing financial challenges, reduced federal funding and reduced payments for clinical care. However, we are rising to the challenges and continue to have an excellent medical school with outstanding training of medical students and residents, high quality clinical care, and innovative basic and clinical research activities. We support the mission of Saint Louis University which is the pursuit of truth for the greater glory of God and for the service of humanity. The University seeks excellence in the fulfillment of its corporate purposes of teaching, research, health care and service to the community. We follow the Jesuit tradition of treating the whole person.

We welcome your comments and feedback as well as participation as we continue our journey to transform modern healthcare. **MM**

Innovations in Pediatrics: 2019

by Jeffrey Teckman, MD

Our faculty aggressively innovate in, and support, the primary care setting, but also individualize for the chronic, complex care patients and for those with rare diseases.



Jeffery Teckman, MD, is the Drs. James and Patricia Monteleone Endowed Chair Professor of Pediatrics and Biochemistry, Director, Pediatric Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: jeff.teckman@health.slu.edu

Through this issue of *Missouri Medicine* we are pleased to showcase the Department of Pediatrics at Saint Louis University, and some of the outstanding and innovative patient care and research currently underway.



SSM Health Cardinal Glennon Children's Hospital

The Department of Pediatrics of the Saint Louis University School of Medicine-SLUCare is primarily based at SSM-Cardinal Glennon Children's Hospital, and is made up of 127 full-time faculty and 47 part-time and volunteer faculty. The department is divided into 17 academic divisions, including Danis Pediatrics, a primary care pediatric practice, as well a as a complete range of pediatric sub-specialties. Patient care is provided at more than ten sites from Central Missouri through Western Illinois.

Our physicians are proud to be inclusive and to host the region's widest range of payors accepted. As you will see from the contributions to this edition our faculty aggressively innovate in, and support, the primary care setting, but also individualize for the chronic, complex care patients and for those with rare diseases. Basic science research, new drug trials, translational research and educational research are all valued and highly sought after at this institution.

The educational activities of the department include medical students of all levels, 52 resident physicians based at Cardinal Glennon, 30 pediatric sub-speciality fellows, many resident physicians who rotate from partner institutions for pediatric exposure and numerous allied health students. Family-centered rounding, patient education initiatives, music therapy, and links to schools are integrated into this complicated and fast moving health care environment.

On behalf of our department, I invite you to explore this small window into some of our activities through this issue of *Missouri Medicine*. **MM**

Social Media in Primary Care

by Gene LaBarge, MD & Matt Broom, MD

Physicians and their practices should carefully consider ways to engage in social media, as individual practices and receptivity from providers (and patients) will likely differ significantly.



Gene LaBarge, MD, FAAP, (above) and Matt Broom, MD, FAAP, are the Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, Missouri.
Contact: gene.labarge@health.slu.edu

Abstract

Social media has become a standard part of the day for the majority of people in the United States, and reciprocally has become an effective platform and tool for patient engagement within health care. This review provides context for its place in patient education, communication, and treatment, combined with a review of general operational and ethical principles for social media platforms within a primary care practice.

Introduction

The use of social media in primary care has continued to grow considerably over the past decade. As expectations have changed and the endemic nature of social media has evolved, medical practices have become more aware and adept of ways to engage patients with this now established technology. Social media, defined as "electronic communication, especially applications and websites, through which users create and share information, ideas, and personal messages in an online community", is increasing exponentially.[1] Reported social media use by American adults has gone from 5% in 2005 to 69% in 2018, and the impact of social media on both adults and youth is both mixed and incompletely understood.[2]

There is growing awareness of the potential negative impact of social media and other digital technologies on the well-being of pediatric patients. Access to smart phones, tablets, video games and other digital media is the norm, rather than the exception, in most youth circles. Social anxiety, cyberbullying, and abnormal social and cognitive development are some of the neurodevelopmental concerns arising with this increased use of digital technologies. Much of the pediatric literature on digital media has appropriately shifted its focus towards these concerns.[3]

As our understanding of its impact on our youth continues to grow, we must recognize the obvious: that it is not likely to disappear. Acknowledging this, the existing and potential benefits are paramount to understand as well. Rapid information sharing and indirect socialization are opportunities for novel methods in medical care, including primary care. Blogs, microblogs, networking sites, wikis, media sharing sites, and other forms of social media are growing in use in the health care system. Additionally, other digital media fora such as text messaging are often utilized and shown in many ways to be effective.

Social media has provided access to health information that may otherwise not be immediately available to some groups—minorities, lower socioeconomic groups, etc. With this, there are often concerns on the reliability of information and overall quality of what is being received at the end-user (patient) level. It is also unclear whether there is any actual clinical benefit in talking with others



Figure 1. A wide variety of opportunities to engage patients, families, professionals and a large medical community co-exist.

(patient to patient) online about one's health.[4] There are inherently a wide variety of risks, many of which are shared between patients and providers. These can include privacy concerns, confidentiality, risk of communicating potentially harmful or inaccurate advice via a social media platform, or the risk of one's view being perceived as a deterrent by other patients as an undesirable skill for healthcare providers to have.

In this article, we review important areas of primary care in which social and other digital media have impacted practice management and patient outcomes. First, social media is an educational tool for patient families as well as professionals. Second, it is an opportunity for new forms of communication between patient and provider. Finally, this ability to interact rapidly provides opportunity for novel techniques in health intervention. We also consider and discuss the operational considerations for use of social and other digital media within a practice. Effective and judicious utilization of these opportunities begs that we consider the many ethical questions that arise in this time of change.

Novel Ways to Educate

One of the most effective uses for social media in health care to date has been to share information in a rapid and efficient manner. This has taken the form of educational information as well as support, and can be designed for patients or for professional propagation. One clear hurdle in the shift towards patient-centered care has been improved patient understanding of medical conditions and treatment. Digital media allows for immediate access to the public, with opportunity to provide generalized medical information. Blogs and media sharing sites like YouTube are increasingly used as a method by health care organizations to share information regarding medical conditions. Many physician practices and nearly all hospital networks use sites like Facebook and Twitter to communicate pertinent generalized health information with their patients.

Wikis offer similar types of information, and it is beneficial for physicians to be mindful of this method of information sharing. While sites such as Wikipedia may traditionally be dismissed due to concerns about accuracy, they are highly trafficked sites by the public. In 2011 the top 200 medical articles on Wikipedia received over 100,000 monthly page views, and it is reasonable to surmise this number has only increased in recent years.[5] While concerns about accuracy are rational, Clausen et al. found Wikipedia to have very few factual errors, specifically in review of pharmacologic information, and most errors were ones of omission.[6] Microblogs like Twitter are also growing sites for medical information, with thousands of doctors verified to be tweeting, at least on a daily basis.[7] Through its ability to connect millions of people with public tweets, Twitter also has the potential to redefine public health efforts, including dissemination of public health updates, sharing information on disease and treatment, or even potentially assisting with coordination of large scale relief efforts.[8]

Social and other digital media can also be used for intraprofessional education and collaboration as well. Figure 1. By reducing barriers to collaboration, more frequent constructive interaction with peers can improve medical understanding and treatment options. This can be an opportunity for researchers to connect with each other, but also can be an opportunity for research to be more rapidly accessible for practicing physicians in the community. Active social media outlets can also provide a useful alternative source of learning for the difficult-to-reach conference that has to be missed. Following the American Academy of Pediatrics (AAP) and Academic Pediatric Association (APA) social media feeds allows one to stay on top of some of the more significant developments both regionally and nationally.

Communication

Given that greater than 95% of adults and adolescents own a cell phone in the United States, it stands to reason that text messaging would serve as a useful reminder for patients of impending appointments.[2] Multiple large prospective studies have demonstrated improved show rates with text messaging reminders over extended periods.[9] If not already being used, it is a reasonable and affordable plan for primary care offices to utilize similar methods to reduce no show rates.

Other forms of medical compliance have been studied as well, including vaccine administration for parents of young children. Families receiving text messaging reminders for MMR administration prior to their child's first birthday are more likely to be up to date with immunizations than those not receiving reminders.[10,11] This extends beyond adults with small children, however, as text message reminders have been effective in improving vaccination in the general adolescent population. Positive results include adolescents with chronic medical conditions, a population that has been typically under-immunized and difficult to reach for primary care physicians.[12]

It appears patients do not use social media to circumvent health care providers, but to gain additional information with which to complement their understanding, when often the time and access to such information is lacking.[13] A key point is that providers offer recommendations based on their knowledge and training, however typically not on their first-hand experience with a condition, something that is readily available to patients online and via interactions with others.[4]

Treatment

It follows naturally that novel methods of communication and information sharing may provide innovative treatment modalities in medicine. Results of social media and text messaging as a primary or adjunctive method for improved health interventions are mixed. While not social media, per se, text messaging has been utilized in studies more broadly than any other digital media modality and has been frequently studied as an adjunctive method for chronic disease management or disease prevention. It has been linked to improved quality of life scores for individuals with celiac disease, improved glycemic control for patient with moderately controlled diabetes mellitis, and obesity prevention.[14,15] Meanwhile, results are more mixed in individuals with poorly controlled diabetes and eating disorders.[14,16] In our own institution, Broom and colleagues studied whether text messages can be effective as an educational tool to reduce the prevalence of nonurgent emergency department (ED) visits among an urban population with elevated levels of low health literacy. They learned that sending educational text messages to caregivers is an effective way to reduce the number of visits to the ED. Given the relative ease and the minimal expense of sending text messages, these findings have direct implications on the cost of health care, in addition to demonstrating improved continuity and quality of care for patients.[17] Overall, text messaging interventions appear to be effective in promoting changes in health-related behaviors, with further research warranted to better understand limitations.

Social media as a treatment modality is less well understood. Novel approaches are being considered, however, fewer original research studies using social media as treatment are reported. One promising area is provision of vaccine information and social media outlet opportunities for vaccine-hesitant families. Glanz et al. demonstrated improved vaccine rates for patient families who received additional online vaccine information with social media outlet opportunities as compared with usual care.[18] This study suggests Web-based vaccine information with social media applications during pregnancy may have a positive influence on parental vaccine behaviors.

Within the realm of treatment research, social media has an interesting added benefit. With establishment of the Patient Centered Outcomes Research Institute, researchers interested in honing their focus on topics that are most important to populations have the opportunity to "crowdsource" using social media outlets.[19] This enables researchers to establish research priorities that are most valuable to affected individuals, leveraging these capabilities to a wider and more receptive network of patients.

Smailhodzic and colleagues reviewed social media in healthcare in 2016, finding patient benefits to be localized in the following areas: improved self-management and control, enhanced psychological well-being, enhanced subjective well-being, and improved relationship between healthcare professional and patient.[13] Utilization has been focused towards social and emotional support of chronic conditions, with limited data on treatment outcomes. Further research will help clarify the most effective use for social media as a treatment modality.

Approach and Engagement

Historically there has been a reticence for providers to embrace the use of social media as a professional objective for their practice. Reasons have included lack of perceived value in maintaining a professional presence on social media, lack of clarity whether or not families were interested and subsequently how they would utilize it, and perhaps most notably, concerns about underlying risk to the individual practice. Risks within this context are many and include violations of HIPAA, managing a new arena of online professional interactions with patient families, impact with how the online presence and interaction is framed (and more importantly, perceived) to followers and the boundaries that a practice chooses to place on this service.

As some authors have described, patients tend to utilize social media for health-related concerns as an area

of support. This area of support is one in which a physician practice may have challenges in providing equivalent perceived presence, given the limitations of direct interactions with patients via social media. Interestingly, a family's social media use may have significant impact on the patient-provider relationship. This has been shown to increase dialogue and allow for a more open discussion. It also serves as a mechanism for patient empowerment and increased confidence when approaching challenging discussions with their physician.[13] Unfortunately, sometimes patient-physician social media interactions result in a negative experience by one or both partners. Patients and families may feel that their personal research from online communities is not valued, or that their concerns are not being heard.[20,21] Providers may feel that their training and experience, independent of what has been portrayed and discussed on social media, is not being given due credit and validation. Balancing these opposite perceptions and viewpoints can be a challenge when working to build a communication partnership with a family.

The inherent nature of social media as a partially unregulated, informal mechanism creates a theme of inconsistent quality of information and frequent lack of structure/roles for communication between medical providers and patients. These types of interactions will arise with patients independent of whether a provider maintains an online presence, as families will bring them thoughts or material found online directly into the office for a discussion. Perhaps the most successful method for anticipating such interactions is for providers to, in advance, discuss their appreciation of patients being invested in their own health—and that the practice will aim to work with families in helping to guide them via a very challenging online environment.

Notably, online support that families receive will differ considerably depending on the clinical issue, medical history and impact across other patients. For example, an open social media request for personal choice of the best primary care physician differs greatly from seeking medical management insights from a closed group of social media contacts that are linked together by all having a child with a rare pediatric disease. Providers do need to maintain an awareness regarding their responses to patient inquiries about information acquired via social media circles. While providers may choose to not be involved with or engage in social media, they likely will still, in some way, become a topic on social media. The question will be how to manage these interactions, perceptions and opinions via the wider online community.[22,23]

Operational Considerations

For those practices interested in engaging with patients and families via social media, there are several critical recommendations to best mitigate risk from these interactions.[24] The first is to use encrypted software within a closed system. As HIPAA violations should be of the highest level of concern, having a secure, reliable system is paramount. Next, setting up clear expectations on the type of interactions the individual provider or practice will have with patients is important. This includes the expected period for a provider to respond to any interaction by the patient, specifically indicating that the service is not one for emergency questions or cases. Upon families enrolling in the practice, or if laying out a new policy for the practice, obtaining signatures from families indicating an understanding of the policy prior to them enrolling into such interactions is strongly recommended. Although some previous studies have discussed value of interactions via professional Facebook or Twitter accounts, defining the differences between interactions as a professional voice [to all] online versus one that is able to provide specific medical insight to an individual is very different.[25] As a result, practices may consider not being involved on third-party accounts such as Facebook, Twitter, Instagram, etc., regardless if there appears to be external pressure from patients regarding future interactions and access via those accounts. Educating patients and families about the specific practice social media policy, and what the practice is actively doing to protect all patient data can be of great benefit as well.[24]

It is also important to recognize that electronic patient interactions often may be taken out of context. So much of successful medical communication relies on reading non-verbal cues, understanding culture, and what may also be occurring within the room during an interaction. Although often convenient for patients and providers, social media may have a negative impact on communication as well—particularly if there are concerns related to medical literacy, challenging medical diagnoses or decision-making that is involved, or stress related to timing of communications.

Ethical Considerations

Despite having a clear practice social media policy in place, providers and nurses may both be approached via social media for a practice-to-patient interaction that is outside of the previously defined scope of care. Practices need to remain transparent and clear with their entire staff regarding these interactions. Although risk impacts providers directly, any nursing or staff member associated with a practice may have a similar HIPAA violation based

on their online interaction with a patient or family member that results in increased risk to the practice overall. It is important to underscore the foundational concept that is HIPAA within the world of social media, as it holds the largest element of risk to any provider or practice with regards to their online presence.

Building on the interactions discussed above, many providers have concerns related to their ethical involvement on social media, particularly within primary care. Given the near endemic nature of social media as a daily tool throughout society, not engaging in some way appears to be off-target for many physicians. The primary issue that arises within the context of social media is that of online professionalism. Many authors have previously discussed this in significant detail. Perhaps the best framework regarding the recommended approach to professionalism-considerations in social media was intimated by Chretien and Kind.[24] In general, they recommend physicians follow the standard ethical principles of the American Medical Association in consideration of their online interactions. An important point is that, as physicians are held to a high professional standard in the public eye, perception from something that is observed online often holds a similar impact to that of a witnessed office interaction. As a result, physicians need to be mindful regarding behaviors that may be perceived by patients, colleagues or others as not consistent with the morals and values of the health care profession. By no means does this indicate physicians should avoid an online presence, however it should serve as a point of pause for healthcare providers to consider their approach to both their personal and professional online persona.[25]

Conclusions

Social media has become a heterogenous, endemic part of the world in which we live and practice medicine. A wide variety of opportunities to engage patients, families, professionals and a large medical community co-exist. Physicians and their practices should carefully consider ways to engage in social media, as individual practices and receptivity from providers (and patients) will likely differ significantly. Developing an understanding of the available capabilities, balanced with an appreciation for the risks and pitfalls is important in embracing what has nearly become a standard tool for pediatric medical practice.

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Disclosures

None reported. **MM**

I Get By With A Little Help From My Friends: Models of Psychological Intervention in Pediatric Primary Care

by Debra H. Zand, PhD, Katherine J. Pierce, PhD, Jennifer Ladage, MD, Mary S. Heaney, MD & Heidi M. Sallee, MD

Research indicates that children with mental health problems and their families use more types of pediatric health care services with greater frequency than other children and families.





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Abstract

The pediatric primary care setting is ideal for addressing children's and adolescents' mental health needs. As a result of extensive training in health promotion, consultation, assessment, and treatment of psychological disorders, psychologists are uniquely positioned to support primary care pediatricians in this endeavor. This paper provides a review of models of psychology interventions in pediatric primary care including: care delivery, scope of practice, implementation and recent research. It concludes with a case example and recommendations.

Introduction

Approximately one in five children experience a psychiatric disorder, with up to half of all lifetime cases of mental illness beginning by age fourteen.[1] As noted by Asarnow and colleagues (2015), many health behaviors that influence morbidity and mortality begin in childhood and adolescence, highlighting the need to identify and treat pediatric behavioral health problems to minimize current and long-term sequelae.[2] Because most children and adolescents in the United States have access to primary care,[3] pediatricians are well positioned to screen and address this need through the provision of integrated behavioral health services. By virtue of their training in health promotion, consultation, assessment, and treatment of psychological disorders, psychologists are poised to support primary care pediatricians in this endeavor.

Opportunities for psychologists to impact children's health within primary care settings began in the 1960s. In his presidential address to the American Academy of Pediatrics (AAP) J.L. Wilson encouraged pediatricians to hire their own clinical psychologists to address common emotional or behavioral problems in children.[4] More recently, the American Academy of Pediatrics has called for the integration of behavioral health services within primary care.[5] Pediatric primary care physicians are often the first point of contact for families to address concerns regarding their children's social-emotional well-being, behaviors and development.[6] Well-child visits afford pediatricians the opportunity to promote optimal child development by addressing these concerns within the context of a trusting relationship.[7] Pediatric primary care providers often face significant barriers to providing comprehensive behavioral care including discomfort with their knowledge and skills to address complex mental health issues, time constraints, and poor reimbursement.[8-10] Using psychologists to support pediatricians is one of several promising models guiding the integration of behavioral

Table 1: Psychologists' Roles, Competencies, and Activities within the Pediatric Primary Care Medical Home[15,17-20]

Roles	Activities
Clinician	Provide psychological and developmental assessments, determine DSM 5 diagnoses, and administer evidence based psychotherapies.
Consultant	Provide expertise in developmental psychopathology, evidence based treatment, research methods, and system design.
Educator/Supervisor	Develop evidence based behavioral health curricula; provide supervision and training to team members on curricula
Administrator	Lead efforts to build behavioral health services within P-PCMH; determine the specific requirements needed to build workforce capacity; network with outside agencies to foster collaborative care; provide interventions to enhance team functioning; develop inter-professional behavioral health protocols; collaborate in system redesign
Researcher	Conduct needs assessments; design and conduct quality improvement projects; disseminate findings in peer reviewed journals and at national pediatric conferences; design, implement and empirically test new treatment protocols; secure grant funding

health in primary care. The purpose of this paper is to review current models of psychology interventions in pediatric primary care including: care delivery, scope of practice, and implementation. The paper concludes with a case example and future directions.

Care Delivery

The Pediatric Patient Centered Medical Home (P-PCMH) has become the most common prototype for integrating mental health services into pediatric primary care. As defined by the AAP (2002), the P-PCMH is an approach to providing primary care for children and families that is accessible, continuous, comprehensive, family-centered, coordinated, compassionate and culturally effective.[11] The P-PCMH addresses preventative, acute, and chronic care from birth to transition to adulthood, and allows for pediatric practices to implement different aspects of the approach based on individual practice needs.[12] Currently there are four bodies that recognize, certify or accredit organizations as a P-PCMH.[13] Each body varies in terms of the amount of documentation, application costs and overall efforts required to become a P-PCMH. Common to all approaches is the integration of mental health services into the P-PCMH.

To guide mental health integration efforts in the P-PCMH, the Substance Abuse Mental Health Service Administration's/Health Resources and Service Administration's Center for Integrated Solutions has developed a standard framework.[14] The framework is a 6-level continuum with three primary approaches: coordinated, co-located, and integrated. In coordinated approaches, pediatricians and mental health clinicians practice in separate locations, and view each other as resources. Communication occurs periodically and focuses on specific issues about shared patients. Co-located approaches focus on physical proximity, with the pediatrician and mental health provider practicing within the same facility, but using separate systems. Mental health providers remain autonomous and work in tandem with pediatricians. Patients have separate treatment plans. Finally, integrated care approaches concentrate on changing the practice. Psychologists and pediatricians share common systems and work alongside each other to create and implement one treatment plan. Psychologists have a central role in advising, consulting, and teaching pediatricians about mental health. Patients view their care as a single system that treats the whole person.

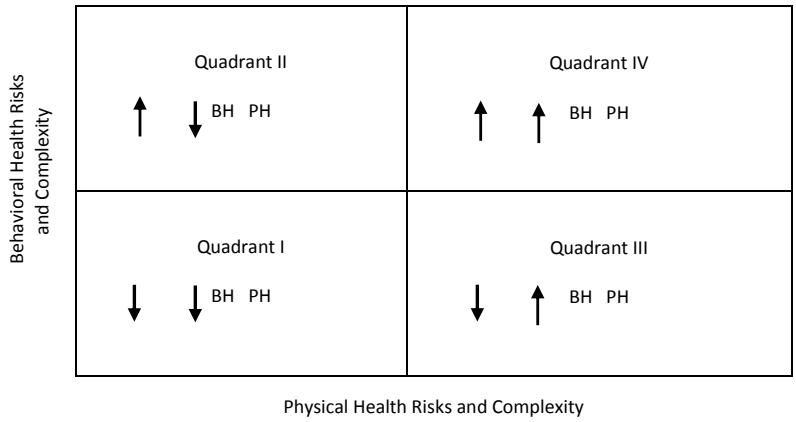
Scope of Practice

Independent of level of behavioral health integration, there are many opportunities for psychologists to collaborate with primary care pediatricians.[15] Within the P-PCMH, pediatricians are responsible for coordinating their patient's healthcare. The scope of the pediatric primary care practice encompasses multiple activities, including health promotion, prevention, diagnosis, treatment, service linkage, and quality assurance and improvement.[16] A comparable range of activities is needed to address child and youth mental health needs within this setting. Psychologists' extensive training enables them to be suited for the numerous roles and responsibilities needed to practice within the P-PCMH,[17,18] which are displayed in Table 1.

Implementation

While much information exists regarding psychologists' roles in pediatric primary care, less information is available on practical implementation strategies. To assist physicians with taking purposeful steps toward integrated care, Ratzliff and colleagues (2017), have developed a model-neutral behavioral health implementation guide. Though not specifically tailored to the integration of psychologists into pediatric primary care, the model addresses several relevant implementation factors for pediatricians to consider.

Table 2: Four Quadrant Model [22]



Based upon a comprehensive review of the literature and expert panel opinion, the authors created a worksheet to assist physicians with identifying and implementing a path toward behavioral health integration. The Goals, Resources, Options and Workflow (GROW) Pathway Planning Worksheet focuses on four sequential phases, which are briefly discussed below within the context of integrating psychological services into pediatric primary care.[21]

Goals

During the first phase, the primary care practice sets behavioral health goals. To assist practices with identifying patient needs, the National Center for Behavioral health has developed the Four Quadrant Model.[22] As shown in Table 2, the quadrants categorize patients by their physical health (x-axis) and behavioral (y-axis) risks and complexity. Quadrants may be used to match patient population needs and settings with the level of collaboration and integration. For example, pediatric primary care practices that serve patients in Quadrant IV (high behavioral health and high physical health risks and complexity such as children with developmental disabilities) may benefit from having a psychologist who is situated within an integrated practice. The psychologist may then conduct onsite developmental assessments and interact with the pediatrician in real time to address co-morbid physical health issues and develop a single treatment plan. Table 2.

Resources

In the second phase, the practice investigates available resources to select the most realistic approach for behavioral health integration. Factors to consider include: geographic location, support of leadership, physical space, available technology, and finances. For instance, depending upon the type of services needed, financing a psychologist may require multiple funding streams. While diagnostic assessment and psychotherapies are third party reimbursable services, prevention interventions such as parenting programs typically are not covered consistently by private or public payers. Additionally, reimbursement for real time brief mental health consultations are relatively small and, in Missouri, must be linked to a presenting physical health problem. In cases in which the mental health concern cannot be linked to a physical health diagnosis, pediatric practices may need to consider other funding mechanisms to obtain reimbursement for psychological consultation services. For example, psychologists' provision of mental health services may free up pediatricians to see more patients and generate additional revenue to cover behavioral health services that are not reimbursed by third party payers.

Options

The third phase involves the primary care practice assessing current and future capacities to integrate behavioral health. In this phase the practice addresses options to improve patient access, as well as practice accountability (assessing, monitoring, and improving health outcomes). Psychologists may aid in capacity building by providing increased access to mental health services, supervising mental health providers, establishing new programs, and/or creating quality improvement/quality assurance processes.

Workflow

Finally, in phase four, the practice develops a new workflow to implement changes in behavioral health service delivery. Variables to consider include: hiring additional staff, developing internal communication protocols, creating marketing materials, determining work space allocation, scheduling and billing. For example, depending upon the psychologist's roles and responsibilities, processes will need to be created to address scheduling and billing. To recover costs, staff need to be familiar with mental health billing, securing preauthorization, and pursuing reimbursement.[21]

Evidence Base

While strong evidence exists documenting the effectiveness of integrated primary health care for adults, [23-25] less is known about incorporating behavioral health services into pediatric primary care. To begin to address this gap, Asarnow and colleagues (2015)[2] conducted a meta-analysis of randomized

Table 3: Psychology Services at SSM Cardinal Glennon Children's Hospital's Danis Pediatric Center

Role	Activities	Funding Streams
Clinician	• Conduct developmental assessments, including attachment assessments • Conduct mental health assessments • Determine DSM 5 diagnoses • Conduct evidence based individual and family therapies • Interpret test results • Complete comprehensive psychological reports with detailed recommendations • Develop individualized treatment plans	Public and private insurance
Consultant	• Provide brief consultations to pediatricians on developmental psychopathology and evidence based treatments	Institutional funding
Educator/Supervisor	• Supervise psychometrician • Supervise Positive Parenting practitioners (accredited practitioners provide evidence based positive parenting interventions; conduct brief parenting consultation at time of pediatric appointment) • Teach pediatric residents about normative development and developmental psychopathology • Mentor early career pediatricians • Mentor medical students	Grant funding Public and private insurance Institutional funding
Researcher	• Write and secure extramural grants • Conduct implementation and outcome research on positive parenting services • Publish findings in peer reviewed journals and trade magazines • Present findings at national pediatric conferences	Grant funding

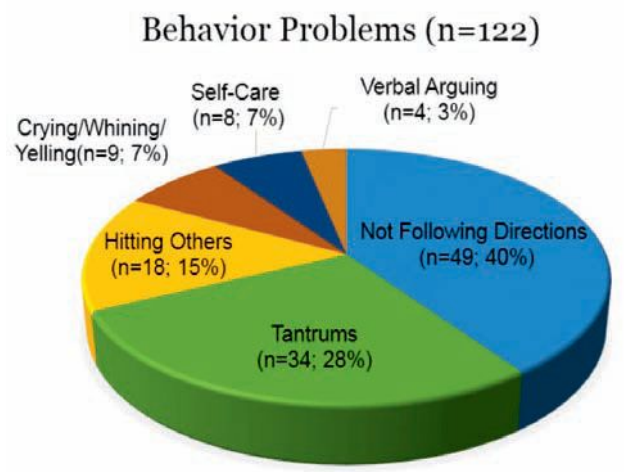
clinical trials to determine whether integrated pediatric health care produced improved behavioral health outcomes compared to usual primary care. Database searches from January 1, 1960, through December 31, 2014, yielded 31 studies that met the following eligibility criteria: 1) evaluated integrated care for behavioral health conditions compared to services as usual; 2) collected behavioral health outcome data; 3) recruited participants through pediatric primary care; and 4) focused on children up to age 21 years. Studies were excluded if they targeted chronic medical conditions and had a score less than 2 on the Jadad Scale for Reporting Clinical Trials. Analyses indicated the strongest effects for collaborative care interventions, with a 73% probability that a randomly selected youth would experience better outcomes after receiving collaborative care. Due to the variability in the types of interventions studied, however, practice recommendations were limited. Additionally, the authors did not distinguish between services provided by psychologists versus other mental health professionals. Pediatric research is sorely needed on comparisons of models, effective team functioning and appropriate roles and skill sets for team members within the pediatric primary care setting.[15]

The Danis Pediatric Center: A Hybrid Model

The Danis Pediatric Center at the SSM Health Cardinal Glennon Children's Hospital (DPC) has 2 locations in Saint Louis City, both of which provide pediatric primary care. Staff include 19 pediatricians, 2 nurse practitioners, 1 physician assistant, 1 licensed clinical psychologist, and 1 psychometrician. In 2016 the DPC cared for 8,434 children through 20,963 encounters. During this period, 74% of the DPC's patients relied on Medicaid as their insurance carrier. Sixty six percent of the patients identified as Black/African-American, 14% identified as White, 6% identified as Multi-Racial, and 2% identified Asian. Race/ethnicity data were unavailable for 11% of the patients. Fifty three percent of the patients were males. The DPC data collected between 7/1/2017-11/30/2017 indicated that 14.9% of caregivers reported worrying about having enough food to feed their families, 6.6% of the caregivers reported concerns about domestic violence, and 12.3% of caregivers reported feeling depressed.

With support from Dr. Robert Wilmott, Chairman of Pediatrics at the Saint Louis University School of Medicine, one of the DPC sites has been offering co-located psychology services with elements of integrated care since July, 2015. The behavioral health practice is comprised of a licensed clinical psychologist who supervises three staff members. Staff are funded through 3rd party reimbursements, external grants, and/or institutional funding. Direct services range from prevention interventions (e.g., 20 minute real time parenting consultations, brief evidence-based parenting programs)

Figure 1. Behavior Problems



to diagnostic assessments, and mental health interventions (evidence based psychotherapies). Patients are referred through the clinic's electronic medical record system, to which all practitioners have access. Practitioner communication occurs face-to-face, as well as through the practice's electronic medical record system. Additionally, it is not uncommon for pediatricians to "stop by" the psychologist's office to seek a brief consultation on developmental psychopathology. See Table 3 for a full description of psychology services at the DPC.

A hallmark program spearheaded by psychology at the DPC is the Improving Mental Health: Parent and Child Collaborative Treatment (IMPACCT) service. Funded by the Saint Louis Mental Health Board, IMPACCT aims to strengthen caregivers' general parenting skills and knowledge as a catalyst for reducing child disruptive behaviors, improving caregiver mental health and enhancing family functioning through the provision of brief evidence based caregiver and family interventions. IMPACCT uses a 3 tier treatment model based on increasing levels of intervention intensity.

The DPC pediatricians refer patients ages 1 to 16 years old who display disruptive behaviors to the program. Sample behavior problems at the time of referral to one of our brief positive parenting services are provided in the above pie chart, with not following directions and tantrums comprising the most frequent behavior problems identified by parents (68%). IMPACCT staff maintain progress notes in the practice's electronic medical record system to provide the referring physician with real time feedback. Regular evaluation data are collected to inform service processes and document outcomes.

Future Directions and Conclusions

The integration of psychologists into pediatric primary care settings is a promising strategy for increasing access to high-quality health care that promotes optimal developmental trajectories among pediatric patients. Comprehensive training and competencies position psychologists to not only provide a full range of direct mental health services to children and their families, but also to serve in leadership roles to advance behavioral health integration. Additional work, however, is needed regarding how to adequately resource primary care practices with psychologists.[20] Undoubtedly, such work will need to include: evaluating outcomes, as well as identifying funding and sustainability strategies to allow for universal access to a full range of services.

Outcomes

Randomized controlled trials and demonstration projects are needed to guide the development of strategies to improve behavioral health services in pediatric primary care.[26] Although Asarnow and colleagues' (2015) meta-analysis identified 31 randomized controlled studies, considerable differences in the interventions studied resulted in few specific recommendations.[2] In addition to tracking the number of patients, visits, and demographics, integrated programs need to track the types of services provided by type of provider, screening and intervention outcomes, care coordination efforts, consumer and provider satisfaction[5] data, and costs.[20] Collection and analyses of these data will enable pediatricians to make informed recommendations regarding what should be implemented, by whom, at what time, on which types of patients, and at what cost.

Funding and Sustainability Strategies

Ongoing funding for integrated mental health services will likely depend upon proof that such programs increase access to care, improve health outcomes, and decrease health care costs. Further research is needed to understand the volume and productivity rates needed to cover expenses without sacrificing the continuum of integrated behavioral health care activities relevant to pediatric populations, including prevention services.[20] The economic sustainability of integrated primary care will require the development of innovative payment models. Across the United States, several payment models have been developed to increase the behavioral health integration in pediatric primary care, such as bundled payments and use of alternative payment methods. Regardless of payment model selected to fully support integrated care, Ader and colleagues (2015) recommend that payments be linked to the: 1) promotion of

the coordination of care between primary care pediatricians and behavioral health providers; 2) achievement of health insurers and group health providing equal levels of benefits for mental health treatment and services that they do for medical/surgical care; and 3) improvement of physical and behavioral health outcomes.[5]

Conclusions

Annually, more than 90% of children in the United States see a primary care provider, making the primary care setting ideal for addressing children's mental health needs.[27] Research indicates that children with mental health problems and their families use a variety of pediatric health care services more often than other children and families.[28] Many of these children and adolescents present in pediatric primary care settings, where parents are seeking help for the developmental, behavioral, emotional, and social concerns of their children.[15,29] The integration of psychologists into primary care settings holds promise for providing high quality health care services to prevent, identify, assess, and treat mental health disorders at both the individual and family levels.[20] The American Academy of Pediatrics recommendations and policy statements[5] regarding the integration of behavioral health services in pediatric primary care, create a pressing need to develop quality metrics to document outcomes and understand moderators and mediators of effects. These data may then be leveraged to enhance public and private funding for these services.

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Bronchopulmonary Dysplasia: When the Very Preterm Baby Comes Home

by Connie Anderson, MD & Noah H. Hillman, MD

Close monitoring for pulmonary hypertension, systemic hypertension and nutritional support are necessary to maximize the growth and development of these high-risk children.





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Abstract

Many infants with severe bronchopulmonary dysplasia (BPD) can be safely managed with oxygen at home. This review covers criteria for home oxygen therapy, monitoring, and weaning protocols for oxygen therapy in the outpatient setting. Although most infants with BPD are weaned from oxygen within a year, they continue to have pulmonary function abnormalities into adolescence. These infants also require evaluation for pulmonary hypertension, systemic hypertension, and a strong focus on adequate nutritional needs for growth.

Introduction

Bronchopulmonary dysplasia (BPD), defined as a need for oxygen at 36 weeks corrected gestational age, affects up to 40% of all preterm infants with birth weights less than 1000 grams.[1,2] The more immature the patient population the higher the risk for BPD. Antenatal steroids and surfactant therapy have decreased mortality in these very immature infants, but BPD has increased because of increased survival. Although often necessary for survival in the smallest infants, mechanical ventilation and lung inflammation are central to the development of BPD.[3-6] Mechanical ventilation at birth stretches the airways, causes airway epithelial injury and differentiation, and diffuse lung inflammation.[7,8] Clinicians are trying to decrease exposure to mechanical ventilation, but BPD rates have not declined substantially with the introduction of less invasive mechanical ventilation.[9]

Improved modes of mechanical ventilation and surfactant replacement therapy have changed BPD from the "Old BPD" described by Northway to a "New BPD".[3,10] The Old BPD was characterized by hyaline membrane formation and epithelial disruption with airway injury, epithelial metaplasia, and fibrosis.[11] The New BPD, in the post-surfactant treatment era (after 1990), is characterized by alveolar simplification, pulmonary microvascular changes, and small airway injury.[12,13] Although the majority of infants with BPD are weaned from oxygen within a year, school-age children diagnosed with moderate to severe BPD continue to have respiratory problems at 6 years of life and changes in lung mechanics persist at least into adolescence.[12-15]

The severity of BPD varies widely amongst the very preterm infants, and the definitions for BPD may need adjusting to better capture the long-term severity of the disease. [16] Some infants will have the diagnosis of mild

BPD at 36 weeks, but go home on room air and taking all feeds by mouth. Other infants will have such severe lung disease they need tracheostomies and continued mechanical ventilation similar to the "Old BPD". This review will focus on the infants with moderate to severe BPD who often go home on nasal cannula oxygen, and the outpatient management needed to optimize their health. Some of these infants are managed by neonatologists in high risk follow-up clinics, others by pulmonologists, and some by their pediatricians.

Home Oxygen: Before Discharge from NICU

Once oxygen requirements are low and the infant is stable, discharging to the home on nasal cannula oxygen is a consideration. There are potential family and financial benefits to sending a child with chronic lung disease home with nasal cannula (NC) oxygen and continuing to wean to room air in the outpatient setting. Our goal for home oxygen therapy is to prevent the effects of chronic hypoxemia, while facilitating improvements in the quality of life and psychological impact for the infant, parents and family offered by the home environment. There is variability in the percent of infants that go home on NC between NICUs, partially due to the multiple things that must be considered before discharge.[17] Determining who goes home with oxygen is based on the child's stability, the parent's ability and the availability of support services in the area that the family lives (Box 1).[18]

Child's Stability

Children being considered for home oxygen should be on <0.5 LPM of NC O_2. [19] The child should have stable oxygen saturations, with saturations that do not fall below 90% for more than 5% of an artifact-free recording period.[20] Although some centers send home infants on > 0.5 LPM these infants are often sicker and have no margin for error during illness.[15,18] Higher flow rates are also often difficult to maintain on portable oxygen tanks. The infant must also have sufficient pulmonary reserve to remain stable during a short-term, accidental disconnection from supplemental oxygen [21]. The child should be able to maintain a minimum saturation of >80% in room air for 30 min before discharge.[19] A determination of what defines a clinically stable child can be debated. Typically if the child has no increased work of breathing, tachypnea or respiratory distress, and has appropriate consistent weight gain, he has a good basis for discharge. [19] An echocardiogram should be performed prior to discharge to assess for pulmonary hypertension and the pulmonary hypertension is stable or improving on the current treatment plan.

Box 1. Criteria for Home Oxygen Therapy

1) Stable on < 1/2L 100% oxygen
- Maintaining saturations greater than 92%
- No apnea requiring intervention for 5 days
- Adequate daily weight gain (20 g/d)

2) Available home health care provider
- Pulse oximetry or apnea monitor
- Home oxygen tanks or oxygen condenser

3) Parental Education Completed
- CPR education and emergency plan in place
- Back-up coverage plan for parents
- Primary medical doctor involved

Parent's Ability

While the child's stability is being assessed, the parent's ability also needs to be assessed. The family needs to feel comfortable with having a child at home that will require extra care and monitoring, and the staff should feel that the family is capable of the additional tasks of home oxygen. They will also need to be capable of managing the medications, oxygen equipment, and home monitor. This ability not only includes the parents, but also includes the other family members and friends that may be involved in the care of this child. Some families will not be comfortable or will not have these abilities, and are poor candidates for home oxygen.[19]

What Needs to be in Place Prior to Discharge

Success after discharge is greatly influenced by how prepared the family is to take the child home on oxygen.[19] Family education for all care givers is required and understanding demonstrated to the NICU staff. An emergency plan needs to be clearly defined and all caregivers are taught infant CPR. For example, if having desaturations or respiratory distress, the care givers may be instructed to increase the oxygen flow, possibly give a nebulizer treatment, call the primary medical provider (PMD) or 911 and know what medical facility to bring the child to. Prior to determining a home plan, conversations with the PMD should include their comfort in co-managing infants on oxygen. Care

givers also need to be educated on the importance of immunizations, influenza vaccine, and RSV prophylaxis. They also need to understand the importance of no smoking around the child while on oxygen therapy and after it is discontinued.

Once the child has been determined to be a candidate for discharge home on supplemental oxygen, arrangements are made for the home medical equipment. Unfortunately, access to appropriate Home Health companies or home nursing can be a limitation in some rural areas. The child is typically sent home on nasal cannula oxygen with portable oxygen tanks (oxygen cylinders) for ease of travel and large oxygen tanks or an oxygen concentrator for in home use.[17] There is no evidence that one oxygen source is better than the other, and often is dependent on availability within a geographic region. Some tanks are generally required as backup for equipment failure or power outage. Equipment education is typically taught by the supplier and includes basic management, the trouble shooting of typical problems, and contact information in the event of equipment failure. A final step before discharge often includes an overnight "rooming in" period for the family and caregivers; which allows them to practice as the solo caregiver while having the security of help from the staff just outside the room.

Monitoring Home Oxygen

Close monitoring of infants on home oxygen is essential and has been done with either apnea/cardiac monitors or pulse oximetry.[22] Although apnea monitors provide some important information, the practical non-invasive method for assessment of oxygenation remains pulse oximetry.[17,22] Previously, the child was sent home on a cardiac/apnea monitor due to pulse oximeters being unavailable and inaccurate with frequent false alarms. As pulse oximeters have improved, oxygen saturations monitoring has become more reliable with stable readings and a preferred form of continuous monitoring.[15] Performing spot oximetry checks in the outpatient setting limits the ability to adequately assess oxygenation needs especially during times that the child may be most vulnerable to hypoxia (feeding, bathing and sleep).[19] Anecdotally, we have not found care givers to be more frustrated by the use of pulse oximetry rather than a cardiac/apnea monitor.

There is controversy about the appropriate target oxygen saturation range for these children. The available evidence suggests that the median oxygen saturation of former preterm infants with chronic lung disease is 95-97%. Chronic hypoxia may contribute to a number of unwanted systemic effects; many which improve when oxygen saturations are maintained over 93%.[17,20,23] Although higher saturations early in life are associated with retinopathy of prematurity, maintaining higher saturations may decrease the progression of ROP and multiple international societies recommend saturations greater than 92% for home oxygen. [17,19,20,23]

Weaning Home Oxygen

Once the child has been discharged, the determination for readiness to wean oxygen begins. Although many infants wean earlier, the average age of weaning is 10 months corrected age.[15] There is very limited research about the appropriate weaning strategy, thus there is a wide range of practices.[17,18,23] Unfortunately, up to a third of infants are weaned from oxygen by their caregivers without medical supervision.[15] Weaning of oxygen therapy is based on clinical assessment, including respiratory status and growth, combined with overnight pulse oximetry results and echocardiogram if pulmonary hypertension is present. If the child is on home medications related to their chronic lung disease (diuretics) we wean these off first. Weaning of albuterol and inhaled corticosteroids is normally done with the input of pediatric pulmonology. Assessment of oxygenation during sleep with either continuous overnight oximetry or polysomnography is recommended when weaning infants from supplemental oxygen.[17,20,23] Overnight oximetry and polysomnography provide more accurate data of oxygenation than spot oximetry checks.[15,17] Spot saturations are not used to wean oxygen due to the potential of missing periods of hypoxia that may occur with sleep and feeding.[15,24] Overnight oximetry is a cost-effective test that is easy to perform in the home as a last weaning step to room air.[20,24] It involves downloading a 12 hour period of oxygen saturation readings from home monitor, and looking for periods of desaturation. A goal of greater than 90% of reading over 98% is often required prior to weaning.[24] However, overnight oximetry cannot rule out obstructive sleep apnea. Therefore, polysomnography in infants can be useful in assessing the degree of upper airway obstruction but the false positive rate may be significant and very little normative data exists. [25] Once it is determined that the child's clinical status and

Box 2. Proposed home oxygen weaning protocol

1. Children are assessed in the Follow-up Clinic every 2-4 weeks.
2. Continuous home pulse oximeters - maintain saturations >93%
3. Once infant determined to be stable, wean oxygen stepwise by 1/8 LPM or 0.1 LPM for each step, pending on the type of flow meter used.
   - Continuous monitoring to evaluate saturations while eating and asleep
   - Instruct family to increase oxygen if saturations are below 93% and to notify the physician managing oxygen (goal minimum saturation level 93-95%)
   - Consider a slower wean for pulmonary hypertension or if growth is stagnant.
4. Infant can first be weaned to room air during awake periods
5. Once stable of room air during the day, perform overnight oximetry test
   - If saturations >90% for 98% of the study, wean to room air
   - Could consider wean if oxygen saturations >90% for 96% of the study with no low desats or if artifact is suspected, except when there are comorbidities (pulmonary hypertension, poor growth, bad ROP)
   - Repeat overnight oximetry study on room air.
6. Once on room air, keep oxygen and pulse ox in the home to use PRN for 3 months or longer (for acute URIs)

oxygen saturations are stable, weaning of oxygen may be started in a stepwise fashion (Box 2). Many institutions, including our own, have used weaning protocols where infants are monitored on room air in the clinic for 30 minutes, then sent home. This form of "room air challenge' could miss desaturations during sleep. Our own practice for weaning oxygen is evolving as more evidence is published, and we have begun to adopt a more comprehensive weaning protocol (Box 2). A current multicenter trial is underway (clinicaltrial.gov NCT01994954) to determine optimal weaning protocols for infants discharged home on oxygen.

Long Term Respiratory Health

Although alveolar simplification is the hallmark of New BPD, small airway injury continues to be prominent in children with a history of BPD.[12,13] Infants discharged on oxygen have higher rates of respiratory medication use in the first 36 months of life.[26] Viral infections in infants with BPD, likely due to increased airway inflammation and narrowing of airways, are a common cause of hospitalization in children under the age of two.[23] School-age children diagnosed with moderate to severe BPD have decreased FEV_1, increased respiratory symptoms, and decreased peak flow measurements at 6 years of life.[13] Changes in pulmonary function testing persist into adolescence and former infants with BPD are more likely to be prescribed asthma medications.[12-14] Although there is some debate about whether preterm infants have a higher rate of "asthma", a recent meta-analysis demonstrated that preterm infants had increased bronchial responsiveness to methacholine challenge or exercise by two fold (OR 1.9; 1.2,2.7) and infants with a history of BPD had an additional 2 fold increase (OR 4.5; 2.7,7.7) compared to term controls.[27]

The airway obstruction is likely due to both a fixed component and a reactive component, which may explain the variable responses infants with BPD have to bronchodilators.[28] There is limited data on efficacy of bronchodilators in the acute treatment of developing BPD and large variations amongst neonatologist in use of bronchodilators, ipratropium (Atrovent), and inhaled steroids like budesonide (Pulmocort). [16,23] Former preterm infants with BPD have an increased incidence of tracheomalacia, which normally resolves by 2 years, and obstructive sleep apnea is 3 to 5 times as common in former preterm infants through school-age than term infants.[28] Fortunately, many of the respiratory symptoms improve over time with additional lung growth.[29] Preterm infants with a history of BPD may require follow-up with pediatric pulmonary specialists.

Pulmonary Hypertension

Infants with BPD have increased risk of pulmonary hypertension (25 to 37% of infants), and may progress to right heart failure if severe. [30] The mortality for infants with untreated pulmonary hypertension beyond 3 months corrected age is roughly 40% within 2 years.[31,32] Screening echocardiograms should be done on infants with established BPD at 36 weeks and then monthly in NICU, and then every 4 to 6 months as outpatients if oxygen requirement persists.[23,33] In infants with BPD and increased PVR, oxygen saturations of 92 to 95% may be appropriate.[33] Inpatient treatment of pulmonary hypertension with BPD includes inhaled nitric oxide,

IV pulmonary vasodilators (flolan) and systemic after load reducers (milronone), and oral medications (sildenafil, bosentan, tadalafil).[34] The most severe cases of pulmonary hypertension are seen in infants requiring continued mechanical ventilation and tracheostomy. Some infants will be discharged home on sildenafil three times a day or tadalafil daily, but these medications may be difficult to get in liquid form from non-compounding pharmacies. Close follow-up with cardiology is necessary for titrating medications and possible needs for cardiac catherization.

Systemic Hypertension

Some infants with BPD have increased systemic blood pressures (>95% for the post-menstrual age) and require medication.[35] Although the pathophysiology of the systemic hypertension is likely multi-factorial, changes in the angiotensin-renin system due to angiotensin converting enzyme 2 in the lung may play a role in BPD. Most infants with hypertension in the NICU requiring treatment will have screening renal ultrasounds and kidney function screening prior to discharge. Infants are treated with a wide variety of medications from diuretics (hydrochlorothiazide, spironolactone) to anti-hypertensive medications (beta blocker, calcium channel blockers, ACE inhibitors).[35] Diuretics for the treatment of the lung disease in BPD have not been demonstrated to have long term benefits [36]. Fortunately, the hypertension associated with BPD typically resolves by 2 years (often by 8 months) and anti-hypertensive medications are weaned or allowed to be outgrown.[37] Hypertension management is often overseen by pediatric nephrology during NICU hospitalization and as outpatient.

Nutrition for Growth

Optimal growth is essential for the infant with BPD to be successfully be weaned from oxygen and to continue the delayed alveolarization that can occur until early adolescence. Infants with BPD often have a higher caloric need, due to increased respiratory effort, and will need additional calorie supplementation (many require 24 to 30 calorie formulas or fortified BM). Energy needs can be 25% higher than infants without BPD, with an average intake of up to 140 kcal/kg/d.[38] One of the criteria for weaning oxygen is adequate growth and weight gain (goal of 20 to 30 grams per day).[39] Although breastfeeding is encouraged, many of these infants will require additional fortified breastmilk or formula to maintain adequate caloric intake and mineral supplementation. Along with additional calories, maintaining adequate micronutrients and vitamins is essential for adequate lung growth. [23,40] As respiratory symptoms improve and growth velocity is maintained off oxygen, caloric intake is often weaned around 1 year of life. Some children with severe BPD will require additional calories drinks (Pediasure, Carnation Instant Breakfast) into early childhood to maintain adequate growth.

Summary

Many infants with moderate to severe BPD can go home on nasal cannula oxygen once they are taking feeds by mouth/g-tube and stable without apnea. Home oxygen therapy requires detailed pre-discharge planning and close follow-up for monitoring and weaning of oxygen therapy. Although the infants normally outgrow their oxygen needs, many of these infants will develop obstructive airway disease. Close monitoring for pulmonary hypertension, systemic hypertension and nutritional support are necessary to maximize the growth and development of these high-risk children.

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Disclosure

None reported. **MM**



Pediatric Fatty Liver Disease

by Ajay Jain, MD

Children with nonalcoholic fatty liver disease (NAFLD) are at increased risk of early onset type 2 diabetes and NAFLD is estimated to increase the risk of early cardiovascular disease by almost five-fold.



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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a condition where there is accumulation of fat in the liver[1,2]. Normally there is some fat in the liver; however when the fat content of the liver exceeds about 5-10% of the liver weight then the condition is called steatosis or fatty liver disease[3].

While fatty liver disease used to be noted in patients who drank alcohol, patients with NAFLD get such disease without a history of any significant alcohol intake. Interestingly, even under a microscope NAFLD looks very similar to liver disease noted in patients with alcoholic intake[4].

Of concern is that NAFLD is becoming a global health problem, with prevalence estimates at 20% to 30% of the general population[5]. In fact, NAFLD is now the most common liver disease in children today with an estimated prevalence of 7 million affected children in the US[6]. Reports of NAFLD in patients as young as 2 years of age have been documented. It tends to be more common in children who are obese but has been known to occur in patients who have normal weight[7].

Children with NAFLD are at increased risk of early onset type 2 diabetes and NAFLD is estimated to increase the risk of early cardiovascular disease by almost five-fold. Additionally in patients, NAFLD is also closely associated with obesity, lipid abnormalities, hypertension, obstructive sleep apnea as well as polycystic ovary syndrome. Recent data also points to an alteration in the gut microbiota[8] in patients with NAFLD as a driver of liver injury[5,9]. There is increasing evidence that the gut microbiome which has a genomic load almost 100 times of the host can modulate nutrient and bile acid signaling within the gut lumen[10] and thus influence gut originating signaling which is known to regulate hepatic health[11-13].

NAFLD has been reported in people of all ethnicities and races. While NAFLD is known to be less common in African Americans it occurs most commonly in Hispanic patients. For reasons not completely understood, Asian Americans are more likely to get NAFLD than any other ethnicity or race.

While in NAFLD there is fat accumulation, when there is accompanying inflammation in the liver, then the condition is known as Nonalcoholic steatohepatitis (NASH). The drivers for progression of NAFLD to NASH remains unknown and research into mechanisms of such injury and its progression is a major focus in the field of gastroenterology and hepatology[14,15]. Additionally the natural progression of NASH in children also remains ill defined. Many children with NASH can develop fibrosis, which is a form of liver scarring[1,4]. Such fibrosis can advance to cirrhosis and ultimately result in liver failure and the need for liver transplantation to sustain

life. In fact, in adults NASH is the second most common cause of liver transplantation. It is generally believed that if this trend is not halted then NASH could fast become the number one cause of liver transplantation in adults[16,17]. Addressing NASH in the pediatric world can have a major impact in reducing complications as children grow to become adults.

An additional concern in patients with NASH is cancer, which is now the third leading cause of mortality in patients with fatty liver disease[18,19]. Primary liver tumors have had a significant rise in patient populations and this this thought to be driven at least in part due to NASH.

Clinical Features

A majority of patients with NAFLD / NASH do not report clinical problems and are asymptomatic. Some children can have nonspecific abdominal discomfort below the rib cage or have increased fatigue[20]. There can also be dark pigmentation of the armpits, knees, knuckles, elbows or neck, which we now know is a sign of insulin resistance. While symptoms of aches and muscle pain, feel of bloating, acid reflux and sleepiness have been reported in patients with NAFLD/NASH, their relationship to the disease process is uncertain and possibly represent complications from obesity which is prominently seen in patients with NAFLD[21].

On examination such patients may have liver or splenic enlargement. Signs of liver failure like jaundice, encephalopathy, ascites, abdominal wall angiomata or palmar erythema are rarely noted at presentation in children. However this is being increasing seen in adult patients[22,23].

Diagnosing NAFLD/NASH

A liver biopsy remains the gold standard for diagnosing NAFLD or NASH. Previous reliance on serum aminotransferases as well as ultrasound of the liver has not proven to stand the test of time or the rigors of reliability, validity or objectivity. In fact patients with NAFLD and NASH can have normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and gamma glutamyl transpeptidase (GGT). Ultrasound remains unreliable in diagnosing or estimating the hepatic fat content or inflammation[1,24].

Nevertheless, with a paucity of a reliable surrogate marker (other than an invasive liver biopsy), ALT is still widely used in clinical decision making. There has also been recent literature to support the use of newer ALT cutoffs, which lowers the ALT level to 26U/L for boys and 22U/L for girls as a predictor for liver disease. Liver transaminases and GGT remain useful in excluding other causes for liver disease like primary sclerosing cholangitis in pediatric patients[25]. Thus patients presenting with ALT elevation are routinely tested for a host of liver diseases like autoimmune hepatitis, alpha 1 antitrypsin, Wilson disease, infectious hepatitis to rule out other etiologies. Rare diseases like inborn errors of metabolism, drug toxicities and lysosomal acid lipase deficiency can also present with fat accumulation in the liver and need to be ruled out[26].

Given this diagnostic dilemma a general approach is that in the absence of other causes of liver disease, NAFLD can be placed high on the differential diagnosis in an obese patient with ALT elevation. As with any other disease process a thorough history, review of systems, physical examination and laboratory testing is mandatory. Certainly, a confirmation of NAFLD/NASH can be undertaken with a subsequent liver biopsy, which can also help in grading the severity of liver damage[3,17].

The liver biopsy is scored based on the NAS (NAFLD activity scoring) system. The degree of hepatic steatosis as well as lobular inflammation is each graded from 0-3. Similarly hepatocyte ballooning is graded from 0-2. The final number is the sum of each of the final steatosis, lobular inflammation and ballooning score, to derive a NAS score. In addition there is grading for the degree of fibrosis. The NAS score and fibrosis can help clinicians in determining the severity of liver disease in patients with NAFLD/NASH[24,25].

Laboratory Evaluation

Since in patients presenting with a high ALT and obesity; while NAFLD would be a consideration, given the low specificity and sensitivity of serological testing for NAFLD it is generally recommended that the following testing be performed to rule out other etiologies. Complete Blood Count (CBC), Liver panel, GGT, Prothrombin Time, INR, Lipid panel, TSH, Creatinine Kinase and testing for celiac disease (total IgA and Tissue transglutaminase)[27].

Additional testing to rule out other specific liver disease would include a viral hepatitis panel. It is also

recommended to test serum ceruloplasmin levels and possibly a 24 hour urinary copper screen if there is suspicion for Wilson Disease (WD). Patients with WD can also have hematological as well as neuropsychiatric problems and a liver biopsy with copper estimation may eventually be needed[28,29].

As noted in recent literature, it is important to rule out autoimmune hepatitis and thus a total IgG, anti-nuclear antibody (ANA), liver kidney microsomal antibody and anti-smooth muscle antibody is recommended. Most hepatologists would also recommend testing for alpha 1 antitrypsin with a serum alpha 1 antitrypsin assay[3,30]. This could be paired with phenotypic/genotypic typing[25]. Since hepatic fat accumulation, advanced fibrosis as well as lipid dysfunction is noted in lysosomal acid lipase deficiency (LAL-D), some centers recommend an enzyme assay for lysosomal acid lipase activity if the presentation is suspicious for LAL-D[25].

While, ultrasound as note above is poorly co-relative of NAFLD/NASH it remains an important modality to rule out hepatic cysts, intra or extra hepatic masses, portal hypertension as well as biliary problems and thus a baseline ultrasound is recommended[26].

Newer Diagnostic Modalities

Several diagnostic strategies are being developed to non-invasively (without liver biopsy), diagnose and longitudinally follow NAFLD / NASH[31]. Estimation of the hepatic fibrosis using a special ultrasound probe which can track hepatic stiffness is increasingly being utilized in research and clinical assessments. Proton Density Fat Fraction (PDFF) which is a Magnetic Resonance Imaging (MRI) based estimation of hepatic fat has also shown significant co-relation with liver biopsy in NAFLD/NASH. Several other blood tests and imaging modalities continue to push the research forward for better diagnostic tools[32].

Progression of NAFLD/NASH

Major lacunae in our understanding of fatty liver disease stem from a lack of well-defined pathways that drive fat accumulation and its subsequent culmination in hepatic inflammation[33]. The earlier idea of a 'two-hit hypothesis', where it was believed that there is triglyceride accumulation as a first hit secondary to metabolic syndrome which then leads to the second hit via oxidative stress and progression to hepatitis via the Kupffer cells is increasingly being replaced by the 'multiple or parallel hit hypothesis[4]. This has taken greater significance due to recent literature supporting the role of gut microbiota, environmental factors, genetic factors and the knowledge that NASH can occur in lean individuals.

It is thus now believed that inflammation may precede steatosis, and that inflammatory changes are driven due to an early Kupffer cell activation and release of cytokines, via several mechanisms which propagate liver injury, ultimately leading to fibrosis and cirrhosis[29].

Treatment/Management

Weight Loss, Exercise and Lifestyle Change

In patients with NAFLD/NASH the only established modality to drive improvement is weight loss and exercise. While diet changes can lead to weight loss and exercise are part of lifestyle modification, they are traditionally very hard to achieve and sustain for long periods. However, it is generally believed that replacing trans and saturated fats with monounsaturated and polyunsaturated fats can reduce cardiac disease in patients with NAFLD[34]. There has also been recent data supporting the use of omega 3-fatty acids and avoidance of processed foods and diets rich in simple sugars[35].

Instead, a diet rich in plant based ingredients has been recommended in several studies. In fact data supports the consumption of whole grains, fruits and vegetables, which are considered low glycemic index foods for beneficial effects in patients with fatty liver disease. Limiting portion sizes is also critically important as part of lifestyle changes in patients with fatty liver disease.

Weight loss has been consistently shown to help patients with NAFLD/NASH. Most studies recommend a gradual weight loss, in association with life style changes. Paradoxically very rapid weight loss can have detrimental side effects and is not encouraged. Several studies have reported an improvement in serology as well as histology upon sustained weight loss and exercise regimen[34]. A multispecialty family and patient centric approach has been most effective in weight management programs.

Additional liver diseases may complicate NAFLD/NASH. In fact data from adult studies supports that alcohol consumption, especially heavy or binge drinking can drive progressive liver disease and patients should be counseled against alcohol consumption. The physician should review the immunization records to verify vaccination against hepatitis A and B[34,36].

Medications

Many medications have been trailed and continue to be tested for NAFLD/NASH. One of the drugs that remains in common use but has not shown to be effective for treatment is Metformin[22]. Several studies have concluded that Metformin is not superior to placebo in significantly modifying histology or ALT in patients with NAFLD. However Metformin has an important role in patients with diabetes. Many researchers have evaluated the role of antioxidant treatment. In fact some natural antioxidants have been reported to have beneficial effects in NAFLD preclinical models and small pilot clinical studies but none of them are recommended for treatment of NAFLD/NASH and their use needs further research.

Among the many other treatments that continue to be used for NAFLD/NASH is Vitamin E[22]. While some reports have suggested that vitamin E may have important benefits in modulating histology and serology in patients with NAFLD, there have been recent concerns with regard to its long term safety. Saint Louis University was closely involved in trials of metformin as well as Vitamin E.

A recently trialed drug for use in pediatric NAFLD is Cysteamine bitartrate. Given its antioxidant role it was, tested in children with NAFLD as part of a multicenter trial with Saint Louis University as a study site. Although there was some reduction in hepatic inflammation as well as a decrease in serum aminotransferase with Cysteamine bitartrate, there was no significant improvement in the severity of NAFLD histological markers against placebo treatment[23].

There has also been an increased interest in the role of probiotics and prebiotics as a therapeutic option for patients with NAFLD/NASH[37]. While probiotics are organisms that can reside as commensals in the host to modulate the intestinal microbiome and influence gut-systemic signaling, prebiotics are ingredients that can stimulate the growth and / or activity of gut bacteria for the benefit of the host[38]. Given that both probiotics and prebiotics have been used in patients with several gastrointestinal diseases (like diarrhea, inflammatory bowel disease, etc.), there is a large body of clinical expertise that affirms to their perceived safety for human use[39]. However a unified approach to their dosing, selection and attestation to their efficacy in patients with NAFLD remains a focus for several research studies.

Bariatric Surgery

While bariatric surgery remains an option[40], it is reserved for patients at significant risks of continued morbidity and mortality in whom medical measures have failed. It has been speculated that improvement in NAFLD/NASH post bariatric surgery is not only due to weight loss but also driven by an alteration of bile acid homeostasis due to the renewed anatomy created via the bypass procedure. It has been postulated that there is a significant influence on liver histology via an alteration of gut derived signals in patients post bypass surgery[41,42]. The surgery is also known to induce adaptive changes in gut morphology as well as changes in the absorption of micro and macronutrients[43,44]. In fact recently Saint Louis University physicians led an NIH funded research workshop evaluating the role of the gut in modulating disease in patients post bariatric surgery[41].

Follow-up

It is generally recommended that patients with NAFLD/NASH have close follow-up. Many physicians routinely measure ALT levels as well as anthropometrics to monitor patients every three to six month; however it is well known that changes in ALT do not always track disease severity. Some centers also recommend a repeat liver biopsy, however protocols for such continue to be developed based ongoing research and the increased availability or noninvasive testing.

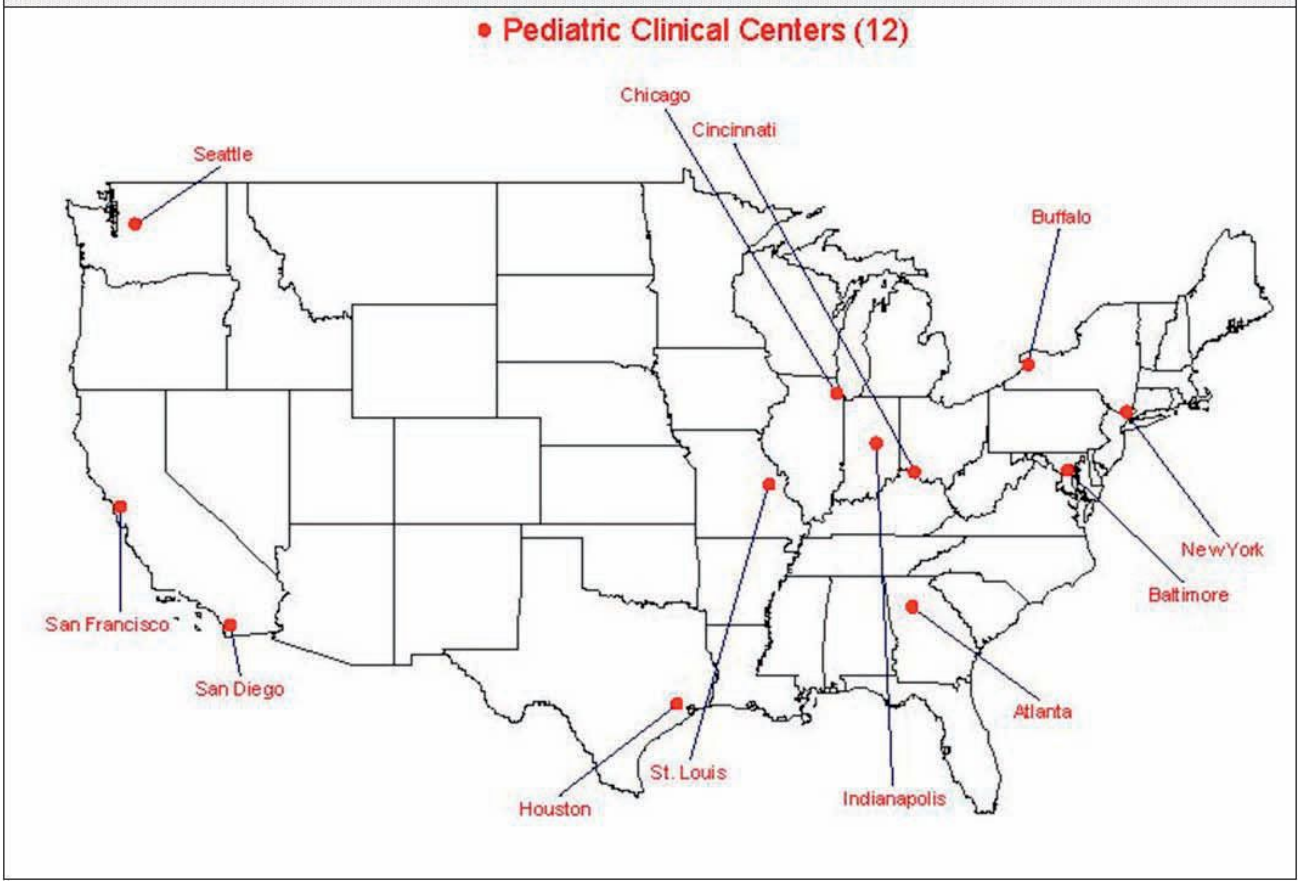
NIH NIDDK NASH CRN

To further our understanding of NAFLD / NASH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored the creation of the Clinical Research Network (CRN) in Nonalcoholic Steatohepatitis (NASH). A major focus of the NASH CRN is to collaboratively work on the etiology, the contributing factors, natural history, associated complications, and therapy of NAFLD and NASH[23,45].

This consortium includes 12 pediatric centers, including Saint Louis University. Figure 1, throughout the US and several adult clinical sites throughout the country.

The NASH CRN has been at the forefront in our understanding of NAFLD/NASH and the development of both diagnostic and therapeutic modalities. Evaluating the

Figure 1: Pediatric Clinical Centers – NASH CRN



utility of Vitamin E, Metformin, as well as the anti-oxidant Cysteamine bitartrate has been systemically tested in children as part of NASH CRN funded studies. The NASH CRN continues to work on developing diagnostics and therapeutics to advance our understanding of pediatric fatty liver disease[31,46]. Figure 1.

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Disclosure

None reported.

MM

Pediatric Intestinal Failure: A Review of the Scope of Disease and a Regional Model of a Multidisciplinary Care Team

by Nisha Mangalat, MD

The care of patients with pediatric intestinal failure requires a multifaceted approach with considerations of nutritional, medical and surgical needs.



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Abstract

The term "intestinal failure" signifies the inability of the body to meet the digestive, absorptive and nutritive needs of the body. In children, intestinal failure is most often due to short bowel syndrome, often a result of necrotizing enterocolitis, a severe GI ischemic pathology that is generally associated with prematurity. With advances in neonatal care, more preterm infants are surviving, and subsequently we care for more children with SBS than ever before. These children require parenteral nutrition (PN) for survival. Neurodevelopmental outcomes are tied to nutrition in early years; thus these children are the most vulnerable to the sequelae of intestinal failure. As such, the development of multi-disciplinary intestinal rehabilitation programs have emerged as the state of the art in the care of children with intestinal failure.

Introduction

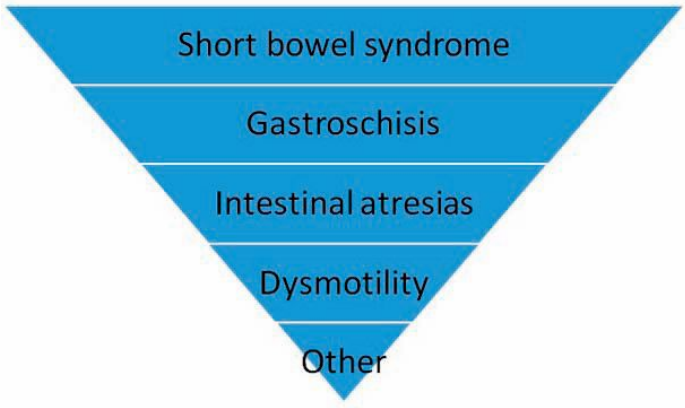
Intestinal failure (IF) is commonly defined as a "reduction in functional gut mass below the minimal necessary for digestion and absorption adequate to satisfy the nutrient and fluid requirements for maintenance in adults or growth in children". [1] Intrinsic to the definition, these patients absolutely depend on parenteral nutrition (PN) for survival.

Etiology

The etiologies of IF are generally categorized as occurring secondary to 1) short bowel syndrome, referring to the spectrum of malabsorption that occurs after reduction of mucosal surface area from congenital or acquired lesions, 2) dysmotility (i.e. intestinal pseudoobstruction), or 3) mucosal enteropathy (e.g. congenital chloride diarrhea, tufting enteropathy, and microvillus inclusion disease). Table 1. At times, patients have features of a few or all the categories of IF (ie. gastroschisis). The most common pediatric cause of IF is short bowel syndrome.[2]

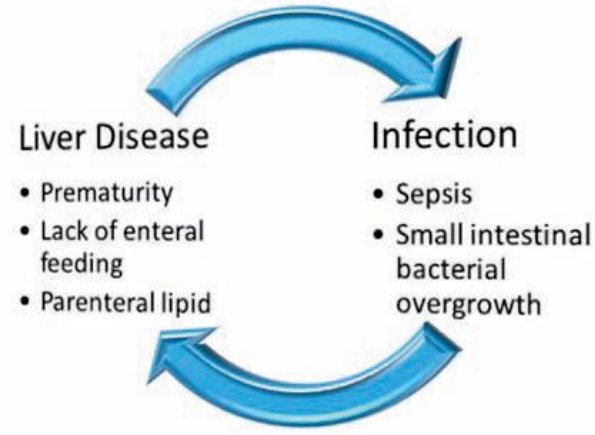
Necrotizing enterocolitis (NEC) is the leading cause of pediatric SBS and subsequently the most common cause of pediatric intestinal failure in developed countries[3]. Though there have many advances in neonatal medicine, the incidence of NEC despite advances in the care of the neonate, the incidence of NEC has remained relatively stable over the previous decades[4]. Another important cause of pediatric SBS is gastroschisis - recent data from the CDC suggests the prevalence of gastroschisis in the United States is increased by 30% from 1995–2005 to 4.9 per

Table 1. Most common etiologies of Pediatric Intestinal Failure



Short bowel syndrome, most commonly due to necrotizing enterocolitis, is the most common cause of Pediatric intestinal failure. Other important etiologies include gastroschisis, intestinal atresias, dysmotility, chronic intestinal pseudoobstruction, or other rare mucosal enteropathies (microvillus inclusion disease, tufting enteropathy, and other congenital diarrhea syndromes).

Figure 1. Relationship between liver disease and infection in IFALD



10,000 births during 2006–2012.[5] Other etiologies of SBS include mid gut volvulus, and long segment Hirschsprung's disease.[6,7]

Morbidity

Children with IF require parenteral nutrition, a complex recipe of appropriate macronutrients (carbohydrate, protein, lipid), electrolytes, and micronutrients delivered through an IV infusion for survival. Chronic PN therapy is absolutely a life-saving nutritional strategy for this population; however, there are many inherent risks that require constant attention and prophylactic action. Intestinal failure associated liver disease and catheter related blood stream infections (CRBSI) are among the most concerning as they are the major sources of morbidity and mortality.

Intestinal Failure Associated Liver Disease

Liver disease, particularly cholestasis progressing to life threatening liver dysfunction, is one the limiting factors in the management of IF.[8] Cholestasis is associated with decreased survival in this population with relative risk of mortality estimated at 20 with conjugated bilirubin ≥ 2.5 mg/dL.[9] While many macronutrients associated with PN have been implicated as the source of the so-called "TPN cholestasis" or "PN associated liver disease", this in and of itself does not define the spectrum of the problem.[10] The more accurate term, "intestinal failure associated liver disease" (IFALD) represents the myriad of issues that contribute to severe liver dysfunction in the infant receiving chronic parenteral nutrition. Figure 1. Factors related to development of IFALD include prematurity, fasting/lack of enteral or oral feeding resulting in impaired bile flow, alterations in enterohepatic circulation, infection, as well as PN related factors (namely lipid). The latter two, infection and lipid, have emerged as major contributors to morbidity and mortality, and recent efforts in therapeutic strategies have been geared toward preventing infection and minimizing risk associated with lipid emulsion. Figure 1.

Role of lipid in IFALD

Standard soybean oil lipid emulsion (SOLE), has been implicated as major player contributing to IFALD, thought to be due to chronic exposure of pro-inflammatory omega-6 fatty acids (FA) and plant derived sterols (phytosterols) that are similar in structure to cholesterol.[11] Mediators of inflammation are generally manifested as cholestasis to the neonatal liver.[12] Prior to 2012, the standard recommended SOLE dose for infants

receiving PN was 2–3 g/kg/day. In 2012, Teitelbaum and colleagues described significant reduction in cholestasis in a cohort of pediatric IF whose lipid dose was restricted to 1 g/kg/day compared to historical cohort treated with standard therapy.[13] A review of 30 pediatric IF patients requiring PN for >3 years utilizing a lipid minimization strategy demonstrated no essential fatty acid deficiency, no need for transplantation, and normalization of biochemical markers of liver disease.[14] Given the inflammatory effects noted with soy based lipid emulsion, alternative sources of lipids have been considered. There have been several studies demonstrating the safety of fish oil based solutions and naturally considered as a regimen that could be used in the management of IFALD.[15-17] However, while fish oil as monotherapy for lipid infusions have shown biochemical improvements in cholestasis, there has not been corresponding improvements in liver histology.[18-20] To answer question whether the benefits of fish oil were seen as a result of newer treatment paradigm of lipid dose reduction, a randomized control trial was designed. This study aimed to prospectively analyze whether a strategy of lipid minimization with standard soy bean oil versus utilization of fish oil based lipid reduced or halted the progression of liver disease. Interestingly, the study had to be terminated prematurely as the overall incidence of cholestasis amongst the recruited subjects.[21] More recently, a combination lipid emulsion of soy (30%, omega-6 FA), coconut (medium chain triglycerides), olive (monounsaturated FA's) and fish oil (omega-3 FAs), collectively called, SMOF-lipid, (Fresnius Kabi, Bad Homburg, Germany) has emerged as an alternative.[11] This SMOF-lipid combination has been shown to improve biochemical liver function in patients with IFALD.[22] To date, there has been no randomized trials comparing fish oil lipid emulsion to SMOF-lipid but both seem to be associated with positive results at least in terms of biochemical liver disease.

Infection Contributes to Progression of IFLAD

Infection and inflammation negatively contribute to cholestasis in infants. Catheter related blood spectrum infection is a major cause of morbidity and mortality, and occurs in high frequency in children with IF who require long term vascular access for PN.[23] The incidence of CRBSI in pediatric patients with IF has been reported as high as 80%.[24] Sondheimer and colleagues reported a retrospective review of 42 pediatric IF patients 67% of which were cholestatic. Interestingly, the cholestatic patients were found to be significantly younger at the time of their first infection.[25] Moreover, advanced liver disease is associated with more infection. Among 30 pediatric patients on chronic PN, those with severe liver fibrosis were shown to have more sepsis events beginning at a younger age compared to those cholestatic patients who had only normal or mild hepatic fibrosis.[26]

A generally accepted mechanism is that increased intestinal permeability results in bacterial translocation in the enterohepatic circulation, driving hepatic inflammation[12]. Small bowel bacterial overgrowth (SBBO) is a common finding among children with intestinal failure and may increase intestinal permeability. Alterations in intestinal motility and anatomy, resection of the ileocecal valve, and acid suppression are all thought to be contributing factors making SBBO a particular risk in the IF population. Cole and colleagues found that the odds of CRBSI was 7 times higher in pediatric IF patients with SBBO as compared to those without [24]. The diagnosis of SBBO is often clinical with symptoms including malnutrition, vomiting, diarrhea, abdominal distension, D-lactic acidosis. More objective diagnosis by culture of direct aspirates of the small intestine is difficult and limited for several reasons: ease/feasibility of testing given the invasive nature of endoscopic sampling (often requiring general anesthesia), sampling error (single site sampled, bacterial overgrowth may be patchy and exist beyond the length of the endoscope), contamination of oropharyngeal flora, current culture techniques unable to capture the large breadth of GI microbes. A non-invasive strategy is utilization of hydrogen breath testing (HBT). Humans do not exhale hydrogen gas during fasting or at rest because anaerobic metabolism does not occur in these conditions. If measurable hydrogen gas is excreted after ingestion of a non-absorbed carbohydrate, this is presumed to be from the metabolism of the carbohydrate by anaerobic bacteria. Therefore, HBT may indicate the relative quantity and activity of anaerobic bacteria in the intestine. However, these breath tests are difficult to administer in pediatric IF patients due to difficulty of breath collection, rapid intestinal transit time, and interpretation of results. There remains a high degree of false-positive and false-negative results.[27]

Cyclical use of non-absorbable antibiotics is the mainstay of therapy for SBBO in most intestinal rehabilitation centers as it often recurs[3,27,28]. However, the optimal management of SBBO is unclear given limited data in children with IF. Typically antibiotics with poor enteral absorption effective against gram negative and anaerobes are utilized. There is suggestion of link between acid suppression and GI infection (presumably including SBBO), suggesting that judicious use or avoidance of acid suppression in setting of SBBO.[3,29] Use of probiotics is typically not recommended in the pediatric IF population as there is published reports of bacteremia associated with probiotic supplementation.[30,31] In one case, gel electrophoresis of the bacterial isolate from the blood was an exact match of the probiotic that the child was taking; suggesting that mechanism of sepsis was via bacterial translocation across the gastrointestinal tract.[31]

Table 2. Pediatric Intestinal Rehabilitation Team

Team Member	Role
Pediatric gastroenterologists/hepatologists	Inpatient and outpatient medical management including malnutrition/growth, recognition and evaluation of liver disease
Pediatric surgeons	Gastrointestinal surgery, central venous catheter placement, inpatient and outpatient surgical management
Neonatologists	Initial medical management of premature and critically ill neonates
Registered dieticians	Experience and expertise in IV nutrition, assessment of micronutrient deficiencies, nutritional education and counseling
GI/Surgery Nurses	Line and ostomy care, patient education
Pharmacists	Preparation of parenteral nutrition, monitoring of drug-nutrition interactions
Social workers	Access available resources, support

Surgical Considerations

Given the prolonged need for intravenous access for parenteral nutrition, preservation of vascular access sites is crucial. The majority of children in the United States receiving home parenteral nutrition therapy have a tunneled catheter. Again, prevention of CRBSI is of paramount importance to assure maintenance of these vascular access sites.

Surgical strategies have been developed to facilitate tapering dilated bowel and lengthening residual bowel to promote absorption, enhance motility and limit bacterial overgrowth. The first of these approaches, the Bianchi operation, was first described in 1980. More recently, the STEP procedure (serial transverse enteroplasty), a less technically difficult operation, was developed. A report from the International STEP registry noted that 48 of 97 patients followed over time achieved complete enteral autonomy.

Children with intestinal failure may be considered for intestinal or multivisceral transplant for severe progressive IFALD, loss of venous access, recurrent life threatening central line infections, or no chance at enteral autonomy due to anatomic factors. Based on most recent published data from the Scientific Registry of Transplant Recipients, as of 2016 the 5 year survival rate for pediatric intestine recipients was 68%, though 5 year graft survival for children <age 18 is <60%. The overall number of intestinal transplants has declined since 2008.[32]

The GIRAF team: A Model of Multidisciplinary Care at Saint Louis University

The care of patients with pediatric intestinal failure requires a multifaceted approach with considerations of nutritional, medical and surgical needs.[3] Table 2. A formal multidisciplinary approach by dedicated intestinal rehabilitation teams has demonstrated improved outcomes including a decreased need for intestinal transplantation.[33] Table 2 describes the minimum key members of the intestinal rehabilitation team. The Saint Louis University/SSM Health Cardinal Glennon Children's Hospital, GIRAF program (Glennon Intestinal Rehabilitation and Feeding team) is the only formal multi-disciplinary intestinal rehabilitation program in the region. Along with providing expert multi-faced clinical care, ongoing bench and translational research, under the direction of Dr. Ajay Jain, explores the mechanisms of bile acids, and endogenous compounds in the "gut-liver" axis, that contributes to the role of liver injury in pediatric intestinal failure. Dedicated clinical care, with state-of-the-art science results in best practices for some of our region's most vulnerable children.

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Disclosure

None reported.

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Principles of Managing Children with Medical Complexity and a New Delivery Model

by Kurtis T. Sobush, MD

Focused efforts to successfully manage children with medical complexity, regardless of how they are defined, can be achieved with allocation of health care resources directed at coordination of care needs to supplement primary pediatric care through structured programs within tertiary care centers.



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Abstract

Children with medical complexity (CMC) have warranted substantial individual provider commitment for pediatric management. New drivers have prompted program creation that focuses even greater care on this small, increasingly influential population. These drivers include enhancing care coordination, aligning value-based reimbursement strategies and managing higher patient acuity in non-hospital environments. This article will review management of CMC and highlight the Complex Medical Care Program at SSM Health Cardinal Glennon Children's Hospital in St. Louis, Missouri.

Introduction

Children with medical complexity (CMC) constitute a growing population in pediatric health care as newer life-sustaining medical care strategies and life-improving medical technologies expand and are subsequently delivered to the extremely sick and vulnerable. This expansion in delivery of care to CMC requires that providers and health care resources align well with the need for frequent high-acuity care over extended time periods, multiple subspecialty care plans, prolonged inpatient hospitalizations, numerous procedures and time-intensive coordination of care.[1,2] Optimal assessment of CMC to assure this alignment must not only factor in aspects related to functioning, disability, and health but also quality of life considerations as defined by the World Health Organization.[3] This review addresses some of the recent studies that assess various management strategies for CMC and offers a description of a CMC program model that identifies patients through high health care utilization criteria at SSM Health Cardinal Glennon Children's Hospital affiliated with Saint Louis University School of Medicine.

Defining the Population of CMC

The definitions of what constitutes CMC have been driven historically by a combination of subjective family caregiver perspectives and provider distinctions while also using more objective criteria like utilization of health care and functional limitations. Four types of medical complexity diagnostic classifications have emerged to allow for population health metrics to be tracked more easily under common subheadings like International Classification of Diseases (ICD)-9 and ICD-10 diagnoses or Medicaid claims information. In addition to these more objective diagnostic classification systems, there are often informal criteria that are developed by institutional programs as they fit within the needs of a hospital or community.

Family caregiver perspectives contribute substantially to defining CMC however these subjective factors are not easily captured by administrative claims information. As an example, the National Survey of Children with Special Health Care Needs was an open sourced, anonymous telephone survey designed to determine parental perception of complexity based on functional limitations and their severity. Notably, there were multiple domains of healthcare needs that were identified as crucial to the perception of complexity to a family caregiver that could be tracked by claims data such as the total number of medications used and use of home/school nursing. Other domains that contribute to overall medical complexity, such as the need for individualized education plans or transportation considerations were not easily available to monitor through administrative claims of payors.[4,5] Studies have focused on qualitative research intended to help define CMC as it pertains to parental experience. Through an aggregate interpretation of multiple qualitative research studies with semi structured interviews, family caregiver experiences help define this difficult to track perception of complexity that attempt to describe the quality of life domain beyond objective criteria like functional limitations. Such interviews have identified that family caregivers of CMC are more concerned with the transition of care responsibility as opposed to the transfer to a home environment with discharge from the hospital setting.[6] Other summaries of parental experiences to help manage CMC were categorized to reflect how the large burden of care on the parent can define CMC while concurrently identifying parental ability concerns to provide such care. These parents faced constant unpredictability, the need to manage the frontline of their child's medical care, and suffering in silence and isolation. Such recognition of restrictive life factors that family caregivers face can be addressed through structured interviews and help justify acquisition of home nursing medical support as professional caregivers become more aware.[7]

Along with qualitative research studies, four types of medical complexity diagnostic classification have emerged to help define the population of CMC based objectively on complex chronic conditions, hierarchical clinical risk groups (CRG), indicators of chronic conditions, and patient medical complexity algorithms.[5] Complex chronic conditions can be identified through ICD-10 categories that hold strong associations with functional limitations and high health resource utilization if a diagnosis associated with greater need for complex medical care is made on a chronic basis. Such diagnostic classifications may not reflect contributing factors of complexity like asthma or mental health concerns since these may have more episodic need for health resource utilization.

CMC may also be identified through CRG, a hierarchical set of pediatric diagnostic groups developed through 3M Health Information Systems (Salt Lake City, Utah) that are distinguished by degree of severity and the presence of multiple conditions. CRG designations of higher severity and multiplicity have been proposed as an identified classification of medical complexity with regards to Medicaid reform.[8] 3 years of clinical information and data are needed for CRG designation which may limit utility in children under the age of 3 years old.

The Agency of Health Care Research and Quality provides an open-source classification system that places ICD-10 diagnosis codes into chronic and non-chronic condition indicators.[9] Chronic condition indicators can be integrated with other classification systems to factor in components of health care utilization through other database systems like the Pediatric Health Information System maintained by the Children's Hospital Association (Overland Park, Kansas). Such classification distinctions have been used to identify populations of pediatric patients that require increased critical care resource utilization like number of ventilator days, time requiring extracorporeal membrane oxygenation and relative need for vascular access needs; those with more substantial chronic condition indicators factor in for greater than 75% of critical care cost utilization.[10] Limitations with this approach include that 3 years of data are preferred to aid classification effectively reducing the indicator utility for infants and toddlers. Additionally, major categories that determine these indicators may not encompass the true degree of complexity for diagnoses like congenital anomalies that are assigned as a singular condition even though multiple organ systems may be affected.

A patient medical complexity algorithm has also been used, focused on ICD diagnostic assignment that allows for user interpretation of degree of complexity based on number of claims made of a particular condition.[11] A summary of pediatric patients that benefit from complex medical care programs is provided in Table 1.

Clinical Outcome and Health Care Cost Improvements in Models that Manage CMC

As programs are developed to manage CMC, there are expected clinical outcome improvements as fragmented care is reduced and additional provider time occurs in

Table 1. Pediatric Patients that Benefit Most from Programs that Address Their Medical Complexity.

- Children that require home or school nursing
- Children with limited access to transportation
- Children that require an individualized education plan
- Those with family caregivers that anticipate difficulty in transition to home care
- Children with severe episodic conditions that utilize substantial health care on an intermittent basis
- Children that have chronic conditions that consistently utilize health care resources
- Younger children that are high utilizers of health care resources but do not qualify as having a chronic condition due to age
- Children that have a high use of critical care resources
- Children with medical management concerns involving multiple organ systems
- Children with congenital anomalies
- Children identified as having substantial number of health insurance claims

more controlled, preventative environments as opposed to environments designed to intervene in an acute crisis. CMC are twice as likely to have at least one unmet need compared to those without medical complexity where opportunities to be seen in these preventative environments are missed for a variety of factors.[12] In a population of CMC that are 12-17 years of age and living in households below the 400% poverty level, CMC and their family caregivers were less likely to utilize nearly all types of health care with the exception of mental health care.[13] The development of structured tertiary care programs have intended to help improve coordination of care by reducing these unmet health care needs while also reducing overall tertiary care center reimbursement claims. Improvement in a number of health services were seen following institution of a structured program intended for CMC. This has included the addressing of unmet needs including services like prescription access, vision/hearing/dental care, provision of respite for family caregivers and better access to family mental health counseling.[14] Cost reduction has been demonstrated in multiple structured programs targeted at CMC with a relatively low budget to provide for the coordination of care services intended to shift utilization patterns from inpatient to outpatient care.[2,15]

Tertiary care center strategies that focus on CMC concerns have demonstrated a variety of positive clinical outcomes. CMC have been shown to have a reduced number of annual well child visits and that those that miss well child visits have an increased utilization of emergency room care.[16] Similarly, quality indicators have identified that CMC benefit from continuity of care as determined through a Bice-Boxerman index which showed a reduction in emergency room utilization and improved care coordination through an adaptation of a Consumer Assessment of Healthcare Providers and System Adult Health Plan Survey. These CMC that visit more than 1 physician's office and 1 type of health care provider prompted by a care coordination strategy results in a better emergency room utilization outcome.[17] Focus on certain patients with CMC including those are facing post-surgical care needs, those with neurological diagnoses, and those that have medical devices have been identified as risks for future preventable inpatient hospitalization and the identification of such risks have justified increased care planning to avoid unnecessary admissions. Efforts placed in reducing passive tobacco smoke exposure, assuring medication adherence and supporting outpatient follow up have been shown to reduce these preventable hospitalizations further.[18] A summary of certain positive health care outcomes attributed to complex medical care programs is provided in Table 2.

Key drivers of overall management of CMC prompt the need to consider transitioning models of medical care reimbursement that is focused more substantially on value-based care with the transition away from fee-for-service considerations. Numbers vary based on the timeline of report and the political climate's impact on drivers of federally based care support as well as policy change at various state levels, but patients identified as CMC tend to constitute between 1-6% of the general population as determined by payor database sets. With this small number, the CMC population is markedly influential as they constitute are far greater percentage of health care cost needs, typically reported as 33%-40% of reported claims as compared to the non-complex pediatric population. These claims have prompted greater focus and the creation of various alternative payment models (APM) to offset this public health care cost burden. These models address the need to define CMC quality measures that include non-medical and social components of care that add to medical complexity and greater use of acute care hospital based services. APMs have been shown to achieve better outcomes at a lower cost through performance based payment models that promote patient-centered, population-based, high quality, coordinated accessible and effective care. Population health based metrics have become

Table 2. Beneficial Outcomes Described following Program Development for Children with Medical Complexity.

- Reduction in overall tertiary care center reimbursement claims
- Enhanced prescription access
- Improvement in access to vision, hearing and dental care
- Respite care accessibility for family caregivers
- Improved family caregiver mental health counseling
- Shift in health care utilization patterns from inpatient to outpatient care
- Improved number of well child visits
- Reduction in emergency room utilization
- Reduced preventable hospitalizations for children with neurological diagnoses, post-surgical care needs, and those requiring chronic medical devices
- Reduction in passive tobacco smoke exposure

increasingly important to define programmatic successes with regards to CMC. Top CMC program and system goals promote improved web-based data communication, modified patient/provider shared decision-making and advocacy for efforts to promote ongoing proposed CMC federal legislation through propositions like the Advancing Care for Exceptional Kids Act (ACE Kids Act of 2017). This legislation is intended to allow improved access to care with an example being enhanced insurance coverage when needed across state lines if unique and complex services are otherwise unavailable in a particular state. Past APM strategies in Ohio and California have been previously reported.[8,19]

The Complex Medical Care Program at SSM Health Cardinal Glennon Children's Hospital and Saint Louis University School of Medicine

As a tertiary care pediatric center in downtown St. Louis, Missouri, SSM Health Cardinal Glennon Children's Hospital previously faced a number of opportunities related to CMC that identified needs for improved coordination of care and added resource services. In December 2013, stakeholders within hospital administration along with community health care providers worked with medical staff leaders to develop the Complex Medical Care Program (CMCP) for this purpose. A 2 year formal review followed that included an assessment of already operational internal multidisciplinary teams, appraisal of the hospital-based electronic medical record to objectively identify the potential CMC population and frame ideas for platform development, financial forecasting and participation in visits to well established program sites that modeled different approaches to care for CMC. The CMCP started officially as an exclusive outpatient program in March 2016 after incorporating aspects of this review.

The program's mission statement has been as follows: "The SSM Cardinal Glennon Children's Hospital Complex Medical Care Program will strengthen the voice of a medically fragile population in need of substantial medical and psychosocial care by further respecting their human spirit, appreciating all factors that can affect a person's state of health, and embracing them in a community of dedicated health care providers."

The CMCP team was designed to provide superior outpatient based comprehensive care coordination that addressed the entire continuum of clinical and community care needs for CMC and their family care providers. This design warranted a physician and advanced practice nurse dyad to be assigned to each patient to optimize bedside face-to-face time while also enhancing focus on "non-bedside" coordination of care with the intent to reduce miscommunication of complex clinical care plans. The following ratios were originally decided on for CMCP provider scope based on review of outside programs that managed CMC: 1) CMCP Physician, 100 patients/provider, 2) CMCP Advanced Practice Nurse, 50-75 patients/provider, 3) CMCP Social Worker, 100 patients/provider, 4) CMCP Dietitian, 100 patients/provider, 5) CMCP Care Coordinator Assistant, 100 patients/provider. These ratios assumed an original growth forecast that would require 2 years to establish 100 enrolled patients. To achieve such rate of growth, inclusion criteria for patients were established to be relatively strict to avoid outgrowing operational capacity in the initial near-term program goals. Such criteria included that patients 1) have 3 separate inpatient hospitalizations or >20 days of inpatient hospitalization in the past year, and 2) have 5 or more subspecialty care services involved in care, and 3) be 10 years of age or younger and 4) not have their coordination of care needs being fully met by another multidisciplinary center (i. e., a cystic fibrosis center). With these inclusion criteria in place, patients were enrolled into the program through an initial internal marketing strategy with SSM Health Cardinal Glennon Children's Hospital providers in March 2016.

Along with targeting the proper population of CMC, a central component of care coordination included the development of the CMCP Individual Healthcare Plan (IHP). The intent of the IHP was to include content that was important to both the providers and the parents, to have a limited number of providers enter information to the plan to limit miscommunication, to be capable of dynamically changing and to be compatible with an internet-based electronic medical record system. A secondary goal of the IHP was to develop discrete means

to capture data points within the currently used electronic medical record product at SSM Health Cardinal Glennon that was provided by Epic Systems Corporation (Verona, Wisconsin) to facilitate clinical research and quality improvement for CMC. Such individualized plans were historically found to be tremendous parental satisfiers and felt to assist health care providers in accessing information quickly and was frequently updated.[20] An Epic based IHP was developed by SSM Health Cardinal Glennon to be utilized with the start of patient enrollment. The content of this IHP includes medication lists, health care provider contact information, home nursing and durable medical equipment provider information, a targeted problem list of the medical history, emergency care guidelines, allergies, pertinent diet information, crisis planning scenarios when needed, pertinent family and social information, health insurance information, and technology/equipment needs. Initial Epic access screens for care providers show an alert that a patient is enrolled in the CMCP and a hyperlink to the IHP is provided. Opening of the link allows for split-screen access to the IHP while other medical record review or documentation occurs simultaneously. Evolving work within the CMCP aims to modify the IHP on a yearly basis to assure it meets emerging needs like increasing the accessibility of care plans on multiple devices, through multiple electronic medical record systems and increasing access to a number of non-clinical staff members (schedulers, utilization review staff, primary care provider office staff, etc.) that have differing alert features.[21]

In the first year of the program, CMCP operational experience, clinical flow practices, and patient/family caregiver feedback offered both the necessary framework to broaden access externally as a community service as well as the recognition that enrollment criteria into the program needed to be more inclusive. The criteria involving the number of subspecialists used by a patient were reduced to 4 for enrollment and the necessary "and" criteria for inpatient time spent was felt to be prohibitive. The decision was made to adopt an "or" strategy for the inclusion criteria mentioned previously. Following multiple community marketing campaign strategies, the program now follows 215 patients that are actively enrolled out of 380 referrals over 2.5 years. 282 total patients have been followed in total in the CMCP since program initiation demonstrating that a portion of patients have either had a reduction in their degree of medical complexity to appropriately depart the program ("graduates"), they left the program for another reason, or they died. Overall referral trends have increased to ~5 per week and enrollment review occurs twice monthly by the CMCP team.

Patients with CMC that are enrolled into the CMCP are assigned to one of four complex medical care physician providers. Each medical care provider has committed a 0.1 full-time equivalent (FTE) to CMCP clinic coverage for one half-day clinic per week. Every patient is also assigned to an advanced practice nurse, 2 of which are committed to 1.0 FTE. In each CMCP half-day of clinic, 2 new patients are scheduled to a 90-minute visit and 4 follow up patients are scheduled to a 30-60 minute visit. All patients are further seen with an overlapping visit strategy by both a 1.0 FTE dedicated CMCP dietitian and social worker at each CMCP clinic visit.

The demographics of the enrolled patients in CMCP are included. The average age is 2.8 years. Serving a bi-state metropolitan area, 67% of patients are Missouri residents and 33% of patients are Illinois residents with 1 patient from Kansas. 30% of patients reside in either St. Louis City and St. Louis County. The racial breakdown is as follows: 1% Asian, 30% black/African-American, 9% multiracial, 59% white/Caucasian, 2% unknown. 38% have utilized traditional Medicaid insurance over the past 12 months, 34% have received benefits through a Medicaid noncapitated managed care plan and 31% have utilized commercial noncapitated health maintenance organizations (HMO)/preferred provider organizations (PPO). When considering various co-morbidities in the previous 12 months, 16% of CMCP patients have required home ventilator support, 22% have required a tracheostomy, 35% have required home supplemental oxygen, 54% have required enteral feeding strategies and 44% were determined to have motor impairment as defined through diagnoses in neurology, orthopedics, or cerebral palsy clinics.

Various clinical outcome trends have been observed in our population of patients that have been enrolled into the CMCP. Enrolled CMCP patients were tracked over 18 months in aggregate starting back in January, 2017 when the CMCP was only 9 months into operation with 48 unique patients. The number of unique emergency room clinical encounters and inpatient admission days were assessed in 6-month blocks during periods of program growth up through July, 2018 when the program size had grown to manage 262 CMCP patients in total. Comparisons of the total number of CMCP enrolled patients at 2 distinct 6-month time blocks (January, 2017 to July, 2017; January, 2018 to July 2018) showed that there was a reduction in the number of emergency room visits from 3.62 visits/patient to 1.98 visits/patient. Similar reductions were seen

Table 3. Lessons Learned from the First Three Years of the Complex Medical Care Program at SSM Health Cardinal Glennon Children's Hospital Affiliated with Saint Louis University School of Medicine.

- Multi-year strategic planning was required to become operational
- A physician and advanced practice nurse dyad assigned to each patient reduced miscommunication about clinical care planning
- Dynamic individual health care plans can be translated into the electronic medical record and shared with community providers
- Patient enrollment growth forecasts were underestimated
- The large majority of patients are under 3 years of age

in inpatient admission days going down from 34.73 days/patient to 12.20 days/patient.

During the same 18-month time block, there were 13.84 telephone encounters documented by a CMCP team member per CMCP patient on average. Family caregivers of those enrolled in the CMCP were surveyed during this time and 80% reflected they were "very satisfied" with their CMCP provided IHP. In addition, the IHP was utilized in multiple health care environments where 84% reported referring to their IHP at home and 96% used the IHP to facilitate discussion with non-CMCP health care providers in the past 6 months.[22] Key learning points from the initiation of this CMCP are listed in Table 3.

Conclusion

Focused efforts to successfully manage CMC, regardless of how they are defined, can be achieved with allocation of health care resources directed at coordination of care needs to supplement primary pediatric care through structured programs within tertiary care centers. The CMCP at SSM Health Cardinal Glennon serves as a model that is focused on highlighting CMC that are identified based on their recurrent needs for health service encounters.

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None reported. **MM**



A Country in Crisis: Opioid Sparing Solutions for Acute Pain Management

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This review provides recommendations for best practices regarding improving pain management via the use of novel alternatives in the emergency department, medical wards, and outpatient setting.



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Abstract

The United States is currently in the midst of an opioid epidemic that has led to previously unforeseen opioid misuse, abuse, and death. A major emphasis is being placed on reducing the exposure patients have to opioids, whenever possible, in an effort to hopefully reduce the risk of dependency, addiction, and overdose. However, opioid alternatives must be chosen carefully to ensure efficacy, safety, and availability for patients within the community. Non-opioid medications and modalities can reliably be used to treat not only opioid naive patients, keeping them opioid naive if possible, but also patients with opioid use disorders. Unfortunately, robust randomized controlled trials comparing non-opioid alternatives to opioids are lacking. Therefore, this review provides recommendations for best practices regarding improving pain management via the use of novel alternatives in the emergency department, medical wards and outpatient setting.

Introduction

The United States is in the midst of a public health crisis. Drug overdose deaths have been on the rise over the past fifteen years with more than 64,000 drug related deaths reported in 2016 alone. Opioids play a major role in preventable drug overdose deaths, with prescription opioid related deaths claiming the lives of 19,354 Americans in 2016 according to the Center for Disease Control.[1] Since leaving pain untreated is not an option, understanding the analgesic effectiveness of non-opioid modalities and medications for the management of acute and chronic pain is paramount to reducing opioid prescriptions.[2] Interventions such as trigger point injection and topical analgesics are gaining interest in the management of musculoskeletal pain as they may treat underlying inflammation and spasm providing relief in lieu of prescription opioids.

This is the fourth essay in Missouri Medicine series originating from the Larry Lewis Symposium in August 2017 concerning the transdisciplinary responses to the current opioid epidemic. The vision of this series is to move beyond solely discussing the epidemic at large and to explore key innovations that can simultaneously support more responsible opioid prescribing while ensuring timely, definitive, and compassionate attention to patient's pain or substance use disorder across a complex healthcare setting. This essay reviews two alternative treatments to opioids for pain with the goal to treat appropriate patients with non-opioid regimens in order to decrease opioid

exposure. The logic is that decreased opioid exposures will be associated with a decrease in the risk of developing an opioid use disorder (OUD) with concomitant decreases in opioid overdoses and deaths.

Trigger Point Injections for Myofascial Pain

Musculoskeletal back pain is one of the leading causes of disability among working age Americans and a common presenting complaint in the emergency department and outpatient setting.[3] A grossly under recognized cause of muscular pain is Myofascial Pain Syndrome (MPS).[4,5] Patients with MPS may present with musculoskeletal pain that is worse with movement, and has a component of referred or regional pain. The vague presenting symptoms can make the accurate identification of trigger point(s) difficult as these findings can mimic other musculoskeletal sources of pain such as fractures, disc herniation, and neuropathy.[6] Focal areas of hyperirritable muscle spasm, called trigger points, are a hallmark of this condition. Trigger points are small localized taut bands or nodules within skeletal muscle that are exquisitely painful when palpated, and fully reproduce the reported pain. They are largely due to repetitive strain, chronic musculoskeletal disorders, or acute myofascial injury.[7] There are no standardized locations in which trigger points arise. Instead, trigger points can develop in any muscle group, but are most commonly identified in the upper, mid, and low back. [7]

History is paramount for diagnosing MPS. Patients presenting with MPS will describe muscular pain exacerbated with movement leading to a decreased range of motion in the affected muscle group, as well as referred pain that does not follow a dermatomal or myotomal distribution.[8] The majority of MPS patients report recent acute trauma or repetitive use of the affected area due to occupational demands. The most common muscles involved include the paraspinal cervical muscles of the neck, the upper trapezius muscles, rhomboids, quadratus luborum, and levator scapulae.[5] Two important distinguishing features of trigger point pain include the history of pain with movement and the presence of very localized spasm that upon palpation feels like a nodule or taut band. Trigger points are not present in specific predetermined locations but rather develop spontaneously within skeletal muscle. A unique and pathognomonic characteristic of a trigger point includes a local twitch response with application of firm pressure or the insertion of a needle into the trigger point itself.[10]

MPS referred pain mimics conditions such as headache, radicular back pain, torticollis, temporomandibular joint pain and non-painful conditions such as tinnitus which can complicate or delay the correct diagnosis[6]. Performing a thorough physical exam is vital because trigger point identification as a root cause can significantly change management.[12-14] When attempting to identify trigger points within a muscle it is important to communicate with the patient regarding localized areas of severe maximal pain. Although patients may report global muscle pain and spasm in the affected muscle group, trigger points present as focal taut bands or nodules that are significantly more painful upon palpation than the surrounding tissue.[11] No high quality research (randomized controlled trials, meta-analysis) exist to support the accuracy or therapeutic impact of history and physical exam to identify trigger points, nor the effectiveness of injecting these sites in comparison to placebo, non-opioid, or opioid alternatives. In addition, no laboratory or imaging options exist to identify trigger points. In the essays and textbook chapters referenced, the diagnosis of a trigger point is based solely on the history and physical exam leaving open the possibility of multiple forms of diagnostic and therapeutic bias.

Trigger point management may be used in conjunction with a variety of systemic or topical analgesics, muscle relaxants, or varying non pharmacological modalities including ethyl chloride Spray and Stretch techniques, osteopathic manipulative therapy, ultrasonography, massage, or acupuncture. Unfortunately, high-quality effectiveness research quantifying the potential risks and benefits of these techniques is currently lacking.[9,15] However, the authors' experience suggests that trigger point injection provides targeted and immediate relief via direct mechanical inactivation of severe muscle spasm. The procedure is low risk so can be performed in most inpatient and outpatient settings with minimal supplies.[5,11] Table 1.

Trigger point injection is indicated in patients presenting with muscle spasm and referred pain who have a tender, well defined, taut band that with palpation fully reproduces pain. The success of the procedure depends on accurately identifying the presence and location of a trigger point. The majority of trigger points due to acute injuries will not require repeat injections.[11] The two-part procedure (Figure 1) involves dry needling followed by a low volume injection of local anesthetic. Upon re-evaluation the patient should have a significant reduction in pain. If pain is not relieved, reinjection is not recommended. Discharge instruction should include stretching of the affected muscle groups, remaining active, and avoiding strenuous activity for approximately 72 hours.[10,11]

Table 1. Equipment for TPI[9-11]

Adhesive Bandage	21-25 gauge 1.5-2 inch needle (Use small gauge shorter needle for superficial trigger points and large gauge longer needle for larger trigger points)
1-2 mL syringe	1 mL local anesthetic

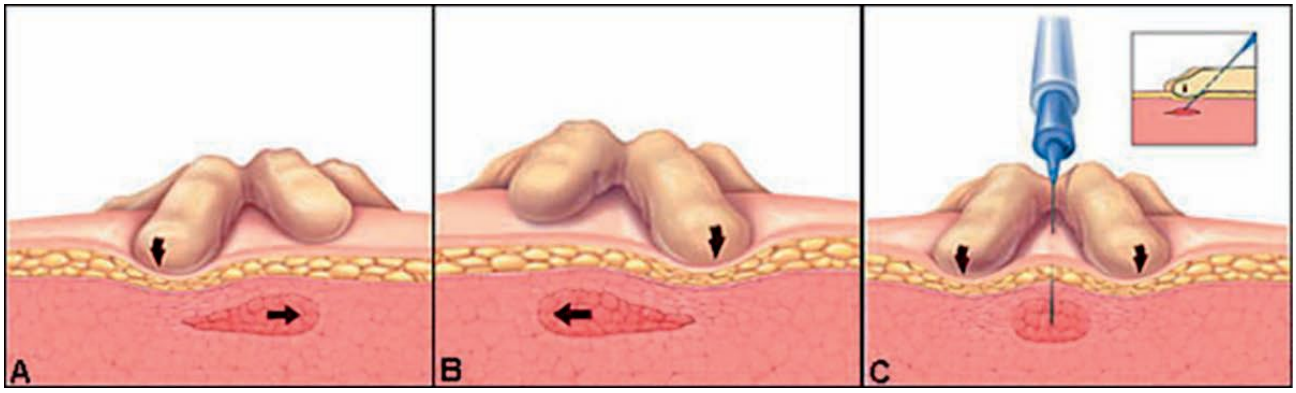


Figure 1. How to perform a trigger point injection. [9,10]
The practitioner should hold firm pressure on either side or pinch the trigger point in between their fingers. The needle should then be inserted at a 30 degree angle deep enough to engage the trigger point. This is followed by withdrawing the needle slightly, almost all the way out of the skin, before redirecting it into the trigger point to inactivate different quadrants of the spasm. After breaking up all quadrants of the trigger point, local anesthetic should be infiltrated into the center and the needle withdrawn. When the procedure is completed an adhesive bandage should be applied.

The most common complication from TPI is vasovagal reaction,[18] though a single case of necrotizing mediastinitis and one of intramuscular hematoma has been reported.[19,20] Overlying cellulitis at the desired injection site and allergy to local anesthetic are the only absolute contraindications. Overall, the management of trigger point pain with a trigger point injection is a safe and relatively low risk procedure that can be easily performed in the inpatient and outpatient setting. Licensed physicians performing or directly supervising the trigger point injections can bill for the procedure using appropriate documentation, diagnosis, and CPT coding.

Topical Analgesics in the ED

Topical analgesics serve as a viable therapeutic modality for managing acute and chronic painful conditions including neuropathic pain (herpetic and post-herpetic neuralgia), musculoskeletal pain (sprain, strain, overuse injuries, contusions, tendinopathies), burns and flares of rheumatoid arthritics (RA) and osteoarthritis (OA)[21]. The advantages favoring topical analgesics include painless and efficient medication delivery, minimal side effects, and improved patients' adherence and acceptance. Furthermore, their application is associated with direct access to target site, avoidance of first-pass metabolism, short-lived adverse effects and the ease of dose termination. Lastly, these analgesics possess comparative analgesic efficacy to their oral or parenteral equivalents but without systemic adverse effects.[22,23] However, while systemic absorption for many of these can be low, patients can become toxic from using too many patches or creams containing methyl salicylate (develop salicylism similar to an aspirin overdose) or camphor. Applying them with heat or to areas with breaks in the skin will increase the amount that is systemically absorbed.

Based on one review the best candidates for pain management with topical analgesic would include patients with cardiovascular and gastrointestinal risk factors that limit the use of oral nonsteroidal anti-inflammatory drugs (NSAID's), patients with renal or hepatic dysfunction (impaired systemic drug metabolism and clearance), patient with more than one chronic condition (limits potential for systemic drug–drug interactions), and older patients with multiple comorbidities and potential for severe adverse effects from systemic analgesic administration.[22]

The commonly used topical analgesics can be divided into 4 groups based on their mechanism of action: topical NSAIDs that reversibly inhibit cyclooxygenase enzyme (COX-1,2); topical rubefacients (counter-irritants) that dilate local blood vessels upon application, cause local erythema and warmth, and subsequently decrease painful sensation; topical capsaicin that activates TRPV1 receptors and provide analgesia by causing a reversible degeneration of nerve terminals; and local anesthetics that alleviate pain through blockade of voltage-gated sodium channels.

Table 2
Commonly Used Topical NSAIDs

Non-steroidal anti-inflammatory drugs[21, 23–32]

1. Reversible inhibition of cyclooxygenase (COX-1,2 enzyme inhibition)
2. Topical application results in analgesia and anti-inflammation with reduced rates of systemic adverse effects and toxicity.
3. Indications: Acute sprain, strain, overuse injuries, contusions, tendinopathies, bursitis, exacerbations of osteoarthritis
4. Contraindications: Hypersensitivity to NSAID's, Open wounds, skin infection, skin eczema, third trimester pregnancy, children and adolescents (limited data)
5. Adverse effects: Pruritus, erythema, skin rash, possible systemic toxicity in case of application of larger than recommended quantities, [25-32]

Generic (Brand name)	Dosing (initial)	Dosing (maximum/24h)	NNT/NNH (when available)
Diclofenac sodium solution (150ml) 1.5%, 2 % with/w/o topical solution (Pennsaid) Cost: $41-78 with Pennsaid $43-97 without	1.5% solution: 40 drops QID 2% solution: 40 mg BID	1.5% solution: 40 drops QID 2% solution: 40 mg BID	NNT = 7 to reduce acute pain by ≥50% within 1-week
Diclofenac 1% gel (100g) (Voltaren) Cost: $23-42	2 g QID	Osteoarthritis:8g/24h for single joint upper extremity 16g/24h for single joint lower extremity Other: 2-4 g/24h	NNT = 2 to reduce acute pain by ≥50% within 1-week NNT = 5 to reduce chronic pain of less than 6 weeks' duration within 6-12 weeks NNT = 10 to reduce chronic pain of greater than 6 weeks' duration within 6-12 weeks NNH = 51
Diclofenac epolamine 1.3% patch (Flector patch) (30 patches) Cost: $337	1 patch (180mg) BID	1 patch (180mg) BID	NNT = 5 to reduce acute pain by ≥50% within 1-week
Etofenamate 5-10% cream (50g) Cost: $22	5% cream: 5 cm ribbon TID (1.7 g) 10% cream: 5-10 cm ribbon TID (3.3g)	9 g (450 mg)	
Ibuprofen 5% gel (40g) Cost: $13 Ibuprofen 10% cream (50g), Cost: $14	1-4 cm ribbon TID	4 cm ribbon TID	NNT = 4 to reduce acute pain by ≥50% within 1-week NNT = 6 to reduce acute pain by ≥50% within 1-week
Ketoprofen 2.5 % gel Cost: $	5-10 cm (2-4 g) ribbon BID-TID	10cm ribbon (4g) TID	NNT = 3 to reduce acute pain by ≥50% within 1-week NNT = 7 to reduce chronic pain within 6-12 weeks
Piroxicam 0.5% cream Cost: $22-55	3cm ribbon (1g) TID	3cm ribbon (1g) TID	NNT = 4 to reduce acute pain by ≥50% within 1-week

Table 3
Commonly Used Topical Rubefacients, Capsaicin and Local Anesthetics

Topical Rubefacients[21] 1. Rubefacients (typically containing salicylates) cause irritation and relieve pain by inducing counter-irritation (defunctionalisation of nerve ending) 2. Indications: Acute sprain, strain, overuse injuries, contusions, tendinopathies, bursitis, exacerbations of osteoarthritis 3. Contraindications: Hypersensitivity to salicylates, Open wounds, skin infection, skin eczema, third trimester pregnancy, children and adolescents (limited data, fatalities in overdose), application to mucous membranes 4. Adverse effects: Pruritus, erythema, skin rash, systemic (salicylate toxicity) in case of application of larger than recommended quantities.			
Methyl salicylate 10%, 18% + Menthol 3%, 7.5% cream, gel, ointment, patch Cost: $5-12	2-4 cm ribbon QID	4 cm ribbon QID	NNH = 26
Capsaicin[21,33-35] 1. TRPV1 agonist causing irritation/counterirritation 2. Indications: postherpetic neuralgia, polyneuropathies (DM/HIV), post-surgical neuropathy, acute sprain, strain, overuse injuries, contusions, tendinopathies, bursitis 3. Contraindications: open wounds, application to mucous membranes, children and adolescents 4. Adverse effects: severe skin burning, itching, erythema.			
Capsaicin 0.025% to 0.15% OTC (gels, creams, liquids, lotions, and transdermal patches) Cost: $15 for 60g Capsaicin 8% patch (by prescription only) Cost: $800 (per patch) Capsaicin and Camphor/Menthol OTC cream Cost: $5-15	4-6 cm ribbon up to QID	4-6 cm ribbon QID	NNT = 11 to reduce chronic pain within 6-12 weeks NNH = 8
Topical Anesthetics[21, 36—40] 1. Alleviates pain through blockade of voltage-gated sodium channels that decreases ectopic discharges from injured cutaneous nerves and nociceptors. 2. Indications: Acute/Chronic neuropathic pain, acute MSK pain (back pain) 3. Contraindications: Hypersensitivity to amide anesthetics, open wound, application to mucous membranes, skin eczema, severe hepatic insufficiency, children and adolescent (fatalities in overdose) 4. Adverse effects: skin erythema, edema, burning			
Lidocaine 5% Patch Cost: (6) $72-150 Lidocaine 4% Patch Cost: (6) $8-12	1-3 patches daily with 12 h free period	3 patches daily with 12 h free period	

There are several factors clinicians should consider prior to prescribing topical analgesics for various acute and chronic pain, including patients' age, comorbidities, and concomitant medications, as well as pain type, duration, skin sensitivity, allergies, and medication cost.[22] As an example, for patients suffering from acute strains and sprains, topical NSAIDs or topical rubefacients are reasonable options; for pain related to osteoarthritis or rheumatoid arthritis topical NSAIDs, topical rubefacients, and low-concentration topical capsaicin could be considered; and for neuropathic pain, topical local anaesthetic (lidocaine, for example) or high-concentration topical capsaicin are options.[21]

The commonly used topical analgesics with their generic names, dosing, indications and contraindications, adverse effects and cost are presented in Tables 2 and 3. In addition, a number needed to treat (NNT) defined as an achievement of at least 50% pain relief at 7 days in comparison to placebo for acute pain and for 6-12 weeks for chronic pain; and a number needed to harm (NNH)

defined as a development of a harmful adverse events (local and systemic), and particularly serious adverse events in comparison to placebo at 7 days for acute pain and for up to 12 weeks for chronic pain are included.

Conclusion

An increasing array of non-opioid medications and modalities now exist for the management of acute pain. One size pain management does not fit all. As practitioners work to minimize opioid exposure and potential harms maximizing the use of alternatives such as trigger point injections and topical analgesics is paramount. Expanding physician's awareness of multi-modal analgesia with an understanding of regional anesthesia techniques this population can receive adequate analgesia without opioids in many cases.

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The Cardiovascular Effects of Marijuana: Are the Potential Adverse Effects Worth the High?

by Venkat N. Subramaniam, MD, Arthur R. Menezes, MD, Alban DeSchutter, MD & Carl J. Lavie, MD

Three main cardio-vascular pathologies are associated with marijuana usage: peripheral arteritis, coronary vasospasms, and platelet aggregation. Many of the acute and long-term toxic effects of marijuana and THC still remain unknown.





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Abstract

Marijuana is the most commonly abused illicit drug in the United States (US) and much of the Westernized World with a steadily increasing prevalence in usage and abuse over the past decade, especially among adolescents. Much of the available data on 9-tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana, relates to its neurological effects and anti-emetic properties, with very little on the cardiovascular (CV) effects of THC. Available literature shows that THC has three major effects on the CV and the peripheral vasculature in the form of "cannabis arteritis," cannabis-induced vasospasms, and platelet aggregation, with an unknown verdict on the relationship between marijuana use and atherosclerosis progression. This manuscript reviews these effects and possible mechanisms of action. Moreover, limitations on current views of marijuana and indirect causes of CV toxicity will be investigated, such as concurrent drug use, lifestyle, and mental health. The effects of marijuana on the CV system are extremely worrisome and likely need more attention due to the growing legalization of cannabis for medicinal and recreational use across the US. As a result, awareness among health care professionals about potential side effects and toxicities associated with acute and chronic exposure of cannabis will increase in importance.

Introduction

According to the National Institute of Drug Abuse, marijuana is the most commonly used illicit drug in the US and the third most common cause of drug-related emergency department visits between 2004-2011. Table 1.[1] A 2014 study by Terry-Mcelrath et al. demonstrated that marijuana use has steadily increased over the past decade among middle and high school students.[2] Moreover, marijuana use will likely increase due to increasing legalization for medicinal and recreational use in the US. Although cannabinoids are the oldest and most widely used illicit drugs, the clinical and pharmacological effects of cannabinoids have only been recently studied, with much still unknown about the physiologic and pathologic effects of marijuana.

Marijuana is derived from the hemp plant Cannabis sativa, with the biologically active ingredient being a group of cannabinoids and the main psychoactive constituent being 9-tetrahydrocannabinol (THC).[2-4] The THC ligand binds to multiple receptors with especially high selectivity for the Cannabinoid 1 and 2

Table 1. Weighted annual estimates of drug related emergency department visits for different types of illicit drug overdose according to the National Institute on Drug Abuse. Cannabinoids are the third most common cause of drug related ED visits in this country.

	Weighted Annual Estimates							
	Estimates 2004	Estimates 2005	Estimates 2006	Estimates 2007	Estimates 2008	Estimates 2009	Estimates 2010	Estimates 2011
Non-alcohol illicits	991,640	922,018	958,866	974,852	994,583	974,392	1,172,276	1,252,500
Cocaine	475,425	483,865	548,608	553,535	482,188	422,902	488,101	505,224
Herion	214,432	187,493	189,787	188,162	200,666	213,118	224,706	258,482
Cannabinoids	**281,619**	**279,668**	**290,568**	**308,547**	**374,443**	**376,492**	**461,028**	**455,668**
Stimulants	162,435	137,806	107,586	85,043	91,945	93,564	138,632	159,840
Amphetamine	34,085	35,083	32,251	21,545	31,534	37,431	52,388	70,831
Methamphetamine	132,576	109,655	79,924	67,954	66,308	64,117	94,929	102,961

receptors (CB1 and CB2, respectively). CB1 receptors are predominantly expressed in the brain and peripheral tissues, including cardiac muscle, hepatic tissue, the gastrointestinal tract, and vascular endothelium,[5, 6] while CB2 receptors are mainly expressed in immune cells. These CB2 receptors have recently been shown to play a role in inflammatory cytokine regulation.[7]

Research on the psychoactive effects of CB1 and CB2 receptor- induced activation by THC has been studied for decades, but the adverse physiological effects have not been studied in detail.

Pathological Effects of THC

CB1 receptors are mainly located in the cardiovascular (CV) system (CVS), the central nervous system (CNS), and peripheral vasculature. THC causes an acute, dose-dependent increase in blood pressure (BP) and heart rate (HR).[8] Due to a quickly developing tolerance to the psychoactive effects of THC, higher doses and increasing usage frequency are commonly observed. There is evidence to suggest that increased frequency of marijuana use increases the risk of cardiac arrhythmias and myocardial infarction (MI).[3, 9-11] Furthermore, chronic THC use has been associated with increased angina frequency, likely due to a decrease in the angina threshold, diminished sympathetic and parasympathetic nervous system signal transduction, serum aldosterone increases, central and peripheral vasoconstriction, and hypertension (HTN).[12]

For example, a study published in 2017 investigated the association between marijuana use and CV and cerebrovascular mortality.[13] The design study was based on mortality follow up using linked participants aged 20 and above who responded to questions on marijuana usage during a 2005 US national health and nutrition examination survey to data from 2011 public use linked mortality file of the National Center for Health Statistics and Center for Disease Control and Prevention. Of the 1,213 participants, 72.5% were alive. Of the dead, adjusted hazard ratios for death from HTN among marijuana users compared to non-marijuana users was 3.42 (95% CI 1.20-9.79). Moreover, for each year of marijuana use, the hazard ratio for death related to HTN was 1.04 (95% CI 1-1.07) when comparing marijuana users to non-marijuana users. In summary, marijuana users had increased risk of HTN-associated mortality even if a prior diagnosis of HTN was treated. In addition, increased duration of marijuana use is associated with increased risk of death related to HTN.

In the CNS, THC has been shown to increase cerebral vasculature tone and central BP, which in turn has been shown to decrease cerebrovascular blood flow. This decrease in cerebrovascular blood flow has been associated with an increased risk of cerebral vascular accident (CVA) and transient ischemic attack (TIA). This has been reported in three studies,[14] which suggested a correlation between TIAs and a reversible effect of cannabis on the cerebrovasculature attributed to transient vasospasm and/or increase in central BP decreasing cerebral flow.[14] Furthermore, it has been suggested that cannabis use may increase the risk of CVA among patients with increased risk of CV disease (CVD) with or without anti-stroke medications, such as anti-platelet medication.[15] It has also been reported that cocaine and/or marijuana use in young adults with an MI, is associated with worse all-cause and CVD mortality.[16]

Marijuana has been reported to have inflammatory effects on the peripheral vascular system. The pathophysiology is extremely similar to thromboangitis obliterans (Buerger's disease), an inflammatory and

thrombotic disease of the small and medium arteries and veins of the hands and feet associated with tobacco use.[17-20] Additionally, cannabis usage has also been associated with claudication, Raynaud's phenomenon, ischemic ulcers, and digital necrosis. Angiography of chronic cannabis users demonstrated atherosclerotic changes ranging from mild atherosclerotic plaques to total occlusion. Some users have even had improvement with marijuana smoking cessation.[17, 21]

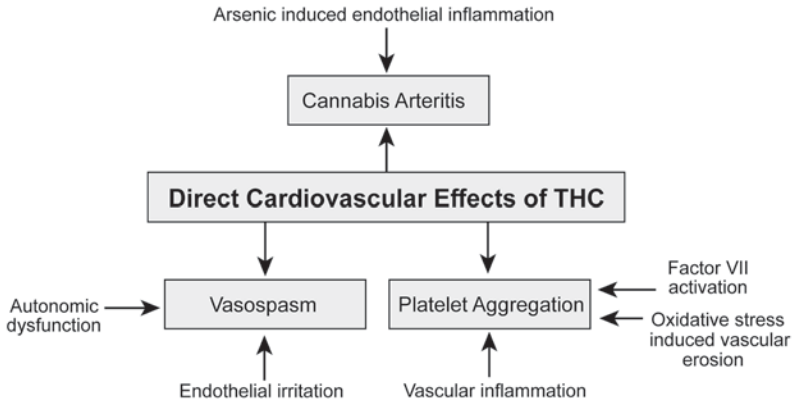


Figure 1. The direct effects of marijuana on the cardiovascular system.

With decades of research and an increase in the amount of marijuana usage among adults, as well as teenagers, the adverse effects of THC on the CVS still remains unclear. In this review, the current state of the literature on marijuana usage and adverse CVD events will be examined along with clarification on possible connection between marijuana and CV pathology.

Marijuana and the Cardiovascular System

There is a growing body of evidence that demonstrates an association between marijuana use and adverse CVD events. The current literature proposes that marijuana adversely affects the CVS through three different possible mechanisms – cannabis-induced arteritis, vasospasms, and platelet aggregation.[22-24]

Cannabis Arteritis

Cannabis arteritis was first described in the 1960s, with over 50 cases documented in the literature since then. Furthermore, numerous studies and case reports describe a thromboangitis obliterans-like disease that affects young adults who smoke marijuana.[25] In 2013, Desbois et al. described the different arterial pathologies associated with cannabis smokers, including CVA, MI, and lower limb arteritis.[26] In these cases, the onset of CVA and MI was usually within one hour of marijuana use. Moreover, compared with thromboangitis obliterans, individuals diagnosed with cannabis arteritis were younger, more often male, and had more frequent unilateral limb involvement.[26] The mechanism of the vasculitis is currently not fully understood, but many reports suggest vasculopathy secondary to an arsenic-containing by-product, which has been associated with endothelial inflammation.[26]

In 2005 and 2007, Combermale and Peyrot et al., respectively, reported cases of vascular inflammation among cannabis users.[18,27] Combermale et al. reported a 38-year old chronic marijuana smoker who presented with dry necrotic lesions on the left big toe.[27] Imaging revealed proximal arteriopathy of the lower limbs. Furthermore, the development of the arteritis paralleled the patient's cannabis use. The necrotic lesions secondary to arterial insufficiency were successfully treated with hyperbaric oxygen therapy.[27] Peyrot et al. reported of a 30-year-old habitual cannabis smoker without any significant medical history, including no vasculopathies, who presented with digital necrosis of the right toe.[18] Arteriography revealed distal segmental arterial lesions that occluded the popliteal artery. After ruling out other causes, the vasculopathy was attributed to cannabis use.[18] Figure 1.

Cannabis-Induced Vasospasms

Reversible arterial vasospasm is considered the most common cause of marijuana-induced vascular events.[22] While, the underlying mechanisms for this are unclear, numerous case reports have associated THC with coronary vasospasm-induced cardiomyopathy.[28-31]

Basnet et al. reported a healthy 17-year-old adolescent who presented to the emergency room complaining of burning chest pain radiating to the jaw that awoke him from sleep.[30] He admitted to marijuana use and denied cocaine use. The Electrocardiogram (ECG) demonstrated ST-segment elevation in the lateral leads followed by a blood troponin of 0.23 U/l (normal, 0.00-0.04 U/l). Echocardiogram revealed a hypokinetic apex. Cardiac magnetic resonance imaging was performed, and it was suggested that symptoms and objective cardiac

findings were secondary to transient myocardial ischemia. This report was one of the first to describe coronary vasospasms in an adolescent likely from marijuana abuse. Another case reported by Gunawardena et al. described a 29-year-old male who presented with acute coronary syndrome following consumption of marijuana. He had dynamic ST-segment elevation in different leads and a markedly elevated troponin.[28] Coronary angiography did not elucidate any occlusive atherosclerotic disease. There was evidence of slow flow in the left anterior descending artery, which improved with intracoronary nitrate therapy. A diagnosis of coronary vasospasm was made, and it was inferred that cannabis consumption was the primary cause. In both reports, coronary angiography did not demonstrate occlusive atherosclerotic disease.

Mendiabal et al. reported that chronic marijuana use may result in autonomic nervous system (ANS) dysfunction, leading to cycles of vasoconstriction and vasodilation independent of skeletal muscle activity.[32] It was suggested that baseline ANS dysfunction coupled with THC-induced irritation of the vascular endothelium could possibly explain the increased risk of vasospasm in chronic marijuana users.[32]

Cannabis-Induced Platelet Aggregation

While cannabis has been shown to be pro-thrombotic, little is known on the mechanism of THC-induced platelet aggregation.[22] In 2004, Deusch et al. demonstrated the presence of CB1 and CB2 receptors on platelet cell membranes.[33] Furthermore, it was also shown that the expression of glycoprotein IIb-IIIa and P-selectin on platelet membranes increases during CB1 activation in a dose-dependent manner.[33] These results suggest that THC may act directly on platelets and may activate the clotting cascade initiating the formation of a thrombus. In fact, there are many published case reports describing young adults with non-atherosclerotic dependent thrombi, most likely secondary to chronic marijuana use.[22, 34, 35] For example, in 2012, Dahdouh et al. published a report of a 20-year-old cannabis user with no CVD history who presented with acute MI.[23] Coronary angiography revealed a large, occlusive thrombus in the left anterior descending artery which was attributed to THC use.[23]

Research has shown that CB1 and CB2 receptors exist on platelet membranes and that high concentrations of cannabinoids can induce non-reversible platelet aggregation.[36] One possible mechanism for platelet aggregation by cannabinoids is an indirect action closely associated with the vascular wall. Once cannabinoids enter the bloodstream, an inhibition of parasympathetic activity possibly induces an inflammatory effect in the arterial wall which through oxidative stress causes endothelial erosion, factor VII activation, which ultimately leads to thrombus formation.[34, 37-40]

Cannabis and Atherosclerosis

Stimulation of the CB1 and CB2 receptors has also been shown to modulate the function of cytoskeletal elements in the vessel wall, which may elicit an inflammatory cascade, resulting in atheroma formation.[41] Because pulmonary and CVS are populated with CB1 and CB2 receptors, marijuana use has been hypothesized to be involved in the progression of atherosclerotic disease.

Ironically, CB1 and CB2 receptors may play antagonistic roles to one another in CV atherogenesis. CB1 has pro-inflammatory effects on macrophages and monocytes and a pro-atherogenic relationship with the endothelium. CB2 receptors demonstrate anti-inflammatory and anti-atherogenic capabilities along with promoting lipid homeostasis. Interestingly, both play a role in decreasing the area of necrosis in ischemia-reperfusion injury to the heart.[42] This antagonistic interaction between the CB1 and CB2 receptor is known as the marijuana paradox-smoking marijuana may decrease the angina threshold and precipitate coronary artery events, but animal models suggest marijuana could modulate atherogenesis in appropriate doses.[42]

Marijuana is Not Just THC

Marijuana contains almost 500 compounds, including 70 cannabinoids which provide the psychoactive effect.[43,44] When a user smokes marijuana, they do not solely ingest THC but rather a host of other chemicals.[45] From the combustion of marijuana, chemicals, such as acetaldehyde, ammonia, benzene, carbon monoxide, hydrogen cyanide, and polycyclic hydrocarbons, are inhaled.[45] For example, Groternhermen et al. found that there are numerous adulterants in marijuana, and these compounds could also contribute to CVD processes.[45] For instance, during the marijuana plant cultivation, farmers may spray chemicals and fertilizers that contain N-nitrosamines compounds that persist for years.[46] Moreover, other chemicals, such as sulfur, copper sulfate, and Ceresan M (a mercury containing compound), are also present on some forms of marijuana.[45] Even arsenic has been found on marijuana,

in the concentration of 2 mg of arsenic per 100 grams of marijuana, which is considered "a medical dose."[47]

Marijuana that is grown "naturally" rarely arrives to the consumer in one step and is generally passed down from person to person because it is sold on the black market.[45] Marijuana that is sold in the black market has been shown to contain a wide variety of insecticides and fungicides containing toxins, such as aldicarb, carbaryl, Diazinon, malathion, maneb, parathion, and zineb.[48] Moreover, drug dealers may adulterate marijuana with other psychotropic substances, such as paraquat, Lysergic acid diethylamide (LSD), or opium, thus raising the perceptive potency but increasing the pathologic side effects.[49] Bell analyzed a sample of hashish, a concentrated form of marijuana, which contained 25% opium and camphor. Lastly, Johnson et al. analyzed over 8,000 different samples of marijuana and found adulterants, which included tobacco, phencyclidine, catnip, heroin, methamphetamine, LSD, peyote, mescaline, belladonna, and numerous other poisons.[50] Also, black market "drug dealers" might also purposely adulterate marijuana to increase the weight of the substance therefore selling less marijuana for the same price.[45]

Man-made and natural formed toxins are not the only impurities that exist on the marijuana plant. Because marijuana is a naturally growing crop, many biologically active organisms also grow on the plant.[45] It is well known and well written that spores of fungi infest cannabis.[45, 51-54] One of the main fungal species that exist on marijuana is the Aspergillus species, more specifically Aspergillus fumigatus.[55] The Aspergillus species is known to produce aflatoxins, which could have serious acute effects on the CVS, including vascular erosion and degradation, disruption of protein synthesis in cardiac myocytes, and mitochondrial disruption in heart tissue.[56, 57] The aflatoxins themselves can survive for years on the marijuana plant, in marijuana cigarettes, and more importantly in the water that is used for smoking marijuana through water pipes ("bongs").[45] These toxins generally do not produce reactions in healthy young subjects, but can produce life threatening reactions in older adults and especially in immunocompromised patients.[58-60]

Fungal spores are not the only organisms that can survive on the marijuana plant; bacteria have also been shown to grow, survive, and reproduce on marijuana.[61] Ungerleider et al. identified contaminants on marijuana cigarettes supplied by the National Institute of Drugs Abuse, which included Klebsiella pneumoniae, Enterobacter cloacae, group D Streptococcus, and some Bacillus species.[61] Moreover, Taylor et al. isolated Salmonella muenchen[62] and Kurup et al. isolated some Thermoactinomyces species.[63]

Medical marijuana obtained from dispensaries are similar in form to recreational marijuana which is often purchased by the patients undergoing chemotherapy to control nausea/vomiting, to control pain or neuropathy or to stimulate appetite. Thompson et al. obtained twenty cannabis samples from different dispensaries in northern California for microbiome analysis.[64] Upon analysis, many of the samples consisted of multiple pathogens that would probably be attributed to hospital-acquired infection in addition to gram-negative bacilli and fungal pathogens which can pose grave risk to immunocompromised patients.[64]

These publications illustrate that when a user smokes marijuana, numerous other chemicals, poisons, and toxin producing fungi and bacteria enter the bloodstream along with THC. All of these contaminants in marijuana could also play a role in the development of life threatening CVD episodes.

Concomitant Drug Use and Lifestyle

Marijuana has been known as a "gateway drug" for decades, and its regular use in adolescents is clearly associated with an increased risk for abuse and dependence on other illicit drugs.[65, 66] Cannabis use might be a marker for illicit behavior which can result in the advancement to "harder" illicit drugs once available to the user.[66, 67] Patton et al, reported that cannabis smokers who used weekly were eight times more likely to use tobacco and progress to nicotine dependence.[68]

In 2017, Jin et al. performed a follow-up study on 712 Danish teenagers aged between 15-19 who smoked marijuana, and utilized a questionnaire to study changes in body mass index (BMI), lifestyle, socioeconomic status, alcohol, and tobacco use among other parameters.[69] This publication reported that cannabis use was associated with significant increases in cigarette smoking and alcohol intake, and inversely associated with physical activity levels.[69] However, there was no association between cannabis use and changes in BMI or long-term weight change into midlife. Some limitations to this study, however were that the data was gathered via questionnaire and adolescents might not have been fully honest with weight history or dietary intake.

The result of this study is similar to other publications investigating the direct correlation between marijuana use

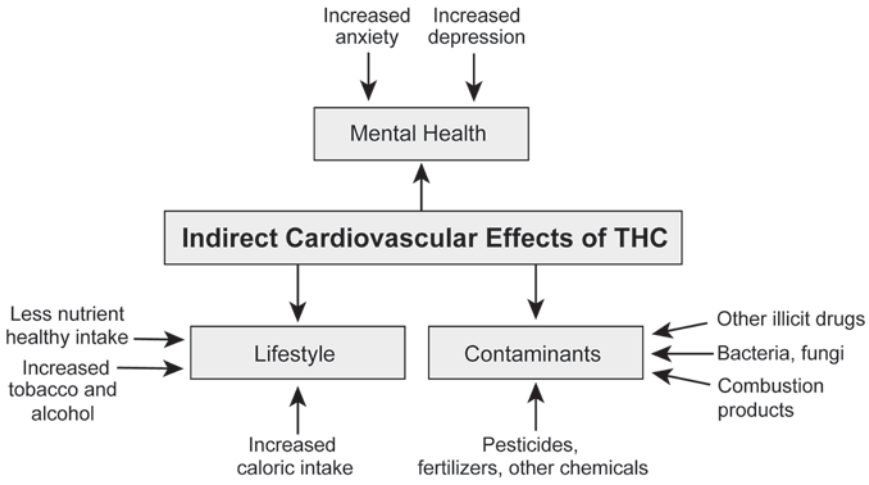


Figure 2. The indirect effects of marijuana on the cardiovascular system

and other illicit drug use. In 2000, Gledhill-Hoyt et al. released a study that reported that college students who used marijuana within the past 30 days also had increased rates of tobacco usage, binge alcohol drinking, and other illicit drugs, except for LSD.[70] Moreover, they reported that out of the students who tried marijuana for the first time, 34% started to use marijuana regularly along with engaging in increased binge drinking behavior.[70]

Smit et al. examined dietary intakes and nutritional status of marijuana users and non-current marijuana uses in US persons aged 20-59 years of age using date from the third National Health and Nutrition Examination Studies.[71] They found that marijuana users had higher intake of energy and nutrients compared to their non-current marijuana counterparts, although there was no significant change in BMI. Also, the authors found that current marijuana users smoked more cigarettes and consumed higher amount of sodas and alcohol, when compared to their counter cohort. It was also reported that marijuana smokers had less folate and carotenoids in their blood possibly secondary to increased oxidation from both marijuana and tobacco smoke inhalation.

From these studies, it seems reasonable to suggest that marijuana use does lead to additional drug use, especially tobacco and alcohol, the latter being a known cardiotoxin. Moreover, marijuana users have a lifestyle that is low in healthy nutritional intake and exercise and high in fat and non-nutritional calories from "junk food" and beer, all of which can have deleterious effects on the CVS.

Marijuana and Mental Health

As mentioned above, the increased usage of marijuana can have toxic effects on the CVS directly, but similar to the physiologic effects of marijuana, very little is known about the indirect cardiotoxic nature of marijuana through psychological disease.[72] The acute effects of marijuana can exacerbate underlying psychosis and psychotic disorders [73, 74] and chronic use can cause anxiety, depression, and decreased motivation.[75] For example, a survey by Thomas et al. reported that cannabis use and anxiety were directly associated, and females were more likely to have an increased level of baseline anxiety after THC administration.[76] Moreover, questionnaires have also shown that chronic users have increased depressive episodes in both male and female adolescents and adults without concurrent usage of other illicit drugs.[77, 78] The current state of the literature does not propose a mechanism that connects marijuana administration and anxiety or depression.[73, 79]

Chronic anxiety, panic disorder, and phobic anxiety have been linked to increased CVD morbidity.[80, 81] In 1994, Kawachi et al. released two studies which reported that increased anxiety, whether phobic or acute, have direct association with coronary heart disease.[80,81] Chronic use of marijuana can cause chronic anxiety and this over time could be an indirect contributor towards CVD mortality.

Numerous studies have also shown various physiologic mechanisms linking depression and CVD.[82] One possible mechanism uses stress as a possible factor. Patients with depression are generally under a constant state of stress with chronic upregulation of the hypothalamic-pituitary-adrenal (HPA) system and the sympathetic nervous system, leading to excess adrenergic and serotonergic activity.[83, 84] Chronic upregulation of the HPA and sympathetic nervous systems cause abnormal physiologic responses, such as unregulated platelet function, autonomic tone, inflammation, and endothelial function.[82] As mentioned previously, abnormal platelet function, arrhythmia, and endothelial dysfunction and inflammation are all factors that connect marijuana usage with increased CVD episodes. Figure 2.

Conclusion

Marijuana is the most common illicit substance used in the US and the rate of usage is only increasing. Most of the research into THC is mainly focused on combating the side effects of anti-cancer chemotherapeutics. However, research is starting to focus on the systemic and CVD adverse effects induced by THC. This brief review has organized three main pathologies associated with marijuana usage and the CVS – peripheral arteritis, coronary vasospasms, and platelet aggregation; however, many of the acute and, more so, long-term potentially toxic effects of marijuana and THC still remain unknown. As more and more states legalize the use of marijuana for recreation and medicinal use, more research will be needed to explore the safety and therapeutic profile of THC. Since fewer and fewer people are users of inhaled combustible marijuana smoke, and almost all studied risks of cannabis are based on users of such inhaled combustible smoke, the risks related to the cannabis use also need to be updated.[85] In addition, increased collaboration among cardiologists, drug users, and addiction experts to further understand the potential health consequences of increased cannabis use is very important.[85]

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Disclosure

None reported.

Editor's Note

See "Marijuana is More Dangerous Than You Think" on page 88 of this issue. **MM**

Malignant Hyperthermia

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Malignant hyperthermia is a life threatening pharmacogenetic disorder of skeletal muscles causing hypermetabolic response to volatile anesthetic agents and depolarizing muscle relaxants.



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Abstract

Malignant Hyperthermia (MH) is a life-threatening pharmacogenetic disorder which results from exposure to volatile anesthetic agents and depolarizing muscle relaxants. It manifests as a hypermetabolic response resulting in tachycardia, tachypnea, hyperthermia, hypercapnia, acidosis, muscle rigidity and rhabdomyolysis. An increase in the end-tidal carbon dioxide is one of the earliest diagnostic signs. Dantrolene sodium is effective in the management of MH, and should be available whenever general anesthesia is administered. This review also aims to highlight the genetics and pathology of MH, along with its association with various inherited myopathy syndromes like central core disease, multi-mini core disease, Native-American myopathy, and King-Denborough syndrome.

Introduction

Malignant hyperthermia (MH) is a rare life-threatening pharmacogenetic disorder of skeletal muscles that presents as an exaggerated hypermetabolic response to volatile anesthetic agents and depolarizing muscle relaxants. The hypermetabolic response includes an uncontrolled increase of oxidative metabolism in skeletal muscles, that saturates body's capacity to supply oxygen and regulate body temperature thus leading to a state of circulatory shock. Numerous factors are known to trigger MH. Various factors associated with the development of MH are age, environmental temperature, type of anesthetic agent, genetic makeup and family history. Inhalation anesthetics such as halothane, sevoflurane, desflurane, isoflurane are known triggers for these episodes. Depolarizing muscle relaxants such as succinylcholine are the most common triggering factor for MH. The underlying defect comprises of mutation in ryanodine receptor *RYR1*, which causes enormous increase in myoplasmic calcium leading to exaggerated muscle contraction. A comprehensive investigation protocol should be followed in all patients to ensure early diagnosis and prompt treatment and to avoid life threatening complications. Genetic testing should be recommended for affected individuals and family members, to address the susceptibility to this grave condition.

Genetics

MH is inherited as an autosomal dominant disorder with variable penetrance. The prevalence of genetic abnormalities associated with MH susceptibility is 1 in 400 individuals.[1] MH is most commonly associated with mutation of the *RYR1* gene (Ryanodine receptor-1) or less common loci *CACNA1S* gene (calcium voltage-gated channel subunit alpha 1 S).[2] The mutations affect the long arm of chromosome 19 (19q13.1)

involving the ryanodine receptors.[3] More than 40 different mutations of *RYR1* are known to be associated with malignant hyperthermia. All these mutations are clustered in three domains within the protein designated as MH1-3. MH1 and MH2 are located at the N-terminus of protein which interacts with L type calcium channel. MH3 is located at transmembrane and form the C-terminus of protein. MH is also associated with the mutations in the *CACNA1 S* gene which encodes the alpha-one subunit of the dihydropyridine receptors (DHPR) of calcium channels.[4] Various inherited myopathy syndromes like central core disease, multi-minicore disease, central nuclear myopathy and King-Denborough syndrome can predispose to episodes of MH. [5,6] The susceptibility of MH is also associated with variants of *STAC3* gene (SH3 and cysteine-rich domain 3) which is seen more commonly in Native American myopathy of North Carolina. [7]

Epidemiology

The incidence of MH episodes with the use of succinylcholine and volatile anesthetic agents ranges between 1:10,000 and 1:250,000.[8,9] Patients with MH susceptibility do not show any phenotypic changes without exposure to the anesthesia or triggering agent hence it is difficult to diagnose the susceptibility without exposure to culprit agent. Even though MH crisis can develop at first exposure to triggering agent, however, majority patients require a minimum of three exposures to result in a MH crisis. MH episodes are reported in all ethnic groups and occur more often in males than females with a ratio of 2:1.[10,11] The highest incidence is observed in young people, with a mean age of all patients being 18.3 years.[12]

Clinical Presentation

The episodes of MH can occur during anesthesia or in the early postoperative period.[13] The earliest signs include tachycardia, a rise in end-expiratory carbon dioxide concentration despite increase in minute ventilation, accompanied by muscle rigidity leading to rhabdomyolysis, acidosis, and hyperkalemia. The signs are predominantly seen following succinylcholine administration, a potent depolarizing anesthetic agent. Even though a rise in end-tidal carbon dioxide (ETCO) is a sensitive early sign of MH but with a decline in the use of succinylcholine in recent years, a more gradual rise in ETCO is generally seen.[14,15]

Rise in the body temperature is the characteristic sign of MH. Marked hyperthermia can be seen, with an increase in core temperature of 1–2 °C every five minutes. Severe hyperthermia with core temperature higher than 44 °C can lead to a significant increase in oxygen consumption, carbon dioxide production, vital organ dysfunction, and disseminated intravascular coagulation (DIC).[16] Uncontrolled hypermetabolism results in respiratory and metabolic acidosis. If left untreated, rhabdomyolysis can occur resulting in serious consequences of hyperkalemia, myoglobinuria eventually leading to acute renal failure. MH may also lead to congestive heart failure, bowel ischemia, and compartment syndrome of the limbs secondary to profound muscle swelling, thereby increasing the risk of mortality with MH. [6]

Pathogenesis

Malignant hyperthermia is a pharmacogenetic disorder resulting in a hypermetabolic state.[17]The pathophysiology behind MH is related to an uncontrolled release of intracellular calcium ions (Ca^{2+}) from skeletal muscle sarcoplasmic reticulum.[18] This uncontrolled release of calcium causes a rise in myoplasmic calcium which results in myofibrillary contractions and sustained muscle contractions. These contractions eventually result in rapid depletion of Adenosine Triphosphate (ATP) which further results in muscle cell damage and rhabdomyolysis. The depletion in the stores of the energy molecules, ATP, also results in excessive oxygen consumption, increase in glucose metabolism, carbon dioxide production and excessive heat production. The most common cause of impaired calcium regulation in MH is due to the presence of defective *RYR1* gene (ryanodine receptors) in the sarcoplasmic reticulum. Other major proteins responsible for the calcium dysregulation include DHPR (dihydropyridine receptors), FK506, and triadin.

The other known gene associated with MH is *CACNA1S*, which encodes for the α subunit of L-type voltage-gated calcium channel. Mutations in this protein affect the residue, R1086, which is located in the large intracellular loop connecting domains 3 and 4 and inhibits the *RYR1* activity. As these channels activate *RYR1*, the mutation results in a drastic increase of intracellular Ca^{2+} thus causing muscle excitability.[4]

Conditions Associated with Malignant Hyperthermia

In Table 1 we discuss in brief about the various inherited myopathy syndromes susceptible to MH. *RYR1* receptor mutations may predispose these conditions to develop MH, therefore depolarizing muscle relaxants and volatile anesthetics must be avoided.

Diagnostic Criteria

The Clinical Grading Scale for Malignant Hyperthermia

A grading scale was developed by Larach, to clinically diagnose malignant hyperthermia.[19] The different grading

Table 1. Conditions associated with Malignant Hyperthermia

CONDITION	PRESENTATION	INHERITANCE
Central core myopathy	Characterized by hypotonia in infancy, delay in motor development and lower limb muscle weakness.	Autosomal Dominant
Multi-mini core myopathy	Characterized by hypotonia, delay in motor development, muscle weakness mainly in lower limbs, and musculoskeletal abnormalities.	Autosomal Recessive
King-Denborough syndrome	Characterized by hypotonia at birth, mild proximal muscle weakness, delay in motor development, joint hyperextensibility and dysmorphic facial features including ptosis, low-set ears and high arched palate, micrognathia, malar hypoplasia, hypertelorism, along with palmar simian line, pectus excavatum, winging of scapulae, lumbar lordosis and thoracic scoliosis.	Autosomal Recessive
Native American myopathy	Most commonly seen in Lumbee Indians of North Carolina. Characterized by congenital weakness, arthrogryposis, cleft palate, short stature, talipes deformities and kyphoscoliosis. *STAC3* mutations predispose them to develop MH provoked by anesthesia, therefore depolarizing muscle relaxants and volatile anesthetics must be avoided.	Autosomal Recessive

components of scale include rigidity, muscle breakdown/rhabdomyolysis, respiratory acidosis, temperature increase and cardiac involvement. Each of the clinical manifestations is differentially weighted in scale and associated MH rank and MH likelihood are then calculated. The likelihood and rank, range from 'almost never' to 'almost certain.' Table 2.

Table 3 highlights the total criteria points corresponding to Malignant hyperthermia likelihood and MH Rank.[19] The total points based on criteria explained in Table 2, range from 0-108 with '0' indicating MH likelihood to 'almost never', range 3-9 points indicates MH likelihood of 'unlikely', 10-19 points indicated MH likelihood of 'somewhat less likely', 20-34 points indicate MH likelihood of 'somewhat greater than likely', 35-49 points indicate MH likelihood of 'very likely' and 50-108 points indicate an MH likelihood of 'almost certain.'

Muscle Susceptibility Testing

The gold standard diagnostic test for malignant hyperthermia is an In-Vivo Contracture Test (IVCT) also known as Caffeine-Halothane Contracture Test (CHCT). Two of the widely used form of the test are IVCT developed by European Malignant Hyperthermia Group (EMHG) and CHCT by North American Malignant Hyperthermia Group (NAMHG).[20,21] Both tests utilize a muscle biopsy and subsequent observation for contraction in muscle after treating it with caffeine and halothane. According to the EMHG protocol, an individual is considered positive for susceptibility when both caffeine and halothane test are positive (MHS-Malignant Hyperthermia Susceptibility), and unsusceptible when both tests are negative. If one of the tests is positive, individuals are diagnosed as either MHS(h) or MHS(c) for halothane or caffeine respectively. This inference is same for NAMHG protocol; however, the key difference is use of different concentration and mode of testing agents. The EMHG protocol has a sensitivity of 99% and specificity of 94% while the NAHMG protocol carries a specificity of 78% and sensitivity of 97%.[22,23]

A minimal invasive test, using intramuscular halothane, 5%, and 6%volume can be a suitable alternative to invasive techniques. Schuster et al., hypothesized the concept of injecting intramuscular halothane (MH trigger) and inducing a hypermetabolic response indicated by the rise in Pco_2 (partial pressure of carbon dioxide) following the injection. A significant rise in Pco_2 indicate MH susceptibility (MHS).[24] The test has specificity of 75%, sensitivity of 100%, positive predictive value of 80% and a negative predictive value of 100%.[25] Intramuscular caffeine injection is also believed to reproduce similar results by increasing the local Pco_2 concentration in individuals with susceptibility to MH.[26] Another minimally invasive diagnostic test includes evaluation of ATP depletion in MH by nuclear magnetic resonance spectroscopy.[27]

Genetic testing can also be used to assess susceptibility for malignant hyperthermia. There are more than 40 different variants of *RYR1* genes associated with central core disease.[28,29,30] These variants can cause central core disease (CCD), Malignant hyperthermia (MH) or MH with variable penetrance CCD. All individuals with these variants should be considered as MH susceptible, while they may or may not have CCD. The diagnosis of these genomic variants can be carried out by parallel sequencing or next generation sequencing (NGS), which is considered as a rapid, cost effect and accurate approach as compared to traditional

Table 2. Clinical grading scale for malignant hyperthermia

CLINICAL PROCESS	INDICATOR	Points
RIGIDITY	Generalized muscular rigidity without shivering due to hyperthermia during or immediately following emergence from inhalational anesthesia.	15 points
	Spasm of the masseter muscles shortly after succinylcholine administration.	15 points
MUSCLE BREAKDOWN	CK >20,000 IU after anesthesia with succinylcholine.	15 points
	CK >10,000 IU after anesthesia without succinylcholine.	15 points
	Cola-colored urine in perioperative period.	10 points
	Urine myoglobin >60 mcg/L	5 points
	Serum myoglobin >170 mcg/L	5 points
	Serum K >6 meq/L without renal failure.	3 points
RESPIRATORY ACIDOSIS	Controlled ventilation PETCO2 >55	15 points
	Controlled ventilation PaCO2 >60	15 points
	Spontaneous ventilation PETCO2 >60	15 points
	Spontaneous ventilation PaCO2 >65	15 points
	Inappropriate hypercarbia (in anesthesiologist judgement)	15 points
	Inappropriate tachypnea (in anesthesiologist judgement)	10 points
TEMPERATURE INCREASE	Abnormal rapid rise in temperature (in anesthesiologist judgement)	15 points
	Inappropriate perioperative rise in temperature>38.8°C (in anesthesiologist judgement)	10 points
CARDIAC INVOLVEMENT	Inappropriate sinus tachycardia (in anesthesiologist judgement)	3 points
	Ventricular tachycardia or ventricular fibrillation (in anesthesiologist judgement)	3 points
OTHERS	Arterial pH >7.25	10 points
	Rapid reversal of MH signs with dantrolene	5 points
	Positive family history along with positive personal anesthetic history without elevated resting serum CK levels	10 points
	Elevated resting serum CK in patient with positive family history	10 points

DNA sequencing technique.[31] A number of *RYR1* and *CACNA1S* variants have been identified using NGS.[32,33]

Management

Dantrolene was introduced in 1979, and since then is the only drug effective in the management of malignant hyperthermia. It acts by inhibiting the DHPR (dihydropyridine) on ryanodine receptor, thereby inhibiting the release of intracellular calcium.[34,35] The two commonly used preparations of dantrolene in MH are Dantrium®, commonly available in a dose of 20 mg and Ryanodex®, a newly available formulation, is available in 250 mg ampule form. If the symptoms do not resolve with the dose of dantrolene of 10mg/kg, other possible differentials for MH like sepsis, intracranial hemorrhage, baclofen withdrawal and neuroleptic malignant syndrome should be ruled out.[36]

Table 3. Correlation between total criteria point and MH rank & MH likelihood

TOTAL POINTS	MH RANK	MH LIKELIHOOD
0 points	1	MH Likelihood is **almost never**
3-9 points	2	MH Likelihood is **unlikely**
10-19 points	3	MH Likelihood is **somewhat less than likely**
20-34 points	4	MH Likelihood is **somewhat greater than likely**
35-49 points	5	MH Likelihood is **very likely**
50-108 points	6	MH Likelihood is **almost certain**

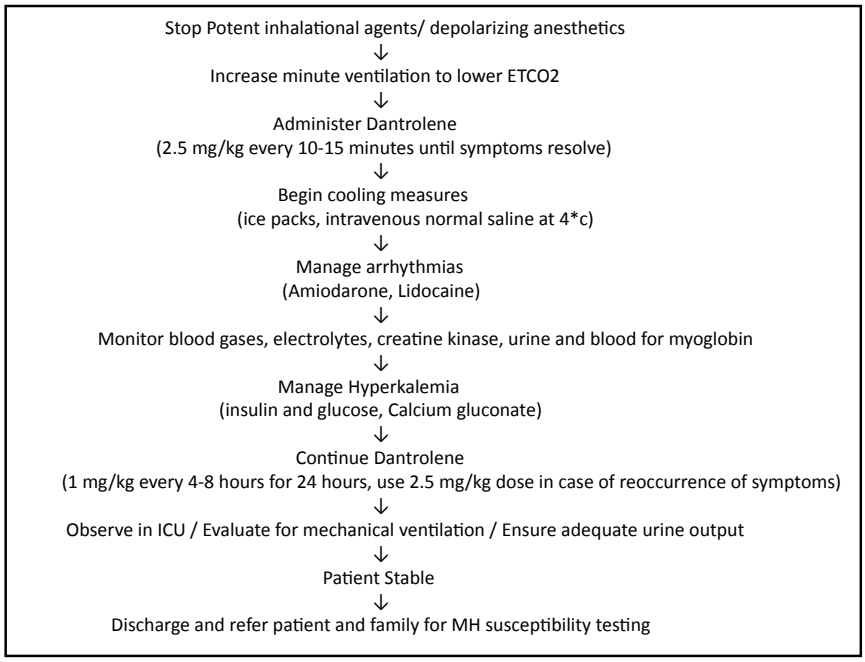


Figure 1. Algorithm depicting stepwise management of malignant hyperthermia

It is crucial to monitor the patients for the first 48-72 hours after dantrolene administration for reoccurrence of symptoms or development of side effects such as transient muscle weakness, phlebitis, gastrointestinal symptoms and respiratory compromise.[37] As rhabdomyolysis is frequently seen in such patients, CK (creatinine kinase) should be checked regularly in ICU (intensive care unit).

Dantrolene can also effectively control hyperthermia from other conditions such as neuroleptic malignant syndrome, MDMA (3,4-Methylenedioxymethamphetamine) toxicity and hyperthermia associated with new onset of juvenile diabetes in the adolescent population. [38,39]

A structured approach should be followed while managing patients with malignant hyperthermia in ICU settings. The stepwise management protocol is as follows in Figure 1.

Conclusion

Malignant hyperthermia is a life threatening pharmacogenetic disorder of skeletal muscles causing hypermetabolic response to volatile anesthetic agents and depolarizing muscle relaxants. Although the mortality in malignant hyperthermia has been drastically reduced from 80% to 1.4% in last few decades with the introduction of dantrolene, it still remains a significant risk factor for susceptible individuals undergoing general anesthesia with volatile agents.[40,41] Strict vigilance should be maintained while administering the triggering anesthetic agents. A structured management protocol should be followed aggressively, in all patients experiencing symptoms corresponding to malignant hyperthermia, to ensure early diagnosis and prompt treatment and to prevent life threating complications from the disease course. Malignant Hyperthermia Association of United States (MHAUS) provides effective information updates, management protocols and detailed task cards on MH.[42] Genetic testing with DNA splicing or contraction test should be recommended to identify the MH susceptibility and prevent future attacks.

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Disclosure

None reported.

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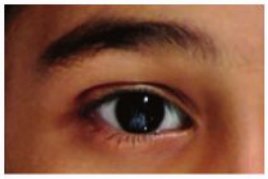
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