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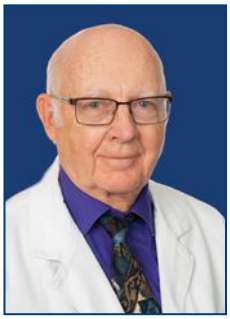
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Through personal experience, I can understand why poor hearing can contribute to isolation and cognitive decline.





"*What are you boys doing?"* asked my puzzled mother. I joyfully answered: "*We're making our ears ring by shooting off cap pistols next to them.*" In a classic 'mom-ism' she replied: "*You boys are going to be deaf some day and you'll be sorry you did this.*"

John C. Hagan III, MD, is a retired ophthalmologist, and editor of *Missouri Medicine* since 2000.

Like most mom-isms, she was so right. At age eight, as with many boys, we were clueless. In my defense, this was in the early 1950s and the need for hearing protection and avoidance of extremely loud sounds was virtually unknown. Thus, for decades I hunted rabbits and squirrels with rifles, and quail, dove, and ducks with super-loud 12 and 16-gauge shotguns. My unprotected hearing was subjected to fire-crackers, lawnmowers, chain-saws and, of course, wildly amped-up classic rock-n-roll. I grew up in a noisy world.

At age 32, as mom said, I paid for my auditory dereliction. While an ophthalmology resident at Emory University, my left ear suddenly started ringing; but unlike in my childhood, it never stopped. A work-up at the ENT department diagnosed tinnitus due to noise induced high frequency hearing loss. Like many right-handed shooters, the hearing loss was

more severe in my left ear; the closest ear to the muzzle of thousands of firearm discharges. It took several anxious years for me to make my peace with left ear tinnitus and learn to ignore the constant ringing.



All our five senses: sight, sound, smell, taste, and touch are precious. The thought of losing any of them is deeply distressing. However, in a variation of Sophie's Choice, upon polling the loss of sight is the most feared. As an ophthalmologist I understand that completely. Right after that though is loss of hearing. Listen to what I have to say about that.

I had a terrifying experience of unilateral complete hearing loss May 9, 2013. I woke up deaf in my better right ear.[1] An emergency ENT work-up disclosed a diagnosis of idiopathic sensorineural hearing loss. This was likely iatrogenic from severe beta blocker nocturnal hypotension. On an urgent basis, I was seen by noted neurotologist Bradley S. Thedinger, MD. He skillfully performed two intra-tympanic steroid injections. Over the next month about 85% of my previously impaired hearing returned. Distressingly, I had tinnitus in both ears.

During my aural illness, my sense of isolation was profound, driving was stressful. I had to re-arrange my ophthalmology lanes to put my remaining hearing ear towards the patient. My assistants told my patients to speak loud and slow. I could hear TV only at such high levels that my wife fled the room. To once again enjoy her company, I began to use closed captions on the TV. How terrible must it be for people with significant hearing impairment.



Increasingly over the next years my moniker could have been, Dr. John "What Did You Say" Hagan. With any significant background noise, like a busy restaurant, I was out of conversations and just nodded my head and said: "yeah, right." Periodically it was recommended I get hearing aids, but I thought "Hey, they're for old people." Then I did the math and realized I *am* an old person. At that point I moved ahead with hearing aids. I was directed by a knowledgeable friend, born hearing impaired, to a highly skilled audiologist and fitted with hearing aids. They were about $4,000 out of pocket for the pair. They have made a world of difference in the quality of my life. My asking: "What did you say?" has dropped probably 95%. I never like to be without them; the first thing I do each morning is put them on. I can understand why poor hearing can contribute to isolation and cognitive decline.

Okay, if you have made it this far, you have given me a fair hearing. (I have been torturing puns for many years.) You must, for your benefit and those of your patients, read the Perspective by Joshua M. Sappington, MD, on "Hearing Loss: The Silent Pandemic That is Finally Being Heard" (see page 350). The importance of personal sound protection is now documented and known, but frequently ignored. A healthy life-style can also reduce the risk of hearing loss as heavy drinking, use of tobacco and cannabis, and many modifiable diseases are associated with hearing loss. The extent of population hearing loss outlined by Dr. Sappington is disturbing as is the relationship of impaired hearing to psychological and neuro-cognitive problems.

Protect and cherish your hearing, make sure your patients get the message, and refer patients that appear to not hear normally for an ENT work-up. Many have thanked me for my concern as they have also found hearing aids of great value. At least four or five of the hard hearing patients I referred were found to have acoustic neuromas. Take action and help our patients live in the 'hear and now.'

Reference

1. Hagan, JC3. 'What I'm Hearing: The Sound and the Fury of Obama-Care (ACA) Implementation'. *Missouri Medicine* 2013;110(4):272-273. **MM**

The Harm from Private Equity's Takeover of Medical Practices and Hospitals

by Andrew Schlafly, JD

Private equity intrusion into medicine is harmful to physicians and their patients.



Introduction

An increasingly harmful trend is the invasion by private equity firms to buy up medical practices, hospitals, nursing homes, and every other aspect of healthcare. By the beginning of 2024, private equity owned at least 386 hospitals, or roughly 30% of all for-profit hospitals in the United States. Thousands of medical practices involving many tens of thousands of physicians have likewise been acquired by private equity in recent years.

The result is more debt, more bankruptcies, higher prices, and less quality care. In 2023, more than 20% of the healthcare companies that filed for bankruptcy were owned by private equity firms as short-term investments. Indeed, nearly all the healthcare entities in the US that are rated with a high risk of default are those that have been acquired by private equity, according to the nonprofit Private Equity Stakeholder Project (PESP). The "aggressive debt-funded growth strategies" of private equities are the cause, explained the PESP healthcare director, Eileen O'Grady.

The bankruptcies are not because private equity firms are running out of money. Just the opposite. Private equity firms are well-heeled with abundant assets, totaling $8.2 trillion (not just billion) in worldwide. Their largesse rapidly increases in part due to tax loopholes for their benefit. As a financial sector that did not even exist 40 years ago, private equity is growing so fast that it has more than doubled in size in just the last five years.

Yet physicians should be forewarned about the immense harm that occurs when a private equity firm purchases a medical practice or hospital. As explained here, private equity typically acquires healthcare entities to load them with debt, while distributing



Andrew Schlafly, JD,[1] is General Counsel of the Association of American Physicians & Surgeons. This is Part one of two articles.

the funds received from the loans back to investors as dividends. This is known as dividend recapitalization, and it leaves the medical practice, hospital, or other healthcare entity with a weaker balance sheet and greater pressure to cut costs and increase revenue. The result is lower quality or an outright denial of medical care, a shortage of equipment, a firing of employees, and in an increase in prices. Patients and physicians lose, at the expense of short-term private equity profits. In many cases, the ultimate outcome is closure or bankruptcy, leaving patients and employees stranded.

Understanding Private Equity Wealth Extraction

Before a physician sells his practice to private equity or becomes an employee of a hospital so owned, it is important to understand what such ownership means. Private equity wealth extraction is how money managers acquire medical entities and then strip their assets, increase their prices, sometimes sell their real estate for a non-medical use or even declare bankruptcy.

An example from 2019 vividly illustrates the harm. Then a private equity firm acquired Hahnemann in Center City Philadelphia, which was a 171-year-old hospital that served primarily poor minority patients. The new owner reportedly did not improve the hospital for 18 months, and then closed it in order to sell its real estate to build luxury apartments. "This seems to have been [the] plan all along, to buy this place, let it fail, and shut it down," observed the 17-year employee and registered nurse Lauren McHugh while physicians also protested. While that approach may be good for private equity profits, it reduces the availability of medical care in a community to the detriment of patients, physicians and other medical practitioners.

Here in Missouri, the acquisition of hospitals has led to a curtailment of services and then, in several cases, a complete closure of the hospitals. "What we've seen over the last 12 to 15 years is a rash of hospital closures, especially rural hospitals, and it is concerning, just because of that lack of emergency services that could be available, and then the length of time it would take to get to another emergency room," observed Melissa Van Dyne, Executive Director of the Missouri Rural Health Association.

Private equity firms are not motivated by providing quality medical care to a community, but rather are squeezing their targets for profits. As part of an acquisition or soon afterwards, private equity firms typically often load the acquired entity with new debt, while using those loans to enrich their investors, or sell off the real estate that the acquired entity may own as the Hahnemann hospital in Philadelphia did. Either way, the acquired entity suddenly has a much weaker balance sheet that makes it a difficult struggle to survive.

For example, in 2021 a private equity firm imposed new debt onto Cano Health, which had operated many primary care offices and other healthcare entities, mostly in Florida. This new debt helped fund a $100 million dividend to shareholders of the private equity firm. Inevitably Cano Health ran out of cash as it tried to service debt that grew to nearly $1 billion by 2024, and it ultimately filed for bankruptcy in what was described as a "spectacular collapse" by Ari Gottlieb, who monitors healthcare startups.

Whenever one of these many bankruptcies occur, court approval is needed before paying back wages, satisfying other obligations and, at the bottom of the list, providing future medical care to patients. This summer Cano Health emerged from bankruptcy under a court-supervised restructuring process.

While many of entities acquired by private equity spiral downward into bankruptcy, as Cano Health did, others survive only by cutting corners on equipment, support staff, or other expenses. The private equity wealth extraction has the effect of transferring assets used for medical care to investor profits, leaving behind a medical practice or hospital less able to provide medical care to patients.

Many, unfortunately, are misled to have an expectation that private equity firms, because they are flush with trillions of dollars in assets, will use their assets for quality medical care of patients. But exactly the opposite occurs. If there is a bankruptcy or closure, then this becomes an attractive tax write-off for the private equity firm such that it can offset its paper loss against unrelated business income. The private equity firm that previously stripped away

the assets earlier comes out ahead overall with tax write-offs from bankruptcies at the end. In essence, the acquired healthcare entity becomes a piggy bank and subsequently a tax shelter for the private equity firm, without any viable long-term future. The victims are patients and physicians.

Economists have the concept called "moral hazard" for when there is a lack of an incentive for a company to protect against harmful risks, such as allowing damage to occur in order to collect on a more lucrative insurance policy. Moral hazards abound when private equity invades healthcare. In the legal profession, there are strict rules against ownership of a law firm by anyone who is not himself a lawyer. Traditionally there have also been state laws against the corporate practice of medicine, but these laws are rarely, if ever, enforced. Physicians, as owners of medical practices, have an inherent motivation to maintain supplies, keep an adequate staff, not replace physicians will less-skilled practitioners, and not leave patients stranded. But private equity firms have no such motivation, and feel no such ethical duty.

The notorious "carried interest" tax loophole allows managers of private equity firms to pay merely the capital gains tax on their compensation rather than the much higher income tax rate that everyone else must pay on their income. The windfall in lower taxes for private equity managers is roughly 17% in after-tax dollars on their bloated compensation. For more than a decade, elected officials of both political parties have tried to close this loophole, but the revolving door between the US Senate and private equity firms has blocked reform. Private equity assets have increased rapidly due in part to this loophole, while has the effect of shifting tax burdens to others.

When entities acquired by private equity do not go bankrupt, the private equity owners sharply increases prices to patients, demand more aggressive coding on insurance claims, and replace physicians with less-skilled alternatives. These changes are necessitated by the new debt load imposed as part of the leverage buyouts, and by the high return on investments demanded by private equity. Medical ethics is sacrificed due to this process.

Medical Practices

In 1988, physicians owned 72.1% of medical practices, which gave them control over their work and the flexibility to see patients who were self-pay outside of insurance. Physicians who owned their practices could also generously provide charity care whenever they had time to do so. But the invasion of medicine by private equity firms, and other factors, have transformed most physicians into employees. By 2018 more physicians were employees (47.4%) rather than self-employed owners of their practices (45.9%). As employees, physicians are bound by the rules of their employers, which are increasingly controlled by private equity money managers today.

Between 2013 and 2016, private equity firms acquired 355 physician practices, some involving hundreds of physicians apiece. Since then, that number has mushroomed further. In the following four years, private equity acquired another 578 physician practices, again typically large practices employing many physicians.

There is a common pattern after private equity acquires a practice. First, the new money managers impose steep cuts in the staff, and substitute less expensive nurse practitioners for physicians. Physicians are disappearing from emergency rooms that are owned by private equity firms. Second, the Wall Street types pressure physicians to provide additional, perhaps unnecessary, medical care while also coding more aggressively with insurance in order to jack up the revenue. This pressure makes ethical physicians feel very uncomfortable.

Physicians are often attracted to these sales of their practices in order to obtain some immediate cash, and be partly relieved of suffocating paperwork duties that plagued their practices while independent. But too often the result is the equivalent of jumping out of a frying pan and into a fire.

The cash enticement can be very appealing to a physician. Private equity typically pays 15 times

DISTURBING TRENDS IN MEDICINE



Changes in Hospital Adverse Events and Patient Outcomes Associated with Private Equity Acquisition

CONCLUSION

Private equity acquisition was associated with increased hospital-acquired adverse events, including falls and central line–associated bloodstream infections, along with a larger but less statistically precise increase in surgical site infections. Shifts in patient mix toward younger and fewer dually eligible beneficiaries admitted and increased transfers to other hospitals may explain the small decrease in in-hospital mortality at private equity hospitals relative to the control hospitals, which was no longer evident 30 days after discharge. These findings heighten concerns about the implications of private equity on health care delivery.[1]

1. Sneha Kannan, MD, Joseph Dov Bruch, PhD, Zirui Song, MD, PhD JAMA. 2023;330(24):2365-2375. doi:10.1001/jama.2023.23147

the physician's annual income to acquire it entirely, or a smaller proportional amount to acquire as little as 30% of it. That purchase price may then be taxed at the lower capital gains rate, leaving the physician with a handsome payday and an opportunity to retire early.

But beware of onerous strings attached, and unwelcomed changes to the practice when the physician does not retire. One study showed that private equity increases prices 20% for insurance claims compared with physicians who are independent. The result could be a reduced patient flow, and the purchase price may have been contingent on not losing patients.

Physicians who want to continue to work are often very unhappy about the conditions under which they must practice, compared with the autonomy they enjoyed when they owned their practice. Many soon long for a return to when they controlled their own schedule.

The fine print in the contracts by which physicians sell their practices to private equity firms could thwart an attempt to regain independence. Private equity firms typically demand and obtain restrictions on a physician's ability to earn a living on his own. Non-compete agreements are valid in 46 states, with only California, North Dakota, Minnesota, and Oklahoma banning these provisions. The new proposed regulation by the Federal Trade Commission (FTC) to ban all non-compete provisions was invalidated on July 3, 2024, by a federal judge. Missouri courts have fully enforced non-compete agreements, and do not typically revise contracts in order to make them more reasonable.

The 2,600-year-old adage "look before you leap," which originated in an Aesop's Fable, applies with particular force to any physician who receives an offer from a private equity firm, either to purchase his practice or to employ him. Conditions buried in a long contract may make the purchase price less attractive, or essentially prevent the physician from practicing again as he may later want to do. A takeover by private equity of his hospital can also adversely affect him, and the community of patients too. Physicians could already be educating their

patients and the public about the long-term harm of selling out to private equity.

Example: US Anesthesia Partners

In 2012, US Anesthesia Partners ("USAP") was created in Texas by the New York City private equity firm Welsh Carson along with several physician partners. USAP then aggressively bought up anesthesiology practices that had exclusive contracts with hospitals in Texas. For $100 million plus loans, Welsh Carson acquired Greater Houston Anesthesiology, which was the largest such medical practice in Houston and 20 times bigger than its second largest competitor there. By using "tuck-in clauses," USAP imposed its higher prices on services that its acquired practices had been providing at its own lower pricing. USAP bought up competitors, each time raising the prices that had been previously been lower due to competition.

Next USAP went to Dallas, first purchasing the largest anesthesiology there, and subsequently purchasing six more, similar to what it did in Houston. After that, USAP made similar acquisitions in Austin, San Antonio, Amarillo, and Tyler. Each time, patients were harmed by the decrease in competition and the increase in prices. By 2024, USAP was handling nearly half of all the hospital-only anesthesia cases in Texas (and a higher 70% in Houston and Dallas), while reaping almost 60% of all the hospital anesthesia revenue paid by Texas insurers, employers, and patients. USAP also paid $9 million to a potential competitor, Envision Healthcare, for it to stay out of the Dallas market for five years.

After a decade of this, in 2023 the Federal Trade Commission sued USAP and the private equity firm Welsh Carson in federal court in Houston, for defendants' alleged violation of antitrust laws. Although somewhat unusual for a non-litigant to file an amicus brief in a district court, the American Investment Council entered the case with top-drawer New York City and Houston law firms to submit an amicus brief in support of Welsh Carson. AIC is a trade association of more than 60 private equity firms, including among its members Apollo, Bain Capital, Blackstone, the Carlyle Group, and KKR, many of which themselves are big players in healthcare acquisitions today.

In May of this year, US District Judge Kenneth Hoyt held that the FTC's antitrust case against US Anesthesia Partners could proceed, but dismissed the private equity firm Welsh Carson from the lawsuit. This denies legal accountability by the private equity firm for the alleged anti-competitive conduct, including the increase in prices that the acquired practices began charging. The private equity firm applauded its escape from this lawsuit, saying that they were "mere investors" and that the FTC's inclusion of it as a defendant constituted "turning decades of corporate law on its head." Unless the private equity firm is somehow brought back into this case or sued separately by the FTC, USAP and its physicians will be ones to bear the brunt of any fines and damages that are assessed.

Conclusion

Private equity is affecting almost every aspect of healthcare today, and causing substantial harm. In the next installment of this article, we will discuss the detrimental impact of private equity investments in surgery specialties.

References

1. Harvard Law School, 1991. Harvard Law Review, 1989-91. Law clerk on the U.S. Court of Appeals for the D.C. Circuit, 1991-92.
2. Vogel Susanna, "Over 20% of healthcare bankruptcies last year were linked to private equity: report," Healthcare Dive, April 17, 2024, https://www.healthcaredive.com/news/private-equity-stakeholder-project-healthcare-bankruptcy/713297/
3. Id.
4. Conte Niccolo, "Ranked: The World's 50 Largest Private Equity Firms," Visual Capitalist, May 16, 2024, https://tinyurl.com/dsvry6je
5. Everett Avery, "Rural concern grows over 2 Noble Health hospitals limiting services," KOMU, Mar 22, 2022, https://tinyurl.com/3uedmh9h
6. Diamond Frank, "In a 'spectacular collapse,' Cano Health files for bankruptcy," Fierce Healthcare, Feb. 4, 2024, https://www.fiercehealthcare.com/payers/spectacular-collapse-risk-bearing-provider-company-cano-health-files-bankruptcy
7. Finnegan Joanne, "Private equity firms are acquiring more physician practices. Which specialties are in highest demand?" Fierce Healthcare, Feb 18, 2020, https://www.fiercehealthcare.com/practices/acquisition-physician-practices-by-private-equity-firms-increases-study-finds-which
8. Gliadkovskaya Anastassia, "Private equity deals drive up healthcare use, costs among physician practices, JAMA study finds," Fierce Healthcare, Sep 13, 2022, https://www.fiercehealthcare.com/finance/private-equity-associated-greater-spending-utilization-jama-study-findst

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Cannabis and Psychosis: Weeding Out Fact from Fiction

by Emma C. Johnson, PhD & Arpana Agrawal, PhD

The state of Missouri is now part of the national cannabis experiment. It is likely a good time for greater vigilance surrounding cannabis use, which should be routinely queried in medical settings, similar to alcohol and tobacco.

Cannabis use remains common in the United States. The rapidly changing landscape of cannabis regulatory policies may be contributing to these trends, although evidence remains mixed.[1] While studies are conflicted about the impact of recreational (RML) and medical (MML) marijuana laws on cannabis use, per se, there appears to be emerging support for an uptick in emergency department visits, traffic injuries and fatalities, and burgeoning cases of poisoning in toddlers and preschool-aged children, possibly due to increasing availability of edible forms of the drug.[2,3]



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Beyond these immediate consequences of cannabis exposure and use lies a vast and concerning literature addressing elevated rates of mental health problems in individuals using cannabis. In particular, individuals with schizophrenia, psychotic disorders, and psychosis are considerably more likely to report chronic cannabis use and problems with cannabis compared to those without these mental health conditions.[4] Similarly, rates of schizophrenia, psychotic disorders, and psychosis-like behaviors are overrepresented in individuals who use cannabis heavily compared to the general population.[5] It has long been assumed that these associations, which

are particularly elevated in individuals who initiate use at an early age, reflect a causal effect of cannabis use and use disorder (CanUD); i.e., a psychiatric diagnosis reflecting tolerance, withdrawal, loss of control, and impairment due to use) on schizophrenia and psychosis. In this selective review, we outline the evidence linking cannabis use and CanUD to schizophrenia and psychosis and detail evidence supporting and refuting causal assertions.

Epidemiological Evidence

The relationship between cannabis and schizophrenia, and whether the former exerts a causal influence on the latter, is an enduring epidemiological hypothesis. In an initial study of >45,000 Swedish conscripts, Andreassen et al.,[6] found that those who reported heavy cannabis use (more than 50 times) were at six-fold greater relative risk for schizophrenia onset, an association that persisted when accounting for premorbid personality features. These large-scale observations are echoed in US epidemiological surveys as well (e.g.,[4,5]). Subsequent contemporary studies have added nuance to this observation, highlighting the exacerbating influence of earlier-onset cannabis use, higher potency cannabis, and heavier use that may meet criteria for CanUD.

For instance, one study reported that daily use of a particular form of high-potency cannabis (> 10% THC) was almost five-fold more common in first-episode psychosis cases in the United Kingdom.[7] In another study that accessed the extant health records of the Danish population, researchers reported that the population attributable risk fraction for cannabis use disorder in schizophrenia has markedly increased over time, from 2% in the early 1970s to almost 30% in males aged 21-25 by 2020, corresponding to an adjusted incidence hazard ratio of nearly 3.0, which the authors contend is consistent with increases in its availability and potency, and consistent with the rising incidence of schizophrenia.[8,9] This study concluded that young males were particularly vulnerable to schizophrenia in the context of CanUD.

Transient and Induced Psychosis, and Schizophrenia Conversion

Heavy and high potency cannabis use can induce psychosis. Less than half a percent of individuals using cannabis report related psychosis that requires emergency medical treatment, with paranoia being the most prevalent feature; younger age is associated with >2.5 relative risk.[10] In a recent study of ED visits for acute psychosis, urinary positivity for delta-9 tetrahydrocannabinol (THC) was associated with agitation and symptom acuity.[11] A mega-analysis of human laboratory studies that involved intravenous THC infusions found clinically meaningful positive symptoms in ~45% of the samples, with conceptual disorganization and hallucinations being common. Notably, negative symptoms (e.g., blunted affect) were also commonly identified.[12] The authors noted a dose-dependent relationship related to both THC concentration and pace of infusion, which roughly corresponded to three-quarters to a full standard joint.[13] These studies suggest that cannabis-induced behavioral alterations are likely to involve a wide range of symptoms that broadly map onto positive, negative, and cognitive features of schizophrenia. In a recent study conducted by us, where participants self-reported symptoms that they experienced upon using cannabis, decreased social contact, cognitive difficulties, and dysphoria/anhedonia were far more commonly reported than paranoia or hallucinations.[14] In this study, younger age of cannabis initiation, longer duration of daily use, and a CanUD diagnosis were robust correlates of these experiences.

Thus, it is known that cannabis use can result in transient or acute psychosis—but what proportion of the individuals who experience psychotic symptoms have a prior history of psychotic disorders or eventually convert to schizophrenia? In our study, even though active psychotic disorders were exclusionary, genetic liability to schizophrenia (measured using published estimates of genome-wide genetic associations with schizophrenia) was associated with cannabis induced experiences, although the association with cognitive difficulties was much stronger than that with paranoia. Another retrospective study found that medical authorizations for cannabis were associated with 1.63 hazards of a psychosis-related ED visit in patients with no record of prior psychotic disorders.[15] Similarly, use of high potency cannabis at age 16-18 was associated with a doubling of the odds of incident psychosis by ages 19-24.[16] A study of the Danish Civil Registry indicates that 47% of those with cannabis-induced psychosis convert to schizophrenia within three to four years.[17]

Meta-Analytic Evidence

A recent umbrella review of 32 eligible studies weighed support for and against several research questions related to cannabis and psychosis (e.g., schizophrenia, schizotypy, psychosis-like experiences).[18] They concluded that while there was notable support for an association between cannabis use and psychosis along the continuum, a majority of the studies were cross-sectional and thus, limited in their inferential capacity. An earlier meta-analysis of 18 studies estimated a meta-analytic odds ratio of ~4.0, alongside a dose-response effect.[19] Examining facets of schizophrenia, one meta-analysis of 65 eligible studies reported that frequent cannabis use was associated with elevated likelihood of positive symptoms, and excitement, but lower severity of negative symptoms and not associated with disorganization.[20] Here as well, the authors concluded that the evidence was not sufficient to prove causation.

Causal or Confounded?

There are numerous alternative explanations that must be considered. From a clinical perspective, researchers have argued that early onset of cannabis use, especially heavy, high frequency use or chronic use of high potency cannabis, may be associated with behavioral traits associated with schizophrenia (e.g., early social disengagement, negative affect), premorbid symptoms, or correlated psychopathology (e.g.,[21]). In other words, individuals may start using cannabis at a young age to cope with behaviors that are harbingers of schizophrenia, and this use may further the course of the illness.[22] Others argue that psychosis consequent to heavy cannabis use may be a form of acute psychosis, which, while of prognostic value in schizophrenia,[23] may also be distinct from it.[24] Younger age and male gender appeared to be risk factors for conversion from onset of psychosis to schizophrenia diagnosis within a three-year period, and this was most pronounced for cannabis relative to other drugs.[17,25] Yet, according to projection modeling, heavy cannabis use would have to be prevented in 2,800 males aged 20-24 to prevent a single case of schizophrenia, which suggests that cannabis-related increases in schizophrenia will be subtle.[26,27] However, given the increasing availability of high potency cannabis, the impact on cannabis-induced acute psychosis, if not schizophrenia diagnoses, may well be expected to shift.[28] Thus, while plausible alternatives to the causal hypothesis exist, no epidemiological data have been able to completely refute an independent effect of (certain forms of heavy or high potency) cannabis use, nor prove it.

Genetic Studies Provide Clues

Cannabis use and CanUD are moderately heritable, with 50% of population differences due to the additive effect of segregating genes, while schizophrenia is highly heritable with genetics implicated in up to 80% of population variability.[29,30] Given this heritability, some of the same genes that predispose someone to schizophrenia might also increase risk of heavy cannabis use, particularly if it is used to cope with early behavioral features. To estimate the degree to which the same genetic factors may influence both schizophrenia and cannabis use, researchers typically turn to studies of twins. Identical twins share 100% of their segregating genetic material, while fraternal twins and siblings share, on average, 50% of their DNA. Comparing the degree of correlation between these types of relatives offers preliminary insight into the role of shared genetics, with studies reporting genetic correlations between cannabis use and psychosis-like experiences of 0.40 – 0.56.[31,32] However, as schizophrenia is rare and thus poorly captured in population-based twin studies, more persuasive evidence for shared genetic mechanisms arises from recent genome-wide association studies (GWAS), which are "hypothesis-free" queries of the association between a phenotype and common genetic variation across the genome as indexed by single nucleotide polymorphisms (SNPs, i.e., changes in individual nucleotide base pairs). The SNP-explained correlation between the current largest GWAS of schizophrenia[33] and CanUD[34] is 0.37, and is statistically greater than the corresponding genomic correlation between schizophrenia and cannabis use [rG = 0.24].[34–36] These findings highlight the importance of considering shared genetic liability, which can also contribute to dose-response patterns of association.

Both CanUD and schizophrenia are also polygenic; that is, many genetic variants of small effects, in combination, shape the genetic etiology of these disorders. We can estimate a score that aggregates across these small effects (e.g., by taking the effect sizes from a large GWAS and weighting



According to a study in the *American Journal of Psychiatry*, individuals who have even one psychotic episode following cannabis use have a 47 percent higher chance of developing schizophrenia or bipolar disorder. And adolescents and young adults are at the highest risk.

a person's own genotype by these effects).[37] One study found that such a polygenic score (or PGS) for cannabis use and CanUD improved prediction of psychotic disorders beyond the corresponding PGS for psychotic disorders themselves, indicating genetic overlap.[38] Another study found that individuals with high PGS for schizophrenia showed stronger associations between cannabis use and risk for psychotic-like experiences, such as auditory hallucinations, suggesting a gene-environment interaction effect between genetic risk for schizophrenia and cannabis use.[39]

Another way to understand what underlies the genetic correlation is by pinpointing the specific genetic variants that influence both cannabis use and schizophrenia. We identified 327 independent genetic signals that were associated with both CanUD and schizophrenia, as well as tobacco smoking, although the genetic correlation between CanUD and schizophrenia was statistically larger than that between tobacco smoking and schizophrenia (rG = 0.37 vs. 0.17).[40] Interestingly, the genetic signals at the intersection of CanUD and schizophrenia appeared to be particularly associated with executive functioning, such that genetic variants associated with greater risk of CanUD and schizophrenia are also associated with liability for lower executive functioning. The strongest pleiotropic (i.e., same genetic signal influencing multiple behaviors) locus included CHRNA2 (neuronal nicotinic acetylcholine receptor, subunit alpha 2), which persisted as a signal even after accounting for tobacco genetics.

Causal Inference from Genetic Studies

True pleiotropy can exist alongside causation, and in some cases, even be indicative of it. Genetically informed studies, especially those that can estimate genetic correlations, are also well suited for the study of causal inferences, using both twin and GWA studies. In one such study, we compared the level of psychosis-like experiences reported by pairs of twins and similarly-aged siblings of whom one reported high levels of cannabis use while their co-twin only reported low levels or no cannabis use.[31] We found that even after accounting for shared genetics, there was a statistically significant residual elevation in psychosis like experiences reported by those who used cannabis frequently or met criteria for CanUD. Thus, evidence for both genetic correlation and non-genetic contributors, which may potentially be causal, was noted.

Similar approaches for causal inference have also been developed to leverage measured genomic data. Borrowing instrumental variable analysis techniques and theory from epidemiology and econometrics, Mendelian Randomization (MR) and related

approaches use measured genomic data to estimate causal relationships between traits.[41] MR can be thought of as analogous to a randomized controlled trial, in that an individual is randomly "assigned" to their genotype at birth, so confounders should be randomly distributed across genotypes (in theory). Generally, recent well-powered studies of heavy use or CanUD have found evidence for bidirectional causal effects of cannabis on schizophrenia and vice versa.[34,36,38,40–42]

The Environment, Prenatal Cannabis Exposure and Psychosis

In the genetic studies reviewed above, the residual association, after accounting for shared genetic liability, is considered to be indicative of "third variable" effects, which may include causation. One such environmental/epigenetic mechanism relates to *in utero* cannabis exposure. Research by our team has found that self-reported cannabis use subsequent to knowledge of pregnancy in the birthing person is associated with increased likelihood of psychosis-like behaviors during middle childhood, although the continued influence of prenatal cannabis exposure on psychosis during adolescence appears less clear.[43,44] Some have theorized that endogenous cannabinoid receptors, notably the ubiquitous CB1 receptors that are expressed during seven to eight weeks of gestation,[45] may serve as a mechanism potentiating the impact of cannabis on other biological systems that subsequently contribute to psychosis. As more birthing individuals turn to cannabis for pregnancy-related nausea, sleep, and mood management,[46,47] we might expect a shift in psychosis within the next two decades, if indeed cannabis contributes *in utero* to psychosis-related fetal reprogramming. However, controlling for maternal psychopathology, which might increase the likelihood of cannabis use during pregnancy, will have to be accounted for when ascribing causal explanations to such findings. Similarly, other postnatal early life adversities, which are likely to shape risk for cannabis use, CanUD and schizophrenia, are worth studying as potential alternate explanations for causality.[41]

Gene-Environment Interplay

Schizophrenia itself (and psychosis less so) is so highly heritable that the assumption of a purely environmental form—that is, solely attributable to cannabis—seems implausible. Therefore, genetic liability for schizophrenia/psychosis may be a prerequisite and cannabis a provocateur for the development of schizophrenia. Several studies of "candidate genes", i.e., the study of investigator-selected genes or genetic variants, which suffer from notoriously high false discovery rates, have yielded no clarity on this issue of gene-environment interplay.[48] More recent studies that can estimate the genome-wide risk for schizophrenia, while finding much support for common genetic mechanisms, have also resulted in mixed support for gene-environment interactions with cannabis use. While several studies found independent but not interactive contributions of cannabis use and schizophrenia genetic liability (e.g.[49]) on psychosis, one study reported that individuals at the highest genetic susceptibility to schizophrenia were more likely to report psychotic experiences if they were cannabis users.[39]

We have previously contended that, if cannabis use is to be viewed as an "environmental" risk factor, then the appropriate explanation may lie in tests of gene-environment correlation rather than gene-environment interaction. Put another way, the use of cannabis—at an earlier age, of a higher potency, and with greater chronicity—in individuals with psychosis is not a coincidence or a chance observation. Rather, individuals who are at high genetic liability for schizophrenia are more likely to use higher potency cannabis (and at an earlier age, and with greater chronicity) because shared genetic factors elicit this heritable "environmental" exposure. Causal studies refute this possibility by documenting the absence of psychotic illness or related personality traits in those with cannabis-related incident psychosis. However, they do not account for all other markers of psychopathology that genetic studies tell us may be related to schizophrenia.

Can We Ever Prove Causation, and Do We Need To?

The dilemma with the causal hypothesis is that —in humans—it is challenging to prove without equivocation. There are guidelines, for instance, the Hill criteria.[50,51] However, such criteria can be unsatisfactory for the etiologically complex relationship between cannabis and schizophrenia.[52] We must then ask if it is vital that causation be proven. Put another way, what do we expect if

cannabis use exerts a causal influence? We may find then that as higher potency forms become more accessible, our physicians may anticipate increased ED presentations for cannabis-induced psychosis. There is no clear evidence of this as yet (e.g.,[53,54] but see[55]). Perhaps the period of vulnerability matters and only early exposure (e.g., prenatal or adolescent) is a risk factor? If this is the case, then we should be concerned as rates of prenatal use are on the rise,[56,57] and policies that vigorously deter use in vulnerable populations is fundamentally important. Relying on industry self-regulation (e.g., "we card" programs) is unlikely to be efficacious and significant investment in sensible policies is necessary.[58,59]

Are individuals with certain genetic risk factors more vulnerable? Genetic prognostication comes with its own challenges, but one approach might be to focus additional prevention efforts towards youth with family histories of mental illness, potentially in routine medical settings. Reflecting on these expectations, two observations are evident. First, there is no instance in which a purely causal explanation exists. For instance, even if policy change were to be the sole reason for increasing cannabis use (and this is unlikely), then the impact on schizophrenia would still be titrated by genetic load for the disorder; that is, we do not expect a non-genetic form of schizophrenia, that is solely due to chronic cannabis use. Second, rational regulatory policy that deters cannabis use in youth and birthing persons, and medical vigilance of use in general is simply sensible practice that does not require a causal bedrock for implementation.

Conclusion

Without a doubt, more research into mechanisms by which cannabis exposure might amplify genetic risk for schizophrenia is needed. It is worth noting that cannabis is federally a schedule I drug, which severely restricts scientific access, especially for federally-funded research. Rescheduling cannabis could greatly facilitate such research, allowing for real-world experiments with greater generalizability. However, lack of mechanistic understanding is not a reason for complacency. The state of Missouri is now part of the national cannabis experiment. It is likely a good time for greater vigilance surrounding cannabis use, which should be routinely queried in medical settings, similar to alcohol and tobacco. Realistic, scientifically-backed information should serve as the foundation to youth prevention, which should be widespread (e.g., pediatrician's office, educational settings). However, many individuals with established patterns of cannabis use are reluctant to quit, because they ascribe self-medication attributes to the drug. In such instances, and for a drug now commonplace, harm reduction approaches may prove to be of considerable utility.[60]

References

1. Pawar, A. K. S., Firmin, E. S., Wilens, T. E. & Hammond, C. J. Systematic Review and Meta-Analysis: Medical and Recreational Cannabis Legalization and Cannabis Use Among Youth in the United States. J Am Acad Child Adolesc Psychiatry S0890-8567(24)00141–2 (2024) doi:10.1016/j.jaac.2024.02.016.
2. Hammig, B., Jones, C. & Haldeman, S. Pediatric Poisonings Associated With Ingestion of Marijuana Products. J Emerg Med 64, 181–185 (2023).
3. Walker, M. et al. The effect of recreational cannabis legalization and commercialization on substance use, mental health, and injury: a systematic review. Public Health 221, 87–96 (2023).
4. Livne, O. et al. Trends in Prevalence of Cannabis Use Disorder Among U.S. Veterans With and Without Psychiatric Disorders Between 2005 and 2019. Am J Psychiatry 181, 144–152 (2024).
5. Livne, O., Shmulewitz, D., Sarvet, A. L., Wall, M. M. & Hasin, D. S. Association of Cannabis Use-Related Predictor Variables and Self-Reported Psychotic Disorders: U.S. Adults, 2001-2002 and 2012-2013. Am J Psychiatry 179, 36–45 (2022).
6. Andréasson, S., Allebeck, P., Engström, A. & Rydberg, U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 2, 1483–1486 (1987).
7. Di Forti, M. et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 6, 427–436 (2019).
8. Hjorthøj, C., Posselt, C. M. & Nordentoft, M. Development Over Time of the Population-Attributable Risk Fraction for Cannabis Use Disorder in Schizophrenia in Denmark. JAMA Psychiatry 78, 1013–1019 (2021).
9. Hjorthøj, C. et al. Association between cannabis use disorder and schizophrenia stronger in young males than in females. Psychological Medicine 53, 7322–7328 (2023).
10. Schoeler, T., Ferris, J. & Winstock, A. R. Rates and correlates of cannabis-associated psychotic symptoms in over 230,000 people who use cannabis. Transl Psychiatry 12, 369 (2022).
11. Gouse, B. M., Boliver, E. E., Oblath, R., Camacho, L. & Brown, H. E. Cannabis use among patients presenting to the emergency department for psychosis: Associations with restraint use, medication administration, psychiatric hospitalization, and repeat visits. Psychiatry Res 323, 115151 (2023).
12. Ganesh, S. et al. Psychosis-Relevant Effects of Intravenous Delta-9-Tetrahydrocannabinol: A Mega Analysis of Individual Participant-Data from Human Laboratory Studies. Int J Neuropsychopharmacol 23, 559–570 (2020).
13. Boggs, D. L. et al. The dose-dependent psychomotor effects of intravenous delta-9-tetrahydrocannabinol (Δ9-THC) in humans. J Psychopharmacol 32, 1308–1318 (2018).
14. Johnson, E. C. et al. Associations Between Cannabis Use, Polygenic Liability for Schizophrenia, and Cannabis-related Experiences in a Sample of Cannabis Users. Schizophr Bull 49, 778–787 (2022).
15. Dubois, C. et al. Medical cannabis authorization and risk of emergency department visits and hospitalization due to psychotic disorders: A propensity score-matched cohort study. Schizophr Res 264, 534–542 (2024).

16. Hines, L. A., Heron, J. & Zammit, S. Incident psychotic experiences following self-reported use of high-potency cannabis: Results from a longitudinal cohort study. Addiction 119, 1629–1634 (2024).
17. Starzer, M. S. K., Nordentoft, M. & Hjorthøj, C. Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis. AJP 175, 343–350 (2018).
18. Groening, J. M. et al. A systematic evidence map of the association between cannabis use and psychosis-related outcomes across the psychosis continuum: An umbrella review of systematic reviews and meta-analyses. Psychiatry Research 331, 115626 (2024).
19. Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M. & Vassos, E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull 42, 1262–1269 (2016).
20. Argote, M. et al. Association between cannabis use and symptom dimensions in schizophrenia spectrum disorders: an individual participant data meta-analysis on 3053 individuals. EClinicalMedicine 64, 102199 (2023).
21. Ringen, P. A. et al. Cannabis use and premorbid functioning as predictors of poorer neurocognition in schizophrenia spectrum disorder. Schizophrenia Research 143, 84–89 (2013).
22. Hill, M. Perspective: Be clear about the real risks. Nature 525, S14–S14 (2015).
23. Arendt, M., Rosenberg, R., Foldager, L., Perto, G. & Munk-Jørgensen, P. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. Br J Psychiatry 187, 510–515 (2005).
24. Núñez, L. A. & Gurpegui, M. Cannabis-induced psychosis: a cross-sectional comparison with acute schizophrenia. Acta Psychiatr Scand 105, 173–178 (2002).
25. Niemi-Pynttäri, J. A. et al. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry 74, e94-99 (2013).
26. Hickman, M. et al. If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. Addiction 104, 1856–1861 (2009).
27. Hickman, M., Vickerman, P., Macleod, J., Kirkbride, J. & Jones, P. B. Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. Addiction 102, 597–606 (2007).
28. D'Souza, D. C. Cannabis, cannabinoids and psychosis: a balanced view. World Psychiatry 22, 231–232 (2023).
29. Verweij, K. J. H. et al. Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. Addiction 105, 417–430 (2010).
30. Owen, M. J., Legge, S. E., Rees, E., Walters, J. T. R. & O'Donovan, M. C. Genomic findings in schizophrenia and their implications. Mol Psychiatry 28, 3638–3647 (2023).
31. Karcher, N. R. et al. Genetic Predisposition vs Individual-Specific Processes in the Association Between Psychotic-like Experiences and Cannabis Use. JAMA Psychiatry 76, 87–94 (2019).
32. Nesvåg, R. et al. Genetic and Environmental Contributions to the Association Between Cannabis Use and Psychotic-Like Experiences in Young Adult Twins. Schizophr Bull 43, 644–653 (2017).
33. Trubetskoy, V. et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604, 502–508 (2022).
34. Levey, D. F. et al. Multi-ancestry genome-wide association study of cannabis use disorder yields insight into disease biology and public health implications. Nat Genet 55, 2094–2103 (2023).
35. Johnson, E. C. et al. A large-scale genome-wide association study meta-analysis of cannabis use disorder. Lancet Psychiatry 7, 1032–1045 (2020).
36. Pasman, J. A. et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci 21, 1161–1170 (2018).
37. Bogdan, R., Baranger, D. A. A. & Agrawal, A. Polygenic Risk Scores in Clinical Psychology: Bridging Genomic Risk to Individual Differences. Annu Rev Clin Psychol 14, 119–157 (2018).
38.Cheng, W. et al. The relationship between cannabis use, schizophrenia, and bipolar disorder: a genetically informed study. The Lancet Psychiatry 10, 441–451 (2023).
39. Wainberg, M., Jacobs, G. R., di Forti, M. & Tripathy, S. J. Cannabis, schizophrenia genetic risk, and psychotic experiences: a cross-sectional study of 109,308 participants from the UK Biobank. Transl Psychiatry 11, 1–9 (2021).
40. Johnson, E. C. et al. Cross-ancestry genetic investigation of schizophrenia, cannabis use disorder, and tobacco smoking. Neuropsychopharmacol. 1–11 (2024) doi:10.1038/s41386-024-01886-3.
41. Gage, S. H. et al. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. Psychol Med 47, 971–980 (2017).
42. Vaucher, J. et al. Cannabis use and risk of schizophrenia: a Mendelian randomization study. Mol Psychiatry 23, 1287–1292 (2018).
43. Paul, S. E. et al. Associations Between Prenatal Cannabis Exposure and Childhood Outcomes: Results From the ABCD Study. JAMA Psychiatry 78, 64–76 (2021).
44. Baranger, D. A. A. et al. Association of Mental Health Burden With Prenatal Cannabis Exposure From Childhood to Early Adolescence: Longitudinal Findings From the Adolescent Brain Cognitive Development (ABCD) Study. JAMA Pediatrics 176, 1261–1265 (2022).
45. Wu, C.-S., Jew, C. P. & Lu, H.-C. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol 6, 459–480 (2011).
46. Vanstone, M. et al. Reasons for cannabis use during pregnancy and lactation: a qualitative study. CMAJ 193, E1906–E1914 (2021).
47. Mark, K., Gryczynski, J., Axenfeld, E., Schwartz, R. P. & Terplan, M. Pregnant Women's Current and Intended Cannabis Use in Relation to Their Views Toward Legalization and Knowledge of Potential Harm. J Addict Med 11, 211–216 (2017).
48. Veling, W. Genetic mediation of the link between schizophrenia and cannabis use. Psychiatry 7, 511–515 (2008).
49. Elkrief, L. et al. Independent contribution of polygenic risk for schizophrenia and cannabis use in predicting psychotic-like experiences in young adulthood: testing gene × environment moderation and mediation. Psychol Med 53, 1759–1769.
50. Hill, A. B. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med 58, 295–300 (1965).
51. Radhakrishnan, R., Wilkinson, S. T. & D'Souza, D. C. Gone to Pot - A Review of the Association between Cannabis and Psychosis. Front Psychiatry 5, 54 (2014).
52. Ganesh, S. & D'Souza, D. C. Cannabis and Psychosis: Recent Epidemiological Findings Continuing the 'Causality Debate'. Am J Psychiatry 179, 8–10 (2022).
53.= Elser, H. et al. State Cannabis Legalization and Psychosis-Related Health Care Utilization. JAMA Network Open 6, e2252689 (2023).
54. Myran, D. T. et al. Association between non-medical cannabis legalization and emergency department visits for cannabis-induced psychosis. Mol Psychiatry 28, 4251–4260 (2023).
55. Wang, G. S. et al. Cannabis legalization and cannabis-involved pregnancy hospitalizations in Colorado. Prev Med 156, 106993 (2022).
56. Volkow, N. D., Han, B., Compton, W. M. & McCance-Katz, E. F. Self-reported Medical and Nonmedical Cannabis Use Among Pregnant Women in the United States. JAMA 322, 167–169 (2019).
57. Young-Wolff, K. C. et al. Rates of Prenatal Cannabis Use Among Pregnant Women Before and During the COVID-19 Pandemic. JAMA 326, 1745–1747 (2021).
58. Apollonio, D. E. & Malone, R. E. The "We Card" Program: Tobacco Industry "Youth Smoking Prevention" as Industry Self-Preservation. Am J Public Health 100, 1188–1201 (2010).
59. Hall, W. The costs and benefits of cannabis control policies. Dialogues Clin Neurosci 22, 281–287 (2020).
60. Lin, L. (Allison), Bonar, E. E. & Coughlin, L. N. Toward a Harm Reduction Approach to Cannabis Use Disorder. AJP 181, 98–99 (2024).

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Easy Availability of Marijuana and Other Cannabis-Derived Products: What is the Missouri Poison Center Seeing?

by Rebecca L. Tominack, MD & Julie A. Weber, RPh

The Missouri Poison Center for exposure to any type of cannabis product shows steady growth—from 130 exposures in 2019 to 535 exposures in 2023, a 300% increase.

There is an old poison center saying: "Children get into what's handy." In Missouri, since the start of legal sales of marijuana for medical use (10/17/2020) and for recreational use (02/03/23), more Missourians have ready access to a wide variety of Delta 9-TetraHydroCannabinol and marijuana products. These adult-only products are therefore available, i.e., "handy," for accidental exposures in children, and sometimes in unsuspecting adults. In particular, THC "edibles" such as gummies, cookies, brownies, chocolate candy, and beverages are innately attractive to children. Children watch, and they know where the edibles are stashed, and simply go help themselves. Delta 9-THC doses of 10 to 40 mg that produce a pleasant "high" in adults can cause very unpleasant, and potentially dangerous reactions in children. Many need evaluation and observation at a hospital.

Marijuana/THC Edibles: Composite Case Scenarios

1. A two-year-old, 13 kg child ate four of the parent's Delta 9-THC cookies, 150 mg each, ingesting a total of 600 mg Delta 9-THC. The child became obtunded and was watched overnight by the parents. The child was brought to the emergency department the next morning because the child was not waking up to eat or drink. In the ED, the child was responsive only to pain, had dilated pupils, tachycardia, and was somewhat dehydrated. The child was admitted for IV fluids and observation. Bradypnea was noted but acceptable oxygen saturation was maintained on room air. Episodes of bradycardia to the 50s occurred, for which atropine was given. Twenty-four hours after presentation the child was more alert and taking liquids and food.

2. An adult ingested 1,000 mg of Delta 9-THC by consuming an entire edible, intended to be divided into 10 doses. They were acting bizarrely and then had a seizure. In the ED, the person was bradycardic and hypotensive, and responded only to sternal rub. Oxygen saturation on room air was 78%. Anticonvulsants, IV fluid boluses, and oxygen by nasal canula were given. Discharge to home was accomplished after eight hours observation.



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Calls to the Missouri Poison Center for Cannabis-Product Exposures

In concert with increased availability, the five-year tally of calls to the Missouri Poison Center for exposure to any type of cannabis product shows steady growth—from 130 exposures in 2019 to 535 exposures in 2023, a 300% increase. The edibles are responsible for the largest share, with a disproportionate rise in young children < six years (Figure 1). Although the Missouri Poison Center strives to manage patients at home when it is safe to do so, fully 50% (221/438) of these young children were evaluated in the Emergency Department of a hospital. Thirty-six percent (80/221)

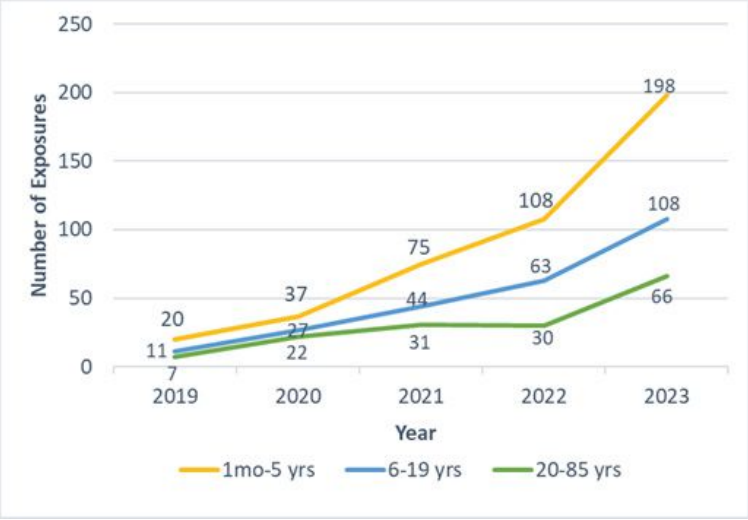


Figure 1. Exposures to marijuana/THC edibles by age group, 2019-2023

were admitted for treatment or observation.

The medical outcome of each exposure at a poison center is categorized as No Effect, Minor, Moderate or Major Effect, or Death (Figure 2). Among these young children, 48% showed Minor symptoms, such as somnolence, ataxia, dizziness, tachycardia, vomiting, and agitation. Twenty-two percent had symptoms judged as Moderate, such as obtundation, respiratory depression, hypotension, hypotonia, and tremor. Major symptoms were demonstrated by eight children, including unresponsiveness, bradycardia, bradypnea/apnea requiring mechanical ventilation, and seizures.

The cost of health care for cannabis-product exposures in Missouri is substantial. According to data from the Drug Overdose Dashboard of the Missouri Department of Health and Senior Services, the average cost of an ED visit for a drug overdose in 2022 was $4,530, and for an inpatient hospitalization was $37,730.[1] Applying these costs to the edibles exposures in the age group one month to five years, the 89 ED-only visits estimated cost to payors was in the neighborhood of $400,000 and for the 80 inpatient visits, $3 million.

Non-Delta 9-THC Cannabis Compounds

In Missouri, legally-sold marijuana and marijuana-infused products are subject to "seed to sale" state regulations, including mandated third-party lab analysis, that are intended to ensure cannabinoid content, quality, and safety in the name of public health. However, there are other open sources of cannabinoid products that are not regulated, and therefore their content, quality, and safety are not assured. These sources are the internet sites and small-volume producers that supply the head shops/gas-station markets. They are in business by misapplication of the 2018 Federal "Farm Bill" that legalized hemp and its derivatives.[2] In other words, other than Delta 9-THC itself, if the cannabinoid is found in the hemp plant they believe they can legally market it.

Many people are already familiar with the first of these hemp derivatives to be marketed. Non-psychoactive CBD (cannabidiol) has been marketed widely for many years as essentially a "cure-all." It is basically benign in overdose, if the product contains primarily CBD, and is not adulterated with unlabeled active quantities of Delta 9-THC.[3]

More recently, Delta 8-THC has become available as the first psychoactive, hemp-derivative compound for recreational use. It is the best studied derivative to date. Delta 8-THC is simply an isomer of Delta 9-THC, having a single unsaturated double bond in a different position. Despite being approximately 50% less-potent,[4] there are many clinical reports of toxicity from Delta 8-THC products in children and teenagers with symptoms similar to Delta 9-THC,[5] but concerningly with a higher incidence of dyspnea and cough.[6]

Composite Case Scenarios: Delta 8-THC

1. A four-year-old child visited the nightstand where mother kept her Delta 8-THC gummies, and ate the entire bag except one, all told 900 mg of Delta 8-THC. They became lethargic, limp, unable to sit, eat or drink and were brought to the ED. They responded to shoulder shaking with eye opening and nystagmus was noted. Oxygen saturation on room air was 93%. An IV fluid bolus was administered and the child was admitted for observation. Eighteen hours later the child was awake and able to eat and walk unassisted.

2. An adult, naïve to all cannabis products, ate a single 25 mg Delta 8-THC gummy and developed severe anxiety, tachycardia, dyspnea, and a numb feeling over the whole body, for which they presented to the ED. After four hours of observation, symptoms largely resolved and they were discharged.

Marijuana and Hemp, Research, and the Marketplace

Marijuana and hemp are essentially the same plant, cannabis sativa/indica/ruderalis, but have

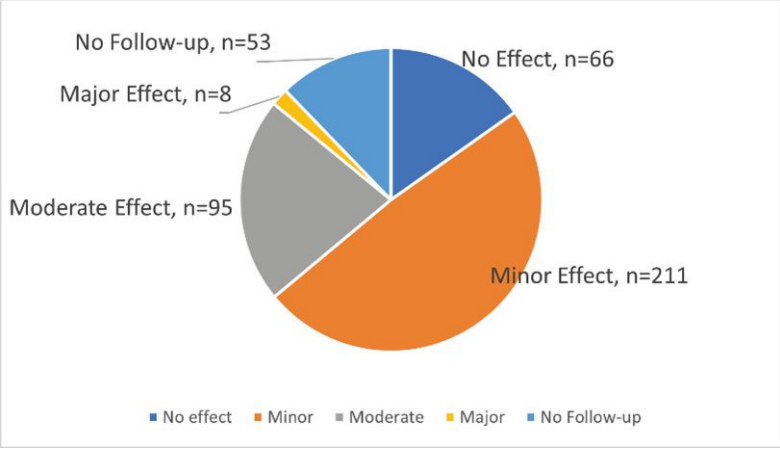


Figure 2. Medical Outcome, Age 1 month - 5 years, marijuana/THC edibles

lineages with different mixes of the three main cannabinoids, Delta 9-THC and the non-psychoactive CBD and CBC (Tetrahydrocannabinol, Cannabidiol, Cannabichromene).[7] Over time, selective breeding has given rise to innumerable varieties and strains with different cannabinoid mixes, known as their profiles. Those high in THC are grown for human medical and recreational use, and those low in THC are grown for industrial fiber, CBD, and oil extraction. Targeted genetic engineering has already been used to accelerate the process of producing varieties with virtually no THC and high CBD content, and varieties with high THC content and not-much-else, to serve the different markets.[8]

However, all cannabis varieties have hundreds of identifiable cannabinoids, terpenes, and other chemicals, although most are present in only trace amounts. Research to isolate and identify these minor compounds aims to find individual components that may have specific medical applicability. *In vitro* and animal test systems can be used to identify, at the least, the affinity for the two human cannabinoid receptors and the isolate's theoretical potency compared to Delta 9-THC.[9] [10]

Organic synthesis of these minor compounds is also advancing.[11] In fact, in several cases it was first synthesizing a specific compound in the lab that enabled the identification of the same compound in the plant.[12] Once a specific cannabinoid can be synthesized, extracting its minute quantities from the plant is no longer necessary. The compound is still considered "a derivative" of cannabis sativa, although it is not sourced from plants. Now available in quantity, it goes into the nebulous marketplace courtesy of the 2018 Farm Bill, and patients might present with adverse effects after using some new cannabinoid with virtually no recognition in the medical community.

Isomeric variation is a relatively easy modification of the core cannabinoid structure, producing Delta 8-, Delta 10-, and Delta 11-THC. Another easy modification is the length of the side chain attached to the aromatic ring. Both Delta 9-THC and Delta 8-THC have a five-carbon side chain. Similar cannabinoids have side chains varying in length from three to seven carbons. The longer the side chain, the more potent the variant. Variants with the three-carbon chain are specified by the suffix "varin," for example, TetraHydroCannabiVarin or THCV for short. Variants with a seven-carbon chain are specified by the suffix "phorol," for example, TetraHydroCannabiPhorol or THCP for short. This is one to keep an eye on, because it is recognized as the strongest natural cannabinoid currently known. It has 30 times stronger affinity for the cannabinoid CB_1 receptor and has a five to ten times more potent psychoactive effect than Delta 9-THC.[13] As a comparison, a psychoactive dose of Delta 9-THC is roughly 10-40 mg, whereas an equivalent dose of THCP is only 1-4 mg.

Due to the development of isolation and synthesis chemistry, the last few years have seen marketed cannabinoid products purporting to contain Delta 8-THC, Delta 10-THC, Delta 11-THC, THCP, THCV, CBN, etc. They are all found in cannabis, and someone is able to obtain or produce sufficient quantity to sell. [14] More are sure to come.

A Cautionary Tale

If these are derivatives of natural cannabis, what could go wrong? Because the Farm-Bill-enabled hemp sources of cannabinoid products are not regulated, their content, quality, and safety are not assured. The actual chemical composition and dose may be different from what is on the label.

As an example, Delta 8-THC is not extracted from the cannabis plant because there are only minor amounts of it present. It is made by processing CBD (cannabidiol) which *is* produced in substantial quantities in many varieties of hemp. As with many organic syntheses, it is prone to side reactions, including production of Delta 9- and Delta 11-THC.

Re-analysis of ten Delta 8-THC commercial products identified numerous impurities, even among those that had a Certificate of Analysis claiming no other compounds were there.[15] Production from low-budget marketers is likely to display even more variability in content, inaccurate quantitation, and potential toxicity.

Any Relationship to the Original "Synthetic Cannabinoids" of a Decade Ago?

"K2 agents," with brand names Spice, Incense, Krokadile, and uncounted others were extremely potent and toxic agents that have decreased in popularity because of dramatic and unpredictable toxicity. However, they are still in use and still a threat for unexpected toxicity.[16] They were first created to investigate the properties of the newly discovered cannabinoid receptors, but were resurrected for exploitation in the recreational drug market. Their structures bear no or little resemblance to the cannabis derivatives. The products' chemical composition continually changed and became increasingly bizarre and their effects unpredictable. No one really knew what they were buying. Effects included psychotic and affective disturbances, intense suicidal thoughts, self-harm behavior, and liver, kidney, and muscle injury. These adverse effects often took weeks to resolve and many did not resolve completely.

Why so toxic? It may be related to differences in cannabinoid receptor interactions between THC, the natural psychoactive cannabinoid found in recreational and medical marijuana, and the synthetics. THC appears to act as partial agonist at CB_1 receptors, by presenting both agonist and antagonist-binding poses in the receptor.[17] In contrast, the K2 agents have full agonist activity at the cannabinoid receptors and are also orders of magnitude more potent than THC. [18]

These differences help explain the significant psycho-toxicity and other undesirable psychological and behavioral effects of the K2 agents that are largely absent in Delta 9-THC and marijuana toxicity. It is unknown whether the clinical outcome of various natural cannabis derivatives will be more like marijuana or more like the K2 agents.

Clinically, Cannabis and Its Derivatives Are Handled the Same: Treat What You See

It does not matter clinically what version of the hemp-derived cannabis compounds have been used by the patient. There is no antidote; care is symptomatic and supportive for all of them. The urine drug screen might be positive for Delta 9-THC, either due to actual Delta 9-THC in the product or due to some degree of cross reactivity. Urine drug screen for Delta 9-THC *may* or *may not be positive* and confirmation by GC-MS *may* or *may not* find the particular cannabis derivative(s). The history of the product used might be all the information available, and even that is likely to be corrupt.

Advice to Give Users

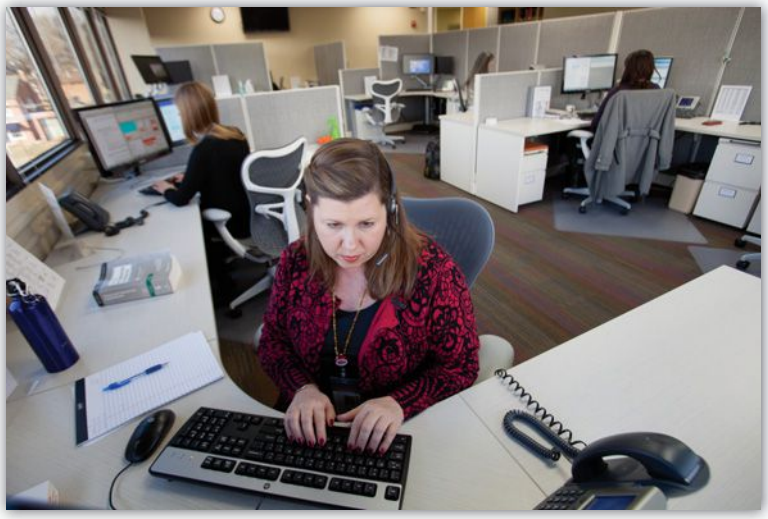
For the many people who want to use cannabis products, these are two risk-reducing suggestions. Purchase products only from licensed state dispensaries so that the possibility of mislabeling or adulteration is minimal. Treat the products, especially edibles, as drugs that are dangerous to children and keep them in a locked cabinet out of reach.

References

1. Missouri Department of Health and Senior Services. Non-fatal Overdoses. https://health.mo.gov/data/opioids/nonfatal-overdoses.php. Accessed August 1, 2024.
2. Cannabidiol-Derived Cannabinoids: The Unregulated Designer Drug Market
Following the 2018 Farm Bill. Zawatskya CN, Mills-Huffnaglea S, Augustoa CM, Vranab KE, Nylanda JE. Med Cannabis Cannabinoids 2024;7:10–18. DOI: 10.1159/000536339
3. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T , Vandrey R. 2017 Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA. 2017 Nov 7; 318(17): 1708–1709. doi: 10.1001/jama.2017.11909
4. Tagen M, Klumpers LE. Review of delta-8 tetrahydrocannabinol (Delta 8-THC) – Comparative pharmacology with Delta 9-THC. Br J Pharmacol 2022;179:3915-3933. doi.org/10.1111/bph.15865
5. Bradley EK, Hoots BE, Bradley ES, Roehler DR. Unintentional ingestion of putative delta-8 tetrahydrocannabinol by two youth requiring critical care A case report. J Cannabis Res. 2023: 5:9 pages 1-6. https://doi.org/10.1186/s42238-023-00176-x
6. Simon TA, Simon JH, Heaning EG, Gomez-Caminero A, Marcu JP. Delta-8, a Cannabis-Derived Tetrahydrocannabinol Isomer: Evaluating Case Report Data in the Food and Drug Administration Adverse Event Reporting System (FAERS) Database. Drug, Healthc Patient Saf. 2023:15 25–38. doi: 10.2147/DHPS.S391857
7. ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. In: Kinghorn AD, Falk H, Gibbons S, Kobayashi J, eds. Phytocannabinoids: Unraveling the Complex Chemistry and Pharmacology of Cannabis sativa. Cham, Switzerland. Springer;2017:1-36. https://doi.org/10.1007/978-3-319-45541-9.
http://online.statref.com.ezproxy1.lib.asu.edu/document.aspx?FxId=178&DocID=1&SessionID=1A48B0BBVJTGUIYT. Accessed January 21, 2013.
8. Smith CJ, Vergara D, Keegan B, Jikomes N. The phytochemical diversity of commercial Cannabis in the United States. PLOSOne17(5): e0267498. https://doi.org/10.1371/journal.pone.0267498
9. Blebea NM, Pricopie AJ , Vlad RA, Hancu G. Phytocannabinoids:

MISSOURI POISON CENTER

The Missouri Poison Center has provided no-cost assistance with drug overdoses and toxic exposures to the general public and healthcare professionals in Missouri for 50 years. The center, located in St. Louis, functions 24 hours a day, seven days a week with multi-channel access to a team of highly-trained nurses and pharmacists (Certified Specialists in Poison Information). They are clinically supervised by a dedicated physician Medical Toxicologist.



Each year the Missouri Poison Center manages nearly 60,000 cases, 20% originating from health care practitioners/facilities and 80% from the general public. It is a particular aim of the center to prevent unnecessary visits to the emergency department. More than 92% of public cases are kept at home by advice to the caregiver, close observation, and follow-up. Assisting home management results in a significant savings in health care expense.

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Drug overdose and critical poisoning cases admitted to health care facilities are given individualized, evidence-based management recommendations as the clinical course of the patient evolves.

The Missouri Poison Center is not-for-profit and is funded by the Missouri Hospital Association, the State of Missouri, SSM Health Cardinal Glennon Children's Hospital, and a federal grant from the Health Resources & Services Administration.

Exploring Pharmacological Profiles and Their Impact on Therapeutical Use. Int. J. Mol. Sci. 2024, 25, 4204. https://doi.org/10.3390/ijms25084204
10. Zagzoog A, Mohamed KA, Kim HJJ, et al. In vitro and in vivo pharmacological activity of minor cannabinoids isolated from Cannabis sativa. Nature Scientific https://doi.org/10.1038/s41598-020-77175-y
11. Nguyen G-N, Jordan EN, Kayser O. Synthetic strategies for rare cannabinoids derived from Cannabis sativa. J. Nat Prod. 2022,85, 1555-1568. https://doi.org/10.1021/acs.jnatprod.2c00155
12. Linciano P, Russo P, Cinzia Citti C, et al. The novel heptyl phorolic acid cannabinoids content in different Cannabis sativa L. accessions. Talanta Vol 235. Dec 1 2021. DOI: 10.1016/j.talanta.2021.122704
13. Citti G, Linciano P, Russo F, et al.A novel phytocannabinoid isolated from Cannabis sativa L. with an in vivo cannabimimetic activity higher than Δ9-tetrahydrocannabinol: Δ9-tetrahydrocannabiphoral. 2019. Sci Rep 9, 20335. https://doi.org/10.1038/s41598-019-56785-1
14. Rossheim ME, LoParco CR, Henry D, Trangenstein, PJ, Walters ST. Delta-8, Delta-10, HHC, THC-O, THCP, and THCV: What should we call these products? J Stud Alcohol Drugs 2023 doi: 10.15288/jsad.23-00008
15. Ray C, Bylo MP, Pescaglia J, Gawenis JA, Greenlief CM. Delta-8 Tetrahydrocannabinol Product Impurities. Molecules 2022, 27, 6924. https://doi.org/10.3390/molecules27206924
16. de Oliveira MC, Vides MC, Lassi DLS, et al. Toxicity of Synthetic Cannabinoids in K2/Spice: A Systematic Review. Brain Sci. 2023, 13, 990. https://doi.org/10.3390/brainsci13070990
17. Dutta S, Selvam B, Das A, Shukla D. Mechanistic origin of partial agonism of tetrahydrocannabinol for cannabinoid receptors. J Bio Chem 2022 Apr. 298(4):101764. doi: 10.1016/j.jbc.2022.101764
18. Yano H et al. Subtle Structural Modification of a Synthetic Cannabinoid Receptor Agonist Drastically Increases its Efficacy at the CB1 Receptor ACS Chem Neurosci. 2023 Nov 1;14(21):3928-3940 MM



Eating Disorders Care and the Promises and Pitfalls of Artificial Intelligence

by Ellen E. Fitzsimmons-Craft, PhD & Nicholas C. Jacobson, PhD

Eating disorders (EDs) are common, serious psychiatric disorders that affect up to 10% of individuals in their lifetimes.[1] Furthermore, a recent systematic review and meta-analysis of 32 studies including 63,181 participants from 16 countries found that 22% of children and adolescents show disordered eating.[2]

EDs are associated with high psychiatric comorbidity, impairment, and mortality, with mortality from anorexia nervosa (AN) being the second highest of all psychiatric illnesses (second only to opioid use disorder).[1,3-7] Large cohort studies over recent decades have also suggested that both EDs and ED symptoms are on a dramatic rise.[8,9] EDs affect people of all genders, races, ethnicities, socioeconomic statuses, and body sizes and shapes, as well as those who live in rural areas and those who are food insecure—despite the stereotypes that abound surrounding these illnesses, EDs can affect anyone.[10]



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Table 1. Benefits and Risks of Generative AI in Mental Health

Type	Aspect	Description
Benefits	Increased Access to Care	Generative AI chatbots can provide 24/7 access to mental health support, helping to bridge the gap in care for individuals who may not have access to traditional treatment options.
	Support for Mental Health Providers	Generative AI can assist with administrative tasks, reducing clinician burnout and potentially improving the quality of care for patients.
	Enhanced Patient Engagement	AI-powered chatbots can engage patients through interactive and responsive conversations, encouraging consistent use and adherence to treatment plans.
	Personalized Treatment	Generative AI can offer tailored interventions based on individual user data, making the treatment more relevant and effective.
	Scalability	Generative AI tools can be deployed at scale, reaching a large number of individuals without significant additional costs.
Risks	Incorrect or Harmful Information	If not properly trained, AI models can provide inaccurate or harmful advice as seen in large foundation models.
	Dependence on Data Quality	The effectiveness of generative AI is heavily dependent on the quality and breadth of the data used to train the models.
	Potential for Misinterpretation	Generative AI may misinterpret user inputs, leading to responses that are not helpful or potentially harmful.
	Ethical and Privacy Concerns	There are significant concerns around data privacy, consent, and the ethical use of AI in mental health.

The costs of EDs are also staggering— $65 billion in the US. in 2018-2019 alone, with reduction in well-being associated with EDs valued at an additional $327 billion.[11] Despite the high personal and societal costs of these illnesses, access to care is extremely limited, with less than 20% of individuals with EDs ever receiving treatment.[12] The problem of access to care for EDs is even worse amongst individuals from racial and ethnic minority backgrounds—these individuals are significantly less likely than their White counterparts to be diagnosed with an ED, receive care for an ED, or to even be asked by a physician about ED symptoms.[10,13-15] There is clearly an urgent need for accessible, evidence-based care for EDs.

There are many reasons for the extremely wide treatment gap in EDs—denial and failure to perceive the severity of the illness, lack of problem identification by providers, stigma, shame, lack of knowledge about resources, and practical barriers such as cost, lack of accessible treatment, and long waiting lists.[16,17] Technology can provide a solution to many of these problems by offering opportunities for scalable approaches to problem identification and evidence-based intervention, anytime, anywhere. Indeed, in the past several decades, the field has made much progress with regard to developing and evaluating technology-based tools for EDs screening, prevention, and treatment,[18-20] with the majority of these tools involving use of traditional web-based programs or mobile apps with visual interfaces.

Generative Artificial Intelligence Use for Care Gap: Potential Challenges

However, we are now at a critical juncture in the field given recent advances in large language models (LLMs) and generative Artificial Intelligence (AI) (Table 1). Generative AI models can generate high-quality text, images, and other types of content based on the patterns and relationships in content in datasets on which the models have been trained. One of the most well-known of these tools is ChatGPT, which launched in November 2022 and is an LLM-based chatbot that can generate text and hold conversations. ChatGPT crossed one million users in just five days of launch and had 100 million active users by January 2023, setting the record for the fastest-growing platform in history at the time.[21]

On its face, this technology could be seen as having great potential for increasing access to high-quality care for EDs, both by supporting mental health providers and offering patient-facing support. On the provider side, generative AI chatbots could assist with documentation and administrative tasks, reducing a major source of clinician burnout and thus potentially improving the quality of care that can be provided to patients with EDs.[22] In one survey of psychiatrists, 70% of respondents somewhat agreed or agreed that "documentation will be/is more efficient" through use of AI tools.[22] Generative AI could also assist clinicians with hypothesis generation; for example, generating reasonable options for possible differential diagnoses.[23]

While it is clear there are numerous ways in which AI may help to address the wide treatment gap for EDs, we must balance these potential benefits against possible risks, while also instituting strong guardrails and regulations to maximize safety.

In the future, one could also see potential for generative AI tools to supplement clinician training in evidence-based treatments or to provide opportunities for simulated practice; it could also be used for quality monitoring and to help ensure fidelity to best practices. Finally, some work has shown that generative AI chatbots could aid humans in offering consistently high levels of support and empathy in patient-facing interactions.[24]

On the patient side, there is potential for generative AI tools to aid in providing mental health screening and self-guided interventions,[25] as well as to offer a venue for supplementing an individual's work in traditional therapy by offering opportunities for skill practice. Indeed, there are numerous reports of individuals using ChatGPT for mental health help.[26,27]

Research on use of chatbots for mental health support has begun to emerge, with tools being developed and evaluated for providing psychoeducation, delivering intervention, offering support, and boosting mental resilience.[28] The majority of mental health chatbots to date have operated on rule-based systems, which in contrast to generative AI, rely on pre-scripted content and operate based on decision trees and algorithms. A recent systematic review and meta-analysis of chatbots for promoting mental health and well-being found that chatbots significantly reduce symptoms of depression (Hedge's g 0.64 [95% CI 0.17–1.12]) and distress (Hedge's g 0.7 [95% CI 0.18–1.22]). (None of the included studies explicitly addressed EDs.)[28] The research also indicated that effects were more pronounced in chatbots that used generative AI, perhaps given the constraints of rule-based systems, which have limited capability to understand user context and intention.[28]

Within the EDs field, our own team also recognized the potential for chatbots as a way to scale access to intervention for EDs. We had the thought that a chatbot could deliver the core content from our effective web-based, cognitive-behavioral EDs prevention program (Student Bodies)[29] in a modern, engaging format—in bite-sized bits of information, showing up in text-like messages, with infographics, emojis, and warm, casual language, while also mimicking some aspects of support from a human coach, such as offering motivation and feedback. We developed the chatbot using a rule-based approach—with all responses written by our team—and the chatbot delivered the cognitive-behavioral program in a series of 10-minute conversations, designed to help users challenge unrealistic body ideals, engage in more healthful eating patterns, and learn more adaptive coping strategies. This is similar to the approach that is being used as of this writing by tools like Woebot and Wysa—chatbots that guide the user through carefully crafted pre-scripted conversations. Our own chatbot was carefully created over the course of more than a year, and our team painstakingly reviewed thousands of lines of conversation from hundreds of users to make iterative improvements.[30] We tested the effectiveness of the chatbot in a randomized controlled trial involving 700 women at high risk for an ED who were randomized to either the chatbot or waitlist control.[31] We found that the intervention group had significantly greater reductions in weight/shape concerns compared to the control group at 3- (d=0.20; p=.03) and six-month follow-up (d=0.19; p=.04). The odds of not developing an ED were also significantly higher in intervention vs. control at both 3- (OR=2.37, 95% CI [1.37, 4.11]) and six-month follow-ups (OR=2.13, 95% CI [1.26, 3.59]).[31]

In February 2022, the National Eating Disorders Association (NEDA) and the company that hosted the chatbot actually made the tool publicly available, following the publication of our strong research findings in the peer-reviewed literature.[31] Over the

course of a year of the chatbot being available on the NEDA website, thousands used it and found it to be helpful. It was most popular in the evening hours, and one-third used it on the weekend, when traditional sources of help are usually not available. Unfortunately, unbeknownst to our team, at some point, the company hosting the chatbot rolled out an AI component across its platform.[32] With this, users could receive erroneous and even harmful information, which in this case involved recommendations for unhealthy diet and exercise approaches that were directly in conflict with the evidence-based approaches for addressing disordered eating originally programmed into the rule-based portion of the bot. While the rule-based bot itself was demonstrated to be a helpful tool, both in the research and in the initial roll-out, this situation exemplified ways in which problems can be introduced in real-world deployment of AI tools.

Generative AI-based approaches are only as good as the data on which they have been trained, and at the same time, advice or content that might be appropriate for one group of individuals may not be appropriate for another group of individuals, highlighting challenges of developing a generative AI tool that can work for all people, for all issues. One report suggested that of the text on which GPT-4 (the LMM behind ChatGPT) is trained, 16% came from books and news articles and 84% from webpages, including not only Wikipedia but also lower-quality text sources like Reddit.[33,34] Within EDs, one report found that popular AI tools, which included ChatGPT and Bard, generated harmful content in response to ED-related prompts 41% of the time.[35]

In contrast to generative AI models that have not been specifically trained to deliver evidence-based treatment for EDs, our team designed and tested an expert-fine-tuned generative AI-powered chatbot, Therabot, for mental health treatment with a team of more than 70 persons across over 100,000 human hours. We then conducted the first randomized controlled trial (RCT) to test an expert-fine-tuned generative AI-powered chatbot.[36] Participants (N=210) were randomized to a four-week Therabot intervention (n=106) or waitlist control (WLC; n=104). Participants were stratified into clinically high-risk feeding and eating disorder (CHR-FED), major depressive disorder (MDD), or generalized anxiety disorder (GAD) groups based on baseline symptom severity. Primary outcomes included disorder-specific symptom changes from baseline to four and eight weeks. Secondary outcomes included user engagement, acceptability, and therapeutic alliance. The Therabot group showed large and significantly greater reductions in CHR-FED (d = 0.627-0.819), MDD (d = 0.845-0.903), and GAD (d = 0.794-0.840) symptoms relative to controls at post-intervention and follow-up. Therabot was well-received and well-utilized (average use >6 hours), and participants rated the therapeutic alliance comparable to human therapists. These results demonstrate the effectiveness of a fully generative AI therapy chatbot for treating mental health disorders, showing promise for CHR-FED, MDD, and GAD symptom reduction. Participants were engaged with Therabot, reported exceptional therapeutic alliance, and rated the intervention highly, highlighting the feasibility of fine-tuned generative AI chatbots for scalable, personalized mental health interventions.

As seen in the Therabot trial, despite some of the challenges that have been observed with tools based on generative AI, there remains the appeal of a tool that could provide a rich, personalized experience for the user and go beyond the bounds of a purely scripted interaction. In a generative AI tool, there is also the possibility that a user can have more control over the experience, more directly shaping the course of the conversation in ways that are more personally relevant to them.

Conclusion

Moving forward, while there remains high potential for tools based on generative AI to help increase access to high-quality care for EDs, there also remain important risks that have to be addressed. As has been shown, these tools are only as good as the data on which they have been trained and there is risk of "hallucinations" and delivery of incorrect and even harmful content.[37] As such, there is clearly a need for tight guardrails and human supervision when testing and even after deploying these tools.

On the provider side, providers need to be trained that generative AI-based approaches are simply tools and should not be viewed as a replacement for the work of a highly-trained provider. Patients need to also understand that these tools are not 1:1 replacements for providers and that there are risks of inaccurate information or advice being provided. On the whole, while it is clear there are numerous ways in which AI may help to address the wide treatment gap for

EDs, we must balance these potential benefits against possible risks, while also instituting strong guardrails and regulations to maximize safety.

References

1.Hudson JI, Hiripi E, Pope Jr HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biological Psychiatry. 2007;61(3):348-358.
2.López-Gil JF, García-Hermoso A, Smith L, et al. Global proportion of disordered eating in children and adolescents: A systematic review and meta-analysis. JAMA pediatrics. 2023;
3.Association AP. Treatment of patients with eating disorders, American Psychiatric Association. The American Journal of Psychiatry. 2006;163(7 Suppl):4-54.
4.van Hoeken D, Hoek HW. Review of the burden of eating disorders: mortality, disability, costs, quality of life, and family burden. Current Opinion in Psychiatry. 2020;33(6):521.
5.Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: A meta-analysis of 36 studies. Archives of General Psychiatry. 2011;68(7):724-731.
6.Smink FR, van Hoeken D, Hoek HW. Epidemiology, course, and outcome of eating disorders. Current Opinion in Psychiatry. 2013;26(6):543-548.
7.Haynos AF, Egbert AH, Fitzsimmons-Craft EE, Levinson CA, Schleider JL. Not niche: eating disorders as an example in the dangers of overspecialisation. The British Journal of Psychiatry. 2023:1-4.
8.Galmiche M, Déchelotte P, Lambert G, Tavolacci MP. Prevalence of eating disorders over the 2000–2018 period: a systematic literature review. The American journal of clinical nutrition. 2019;109(5):1402-1413.
9.Daly M, Costigan E. Trends in eating disorder risk among US college students, 2013–2021. Psychiatry Research. 2022;317:114882.
10.Schaumberg K, Welch E, Breithaupt L, et al. The science behind the academy for eating disorders' nine truths about eating disorders. European Eating Disorders Review. 2017;25(6):432-450.
11.Streatfeild J, Hickson J, Austin SB, et al. Social and economic cost of eating disorders in the United States: evidence to inform policy action. International Journal of Eating Disorders. 2021;54(5):851-868.
12.Kazdin AE, Fitzsimmons-Craft EE, Wilfley DE. Addressing critical gaps in the treatment of eating disorders. International Journal of Eating Disorders. 2017;50(3):170-189.
13.Becker AE, Franko DL, Speck A, Herzog DB. Ethnicity and differential access to care for eating disorder symptoms. International Journal of Eating Disorders. 2003;33(2):205-212.
14.Cachelin FM, Striegel-Moore RH. Help seeking and barriers to treatment in a community sample of Mexican American and European American women with eating disorders. International Journal of Eating Disorders. 2006;39(2):154-161.
15.Marques L, Alegria M, Becker AE, et al. Comparative prevalence, correlates of impairment, and service utilization for eating disorders across US ethnic groups: Implications for reducing ethnic disparities in health care access for eating disorders. International Journal of Eating Disorders. 2011;44(5):412-420.
16.Ali K, Farrer L, Fassnacht DB, Gulliver A, Bauer S, Griffiths KM. Perceived barriers and facilitators towards help-seeking for eating disorders: A systematic review. International Journal of Eating Disorders. 2017;50(1):9-21.
17.Ali K, Fassnacht DB, Farrer L, et al. What prevents young adults from seeking help? Barriers toward help-seeking for eating disorder symptomatology. International Journal of Eating Disorders. 2020;53(6):894-906.
18.Fitzsimmons-Craft EE, Balantekin KN, Graham AK, et al. Results of disseminating an online screen for eating disorders across the U.S.: Reach, respondent characteristics, and unmet treatment need. International Journal of Eating Disorders. Jun 2019;52(6):721-729.
19.SBIRT for Eating Disorders. https://eatingdisorderscreener.org
20.Linardon J, Shatte A, Messer M, Firth J, Fuller-Tyszkiewicz M. E-mental health interventions for the treatment and prevention of eating disorders: An updated systematic review and meta-analysis. Journal of consulting and clinical psychology. 2020;88(11):994.
21.Nerdynav. 107 up-to-date ChatGPT statistics & user numbers [April 2024]. Accessed June 10, 2024, https://nerdynav.com/chatgpt-statistics/
22.Blease C, Worthen A, Torous J. Psychiatrists' experiences and opinions of generative artificial intelligence in mental healthcare: An online mixed methods survey. Psychiatry Research. 2024;333:115724.
23.Kanjee Z, Crowe B, Rodman A. Accuracy of a generative artificial intelligence model in a complex diagnostic challenge. Jama. 2023;330(1):78-80.
24.Sharma A, Lin IW, Miner AS, Atkins DC, Althoff T. Human–AI collaboration enables more empathic conversations in text-based peer-to-peer mental health support. Nature Machine Intelligence. 2023;5(1):46-57.
25.Schueller SM, Morris RR. Clinical science and practice in the age of large language models and generative artificial intelligence. Journal of Consulting and Clinical Psychology. 2023;91(10):559.
26.Landwehr J. People are using ChatGPT in place of therapy—what do mental health experts think? . https://www.health.com/chatgpt-therapy-mental-health-experts-weigh-in-7488513
27.Hale E. ChatGPT is giving therapy. A mental health revolution may be next. https://www.aljazeera.com/economy/2023/4/27/could-your-next-therapist-be-ai-tech-raises-hopes-concerns
28.Li H, Zhang R, Lee Y-C, Kraut RE, Mohr DC. Systematic review and meta-analysis of AI-based conversational agents for promoting mental health and well-being. NPJ Digital Medicine. 2023;6(1):236.
29.Taylor CB, Bryson S, Luce KH, et al. Prevention of eating disorders in at-risk college-age women. Archives of general psychiatry. 2006;63(8):881-888.
30.Chan WW, Fitzsimmons-Craft EE, Smith AC, et al. The Challenges in Designing a Prevention Chatbot for Eating Disorders: Observational Study. JMIR Formative Research. 2022;6(1):e28003.
31.Fitzsimmons-Craft EE, Chan WW, Smith AC, et al. Effectiveness of a chatbot for eating disorders prevention: A randomized clinical trial. International Journal of Eating Disorders. 2022;55(3):343-353.
32.Jargon J. A chatbot was designed to help prevent eating disorders. Then it gave dieting tips. . Wall Street Journal. 2023, June 1;
33.King DR, Nanda G, Stoddard J, et al. An introduction to generative artificial intelligence in mental health care: considerations and guidance. Current psychiatry reports. 2023;25(12):839-846.
34.Zhao WX, Zhou K, Li J, et al. A survey of large language models. arXiv preprint arXiv:230318223. 2023;
35.Hate CfCD. AI and eating disorders: How generative AI is enabling users to generate harmful eating disorder content. 2023;
36.Heinz MV, Mackin DM, Trudeau BM, et al. Evaluating Therabot: A Randomized Control Trial Investigating the Feasibility and Effectiveness of a Generative AI Therapy Chatbot for Depression, Anxiety, and Eating Disorder Symptom Treatment. 2024;
37.De Freitas J, Cohen IG. The health risks of generative AI-based wellness apps. Nature Medicine. 2024:1-7.

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Hearing Loss: The Silent Pandemic That is Finally Being Heard

by Joshua M. Sappington, MD

The recent COVID-19 pandemic had a massive impact on the world socially and medically. Some of these were readily notable while others were a bit more insidious in their presentation. One such complaint which deceptively presented during and after the pandemic was that of hearing loss. Interestingly more and more individuals demonstrated increasing issues with hearing and understanding those around them during and following the pandemic. This is due to a multitude of factors including utilization of telecommunication with video and mask use often brought to light a patient's hearing loss that previously had gone unnoticed.



Substandard sound quality on telecommunications, poor audiologic situations, and the inability to visualize the mouths of individuals they were communicating with lead to patients obtaining consultation regarding their hearing. This led to a significant number of patients presenting with initial concerns about their ability to hear and interact with their world. The majority of patients were previously unaware of the extent of their hearing loss and many wondered if their hearing loss had rapidly progressed. Thankfully it was not an explosion of rapid onset hearing loss, rather the majority of cases were due to presbycusis or age related hearing loss (ARHL) being unmasked due to these audiologic situations. Additionally, cases of conductive hearing loss where there is a mechanical issue with sound transmission from the eardrum and/or ossicles to the cochlea and mixed hearing loss which are cases of conductive hearing loss in addition to sensorineural hearing loss were identified. These conductive hearing loss and mixed hearing loss are often seen in patients with otitis media, otosclerosis, and cholesteatoma.

Presbycusis is the hearing loss that comes with age or as I prefer to tell patients with wisdom. This type of hearing loss is nerve in origin and slowly progresses over the course of a lifetime. It is the most common form of hearing loss seen in consultation. There are significant genetic contributions which are multifactorial in nature and are influenced by noise exposure.

How We Hear

The way we hear is that sound is funneled by the pinna down the external auditory canal to the tympanic membrane. The tympanic membrane collects the sound wave and the three middle ear ossicles the malleus, incus, and stapes then deliver the mechanical energy to the cochlea. The movement of this fluid wave in the cochlea is transformed into electrical impulses that travel along the cochlear nerve to the brain which then processes this information. Hearing



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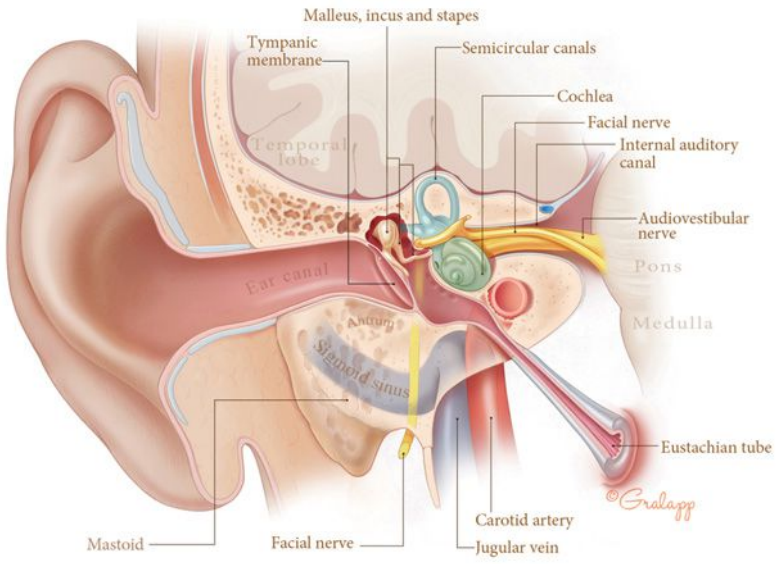
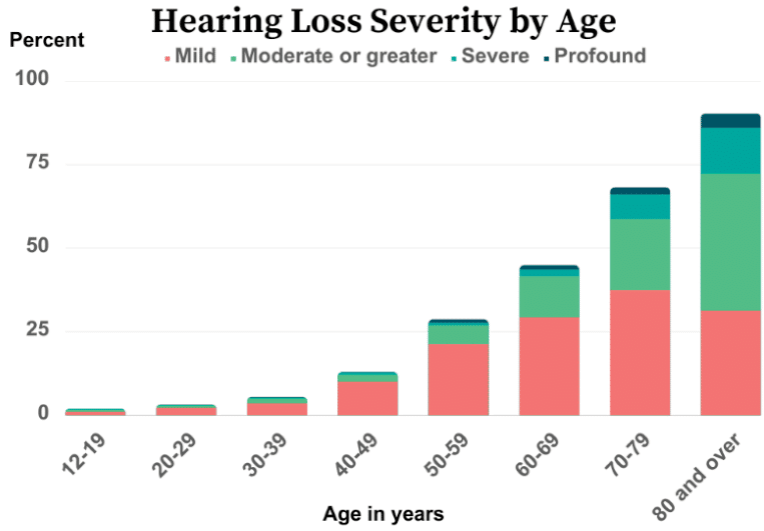


Figure 1. Illustrating the components of the external, middle, and inner ear.



Goman, Adele M. and Lin, Frank R. Prevalence of Hearing Loss by Severity in the United States. American Journal of Public Health. 2016. Found on the internet at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5024365/

Figure 2. Demonstration of hearing loss severity in the US as age increases.

has a mechanical component due to the tympanic membrane and ossicles and a nerve component secondary to the cochlea and the brain. Hearing loss is stratified as mild, moderate, moderate-severe, severe, and profound and described as sensorineural, conductive or mixed. The components of the external, middle, and inner are illustrated in Figure 1.

Scope and Impact of Hearing Loss

There are a small number of medical conditions which are truly inherent to the human condition and hearing loss is one. The World Health Organization estimates that over 430 million or roughly 5% of the world's population have a hearing loss which requires rehabilitation.[1] This data includes 34 million children worldwide which has significant long term implications in educational and compensation outcomes.[1] Hearing loss is deemed to be disabling when a loss greater than 35 decibels is present. It is currently estimated that approximately over 700 million people or roughly 1 in 10 by 2050 will have a hearing loss which is deemed to be disabling.[1] Hearing loss increases with age and this is particularly true as patients transition into their mid- 60s. Approximately 2% of patients aged 45-54 have disabling hearing loss, this number increases to 8.5% for patients aged 55-64 and further increases to nearly 25% for patients aged 65-74. For patients who are 75 and older approximately 50% will have hearing loss which impacts their daily life.[2] Figure 2 demonstrates graphically the increase of hearing loss as patients age.

These statistics demonstrate the impact that hearing loss has as our population ages. According to the US Census the American population aged 65 and older grew five times faster than the total population over the 100 years from 1920-2020.3 In 2020 approximately one in six persons were over the age of 65 this has increased from less than one in 20 persons in 1920.[3] The continued aging of America and the world as a whole means that number of patients with hearing loss will only increase and the impact of hearing loss will also increase. Recently the American Academy of Otolaryngology released clinical practice guidelines for age related hearing loss.[4] Within these guidelines were strong recommendations

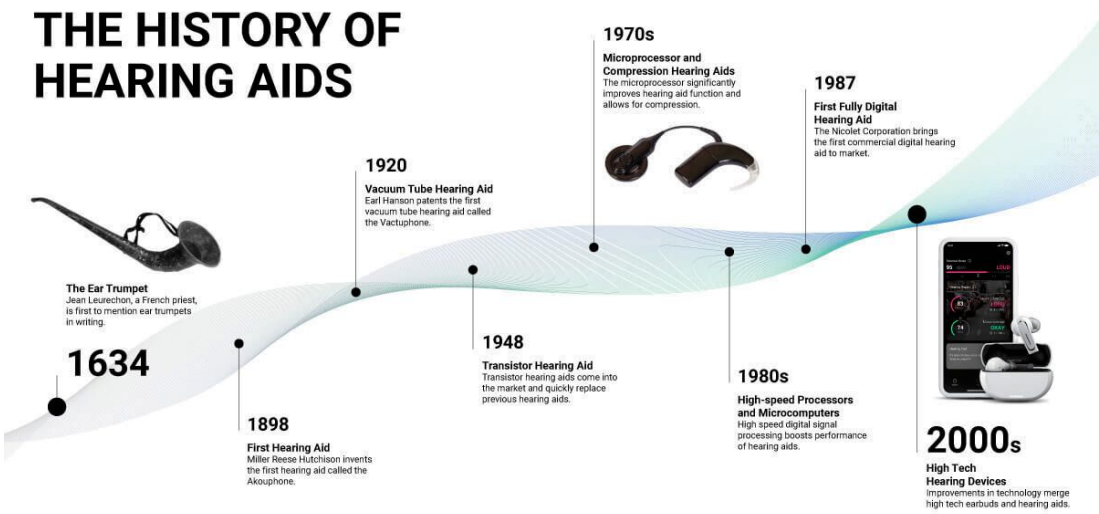


Figure 3. Demonstrating the progression and history of amplification.

for evaluating patients with formal audiologic testing, fitting patients with amplification, referral for cochlear implantation evaluation if the patient loses benefit from amplification.[4]

Evolution and Impact of Amplification for Patients

Patients with hearing loss benefit immensely from hearing restoration. The mainstay of hearing restoration therapy are hearing aids. Hearing aids work by amplifying sounds and presenting it to the eardrum and ossicles for sound transmission. Thankfully today's hearing aids are not our grandparents' hearing aids that we remember from our childhood. The hearing aids of yesteryear were analog technology that were large, bulky, poor performing, and "for old people." This amazing progression is demonstrated in Figure 3. Due to these factors patients would avoid hearing aids like the plague and would do anything they could to abstain from hearing aids. I consult with patients every day regarding their hearing loss and thanks to the improvements in technology with digital hearing aids the improvement in audiologic performance that they obtain with amplification is striking.

Digital hearing aids are discrete, low profile, and patients comment that friends and family note that they are hearing, not that they have a hearing aid. The digital processing allows for improved performance in complex audiologic situations such as meetings, dinners and family gatherings. Additionally, digital hearing aids have the ability to pair via Bluetooth with cellphones and other technical devices which greatly improves their efficacy. Many of my pediatric patients note that their hearing aids are better than their peers' headphones or earbuds. Due to this marked improvement in performance hearing aids are seen as a fantastic option rather than a last resort. Figure 4 demonstrates the differences between digital and analog hearing aids.

A key component to a discussion of hearing aids is cost. Traditionally hearing aids have been an expensive out of pocket cost not covered by insurance. Thankfully this has started to change and more patients have insurance coverage for these devices.[5] Recently over the counter (OTC) hearing aids have become available for patients over the age of 18 with mild to moderate hearing loss.[6] These hearing aids are cheaper and more readily available than professionally fit hearing aids but these come with concerns and limitations. One concern being that without medical evaluation prior to fitting hearing aids medical conditions such as asymmetric hearing loss due to tumors, cholesteatomas, and chronic otitis media can be missed. This can lead to a delay in diagnosis for these conditions and therefore a delay in care for patients and potentially worse outcomes. There has been significant concern from professional societies including the American Academy of Otolaryngology-Head and Neck Surgery, American Academy of Audiology and others regarding the safety of OTC hearing aids.[7,8] There is a clear balance which has been strived for between affordability, accessibility, and safety to ensure that patients are able to obtain hearing aids at reasonable cost but also do so safely.

I often make the analogy of OTC reading glasses to OTC hearing aids. If you are looking for the best

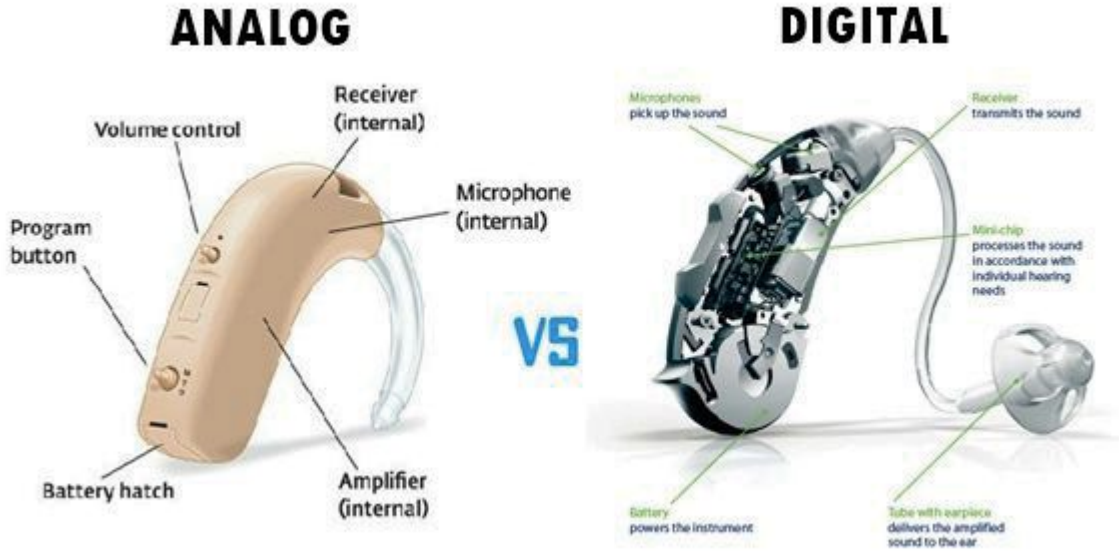


Figure 4 Analog vs Digital Hearing Aid

experience a professionally fit pair of glasses or hearing aid will give you that level of performance. Anyone who has worn glasses or contacts knows that the fit of a pair of glasses or contacts is determined by the skill and expertise of the ophthalmologic team that one works with. Hearing aids are completely analogous to this with patients' experience being tied to their fit with the hearing aid. Unfortunately, I see patients who are hesitant to pursue amplification due to having friends and family members who are or have been poorly fit with hearing aids and therefore have a negative experience with hearing aids. I often make the analogy of a hearing aid being like tailored clothing, you can spend a lot of money on a suit or dress but if it does not fit you the end result will be far from ideal. The manufacturer and cost of the hearing aid is of relative inconsequence to the overall fit of the hearing aid. Patients do not need to purchase top of the line hearing aids and a well fit hearing aid should last five to seven years. When presented with this hearing aids are often seen as being "worth it" to patients as they are used every day for years.

Link Between Neurocognitive Decline and Hearing Loss

A simple question to ask after all of this discussion is why does hearing loss matter and why should hearing aids be a consideration for patients? For generations hearing loss has been seen as a price of aging and patients "deal with it." With hearing loss there can be loss of work with associated compensation loss, social isolation with associated depression, and the inability to understand and integrate information which has the potential to negatively impact neurocognitive health.[9,10,11] If patients are unable to hear and communicate effectively their employment status and/or compensation can be negatively impacted.[9] Additionally, there can be significant safety concerns for patients who are unable to hear and interact with their work environment.[9,10] Evolving studies demonstrate links between hearing loss with social isolation and depression.[11,12] Additionally, there are concerns and ongoing studies to investigate the relationship of hearing loss and neurocognitive decline.[13] A recent cohort population study was completed with 573,088 persons to evaluate the relationship of hearing loss with dementia.[14] The study demonstrated that having hearing loss was associated with an increased risk of dementia for impacted patients with a hazard ratio of 1.07 when compared to patients without hearing loss.[14] Notably patients with hearing loss who did not have hearing aids had a higher risk of developing dementia compared to those who had hearing loss and utilized hearing aids. The hazard ratios for these patient populations was 1.20 and 1.06 respectively.[14] In 2020 the Lancet Commision on Dementia concluded that hearing loss in middle age and late in life was the single largest potentially modifiable risk factor for dementia at approximately 8%.[15,16] There will be additional studies which further delineate the complex relationship of hearing loss and dementia. Additionally, this will impact our understanding of the true morbidity

associated with hearing loss in addition to the quality of life component that patients experience.

An additional consideration is the financial burden that hearing loss imposes on our world. A current estimate from the WHO estimates that unaddressed hearing loss poses an annual global cost of approximately 980 billion US dollars.[17] This cost includes health costs, educational support, loss of productivity and societal costs.[17] If we were to look specifically at severe to profound hearing loss recent analysis has demonstrated that the cost of cochlear implantation and rehabilitation was offset by the gain in productivity for patients.[18] Amazingly this does not include the cost of hearing devices nor does it likely include the cost for caregivers of those with hearing loss. It is currently estimated that more than one billion young adults are at risk for permanent hearing loss due to unsafe listening practices with personal listening devices.[17] Given the natural progression of hearing loss throughout life this number of young individuals at risk for hearing loss will only increase the burden of hearing loss in the future. Investment in hearing restoration today will have a significant positive impact for years to come for patients young and old.

Conclusion

One thing that the recent pandemic demonstrated is that as human beings we are intrinsically social beings. Hearing loss can be slowly progressive isolating patients from family, friends, and a variety of situations which make life worth living. While there are further studies which are needed to demonstrate the quality of life and neurocognitive benefits of hearing aids we can agree on one thing.

Life is far too short to not hear and interact with the people you care about and situations that matter. Thankfully, hearing aids have progressed markedly over the years and the technology only continues to improve. Patients can have significant benefit from appropriately fit amplification which helps to give them their life back. Hearing loss is no longer the price of wisdom as patients have a wonderful option to improve their hearing.

References

1.World Health Organization (2024, February 2). Deafness and hearing loss. World Health Orginization Deafness and Hearing Loss. Retrieved February 10, 2024, from https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

2. National Institute on Deafness and Other Communication Disorders (2021, March 25). Quick statistics about hearing. Retrieved February 11, 2024, from https://www.nidcd.nih.gov/health/statistics/quick-statistics-hearing#:~:text=Nearly%2025%20percent%20of%20those,older%20have%20disabling%20hearing%20loss.

3.United States Census Bureau (2021, March 25). U.S. Older Population Grew From 2010 to 2020 at Fastest Rate Since 1880 to 1890. Retrieved February 11, 2024, from https://www.census.gov/library/stories/2023/05/2020-census-united-states-older-population-grew.html

4. Tsai Do, B.S., Bush, M.L., Weinreich, H.M., Schwartz, S.R., Anne, S., Adunka, O.F., Bender, K., Bold, K.M., Brenner, M.J., Hashmi, A.Z., Keenan, T.A., Kim, A.H., Moore, D.J., Nieman, C.L., Palmer, C.V., Ross, E.J., Steenerson, K.K., Zhan, K.Y., Reyes, J. and Dhepyasuwan, N. (2024), Clinical Practice Guideline: Age-Related Hearing Loss. Otolaryngol Head Neck Surg, 170: S1-S54. https://doi.org/10.1002/ohn.750

5. Gatta, F., & Friend, A., Au.D. (2023, September 12). Are Hearing Aids Covered By Insurance In 2024? Forbes Health. Retrieved February 3, 2024, from https://www.forbes.com/health/hearing-aids/hearing-aids-insurance-coverage/

6. Food and Drug Adminstration (2023, May 3). OTC Hearing Aids: What You Should Know. Food and Drug Administration. Retrieved February 5, 2024, from https://www.fda.gov/medical-devices/hearing-aids/otc-hearing-aids-what-you-should-know

7.American Academy of Otolaryngology-Head and Neck Surgery (2023, May 3). AAO-HNS Summary: FDA Over-The-Counter Hearing Aids Final Rule. Retrieved February 5, 2024, from https://www.entnet.org/advocacy/regulatory-advocacy/over-the-counter-sale-of-hearing-aids/aao-hns-summary-fda-over-the-counter-hearing-aids-final-rule/#:~:text=The%20agency's%20creation%20of%20a,fitting%20adjustment%20by%20an%20audiologist.

8. American Academy of Audiology (n.d.). Consumers and OTC Hearing Aids FAQs Consumers Need to Know. Retrieved February 5, 2024, from https://www.audiology.org/consumers-and-patients/managing-hearing-loss/consumers-and-otc-hearing-aids/

9. Dobie, R., & Van Hemel, S. (2004). National Research Council (US) Committee on Disability Determination for Individuals with Hearing Impairments (pp. 163-171). National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK207836/#:~:text=For%20those%20individuals%20with%20early,result%20in%20limited%20job%20opportunities.

10. Haile , L., et al. (2024). Hearing Loss Prevalence, Years Lived With Disability, and Hearing Aid Use in the United States From 1990 to 2019: Findings From the Global Burden of Disease Study. EAR & HEARING, 45(1), 257–267. https://doi.org/0.1097/AUD.0000000000001420

11. Moradi S, Engdahl B, Johannessen A, Selbæk G, Aarhus L, Haanes GG. Hearing loss, hearing aid use, and performance on the Montreal cognitive assessment (MoCA): findings from the HUNT study in Norway. Front Neurosci. 2024 Jan 8;17:1327759. doi: 10.3389/fnins.2023.1327759. PMID: 38260012; PMCID: PMC10800991.

12. Bigelow RT, Reed NS, Brewster KK, Huang A, Rebok G, Rutherford BR, Lin FR. Association of Hearing Loss With Psychological Distress and Utilization of Mental Health Services Among Adults in the United States. JAMA Netw Open. 2020 Jul 1;3(7):e2010986. doi: 10.1001/jamanetworkopen.2020.10986. PMID: 32687587; PMCID: PMC7372323.

13. Bisogno A, Scarpa A, Di Girolamo S, De Luca P, Cassandro C, Viola P, Ricciardiello F, Greco A, Vincentiis M, Ralli M, Di Stadio A. Hearing Loss and Cognitive Impairment: Epidemiology, Common Pathophysiological Findings, and Treatment Considerations. Life (Basel). 2021 Oct 17;11(10):1102. doi: 10.3390/life11101102. PMID: 34685474; PMCID: PMC8538578.

14. Cantuaria ML, Pedersen ER, Waldorff FB, et al. Hearing Loss, Hearing Aid Use, and Risk of Dementia in Older Adults. JAMA Otolaryngol Head Neck Surg. 2024;150(2):157–164. doi:10.1001/jamaoto.2023.3509

15. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-46.

16. Lin FR. Age-Related Hearing Loss. N Engl J Med. 2024 Apr 25;390(16):1505-1512. doi: 10.1056/NEJMcp2306778. PMID: 38657246.

17. World Health Organization (2024, February 2). Deafness and hearing loss. Retrieved February 22, 2024, from https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

18. Cejas, I., Barker, D.H., Petruzzello, E., Sarangoulis, C.M. and Quittner, A.L. (2024), Costs of Severe to Profound Hearing Loss & Cost Savings of Cochlear Implants. The Laryngoscope. https://doi.org/10.1002/lary.31497

MM

Getting Involved: Let's Hear Your Voice!

by David L. Pohl, MD

Getting others to join you really starts to amplify our medical voice. Additionally, if they are already MSMA members you may help encourage them to become more involved if they realize they won't be a lone voice in the wilderness.

Now that many of us are getting settled "into" the new academic year, it is also time to start thinking of the new calendar year, and the challenges it will bring. Like many new year's resolutions, we start thinking about how to improve our lives, both personally and professionally.

In the last issue, we discussed how we can improve our relationships with our patients. We now need to consider how we can improve healthcare for our patients with action that doesn't directly involve patient care. As we have noted before, one of the things we can do is advocate for our patients. One of the most effective ways we can do that is to get more actively involved with our medical organizations. This can occur at multiple levels—local, state, national, and international; as well as by general and specialty interests.



David L. Pohl, MD, is a Radiologist from St. Louis, Missouri, and the 2024-2025 MSMA President.

Here we will consider involvement at the state and local levels. The most basic way, and many times the most effective way, to get involved is to do just that. Find out when and where your local component society meeting will be held and attend it. If you don't know which component society you belong to, then visit MSMA's website at www.msma.org or email MSMA at communications@msma.org. If you find your component society is one of those that are inactive, consider gathering a group of fellow physicians in your area to rejuvenate it into being once again.

This segues to the next action item which is to invite other physicians in your area to join you. Things are much easier when you have a friend or colleague with you. Getting others to join you really starts to amplify our medical voice. Additionally, if they are already MSMA members you may help encourage them to become more involved if they realize they won't be a lone voice in the wilderness.

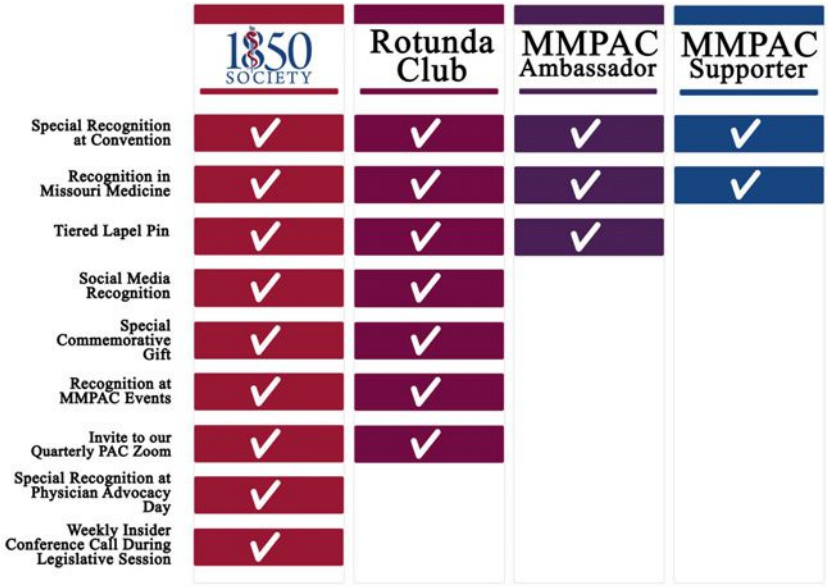
So how do we amplify the medical voice? We realize that not everyone can leave their practice routinely to lobby for medicine and our patients in Jefferson City during the legislative session. For that reason, we have our own lobbyists to present our concerns and positions to the legislature. They represent us, and only us. We are grateful to have several lobbyists who can cover multiple committee meetings and hearings when they overlap (as they all too often

do). What gives strength to our voice is our contributions to the Missouri Medical Political Action Committee (MMPAC). There are several levels of contribution and support which can be tailored to your desires and abilities. Your contributions enable us to more effectively represent you.

Next year, we will hold our Physician Advocacy Day, aka White Coat Day on March 4, 2025. This is one day in which the MSMA, in conjunction with the Missouri Association of Osteopathic Physicians and Surgeons attend the legislative session in our white coats to personally speak to our Senators and Representatives. It makes quite an impression to have the halls of the State House filled with physicians. Though it may take some planning, please try to arrange your practice needs to allow for your attendance on this day, or at least the morning, so we can maximize our effectiveness.

Lastly, please let your colleagues know of your involvement in organized medicine; and how much our voice would be amplified if they also get more actively involved. This is especially important if we promote membership and active participation to those who, for whatever reasons, have not yet joined our ranks. It would be encouraging to see our ranks grow as we actively work for our patients through advocacy. **MM**





The Extraordinary Journey of a Physician-Artist

by Susie Sharpe, MD

Life is a precious, a one-time gift.
How will you achieve your dreams with the one life you have?
I share four keys from my recent TEDx talk.

When I introduce myself as a physician-artist, I often receive puzzled looks. Medicine and art may seem mutually exclusive, yet my journey shows that it is possible to pursue other passions alongside a fulfilling medical career. Reflecting on my 30-year medical career, I've experienced countless unforgettable patients and moments filled with joy, tears, and gratitude. Yet, to feel complete, I needed to fulfill more than one dream.

As physicians, we understand the preciousness of life. In my 2023 TEDx talk (https://www.youtube.com/watch?v=h3WWnhgasvo), I spoke about life as a one-time gift meant to be lived to its fullest. I began by recounting an unforgettable night on call as a medical resident at Yale New Haven Hospital.

It was 5:00 a.m. I had been up all night trying to keep my patient alive. He was on a ventilator with multi-organ failure and hadn't produced urine for days. Despite all my efforts, nothing seemed to help. Then, I saw a few drops of urine trickling into the Foley bag—the first sign my patient was turning around! Overwhelmed with joy, that one ounce of urine felt like "liquid gold." At that moment, I understood the preciousness of life deep in my soul. I realized I had truly become a physician.



When I was an infant in Korea, I nearly died from complications of measles, but a physician there saved my life. Fast forward 30 years, and I found myself paying it forward by saving lives as a physician.

Interestingly, becoming a physician was not my original plan. I grew up dreaming of becoming an artist and studying art in Paris. But everything changed when my family moved from Korea to the United States. At 16, I found myself in a New York City high school, unable to speak any English and feeling utterly lost and desperate.



Susie Sharpe, MD, at three-years-old.

Realizing I had no one to rely on and needed to adapt, I adopted the American name 'Susie.' Faced with a desperate reality, I gave up my dream of becoming an artist and chose a career that offered certainty I could support myself while helping others. However, becoming a physician felt like an utterly impossible dream for a high schooler who didn't speak English. At Wesleyan University, still struggling with English, I recorded all the lectures and chose to major in chemistry—

Susie Sharpe, MD, is a physician-artist-TEDx speaker who recently retired from medicine after a 30-year career. She practiced in Springfield, Missouri, Seattle, and Sarasota. In addition to her medical career, she is an internationally recognized artist, and her work can be viewed at https://art.susiesharpe.net.
This biography first appeared in the *Greene County Medical Society Journal*.



Susie Sharpe, MD, at her recent exhibit in Sarasota, Florida, wearing a dress featuring her own artwork. Her works can be viewed at https://art.susiesharpe.net.

despite having no interest, but because it required the least English. In medical school, I relied on a Korean-English dictionary daily and worked multiple jobs to pay for my education. Fifteen years after arriving in the U.S. without speaking any English, I graduated from Yale Medical School and completed my residency at Yale-New Haven Hospital, achieving what had once seemed like an impossible dream. I quickly jumped into internal medicine practice and became very busy. I love helping patients, easing their physical and mental suffering, and making a difference every day. Medicine is a noble, fulfilling profession, and I'm proud of the impact I've had throughout my career.

However, about 10 years ago, a near-car crash made me realize that if I had died that night, I would never have lived my original dream. Realizing we only have one life to live, I began studying art whenever I could while maintaining a busy practice. Eventually, I held a solo art exhibit—then many more. For the past decade, I've pursued both medicine and art simultaneously, often painting late into the night after a full day at the clinic and caring for my children.

I fully embrace my identity as a physician-artist and have exhibited my art worldwide, from New York to Paris, from Brussels to Madrid—all while maintaining a busy internal medicine practice. As a physician, my goal has always been to lessen suffering. As an artist, my mission is to bring beauty, joy, and healing through my vibrant, bold, and uplifting artwork. I ship my art globally, and the proceeds go toward my charitable work.

During my 30-year medical career, I've learned deeply that life is a precious, one-time gift. Many patients, near the end of their lives, express regrets about unfulfilled dreams. Research shows that only 2% of people fulfill their life dreams. How will you achieve yours with the one precious life you have? Here are four keys I shared in my TEDx talk:



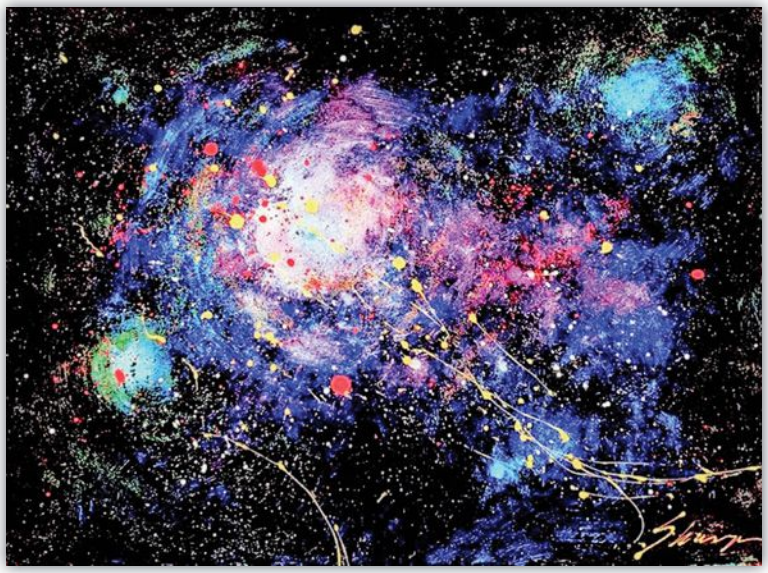
"Carmen Serenade" by Susie Sharpe,MD.



"Celebration of Life" by Susie Sharpe, MD

1. Get clear on your dream. Imagine today is your last day. Is there a dream you wish you had pursued?
2. Visualize your dream. Picture it in great detail, as though it's already a reality. Spend five minutes every morning and night visualizing it.
3. Know your inner enemies. Identify what holds you back: S.E.F.U. — Self-doubt, Excuses, Fears, and Unworthiness. Recognize them, but take action despite them.
4. Take the first step. Show up every day and work towards your dream.

One of my paintings, *Follow Your Dream to the Stars*, represents pursuing and achieving a dream that seems so out of reach. As a 16-year-old immigrant facing "enormous obstacles, I became a physician-artist. You, too, can achieve your dream despite your circumstances. Life is a one-time gift. As Mae West said, "You only live once. But if you do it right, once is enough."



"Follow Your Dreams to the Stars" by Susie Sharpe, MD, exhibited at the recent Paris International Art Fair.

Being a physician is one of the most demanding professions of all, but it is still possible to pursue passions outside of medicine. I hope my journey inspires you to believe that it can be done.

Last fall, I spoke about physician wellness and burnout prevention at the American College of Physicians Missouri Chapter conference. I emphasized the importance of finding time for ourselves and pursuing passions outside of medicine. One of my missions is to help fellow physicians stay mentally healthy and remain in the profession. Our society needs physicians, and finding a balance between societal demands and personal fulfillment is crucial.

I am immensely proud of my fellow physicians and honored to be part of this noble profession. I look forward to hearing from you. (https://art.susiesharpe.net) **MM**

Correspondence

Inspiring Lives & Careers - Dr. Dehner

Louis P. Dehner, MD's article, "A Path Chosen Long Ago and where It Went," (July/August 2024) was so exceptional I am compelled to write you in its continued support. Although many of the particulars are different, I felt like I was reading my own story—medical school, residency, service in the armed forces, life's work here and there and here again as a calling; interaction with coercive change forced by technology and the corporate need for profit. Dr. Dehner's conclusions mirror mine as big picture issues affect medical education "with its shift from a meritocracy to a holistic admission process, the elimination of academic standards of performance, and abandonment of board scores."

I fully agree that medicine with its 2,000-year history of caring for patients has "become incorporated into the current social-political ideology with its agenda."

In addition, the author, whom I have known personally for many decades, is impeccable in all spheres: personal, professional, social, and relational. He is a "physician" in the finest sense of the word. Despite earning international fame, he is as trustworthy as salt and 'Pepper' (his nickname). He has always been active in the medical society for all the right reasons—for the benefit of our noble profession.

Kudos to you and the staff for publishing such a high-quality article. Let's have more of them.

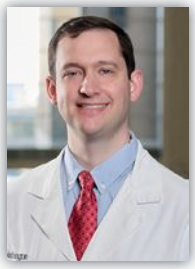
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In the News

Missouri Medicine Announces New Board Member

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

David B. Liss, MD, St. Louis, the new Editorial Board member for Toxicology/ Addiction Medicine. He is Division Chief for Medical Toxicology; Program Director, Medical Toxicology Fellowship; Associate Professor, Emergency Medicine, at Washington University School of Medicine in St. Louis, Missouri.



He replaces **Douglas M. Burgess, MD**, University Health at the University of Missouri - Kansas City, whom we thank for his service.

Marc B. Hahn Recognized by Ingram's Magazine on His Impact on Missouri



Marc B. Hahn, DO, president and CEO of Kansas City University (KCU), has been recognized as one of Ingram's exclusive list of '50 Missourians You Should Know.' Hahn's visionary leadership has positioned KCU as a leading institution in medical and health sciences education and innovation.

"I am humbled by this recognition, for it serves as a reminder of the power of education and innovation to drive positive change in health care," Hahn said. "And I am proud to be part of the Kansas City University team that is driving such positive change."

KCU has experienced significant growth under Hahn's leadership, opening a second campus in Joplin, Missouri, and expanding its osteopathic medical school into one of the nation's largest and most impactful for primary care.



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Update on Asthma Management Guidelines

by Sarah Dubin MD, Pooja Patak, MD & Diana Jung, MD

Optimal asthma management requires a multifaceted approach, addressing clinical, social, and environmental factors to improve outcomes and enhance quality of life.



Sarah Dubin MD, MPH, (pictured) is Associate Professor of Medicine and Pooja Patak, MD, and **Diana Jung, MD**, are Pulmonary and Critical Care Fellows; all are in the Department of Pulmonary and Critical Care Medicine, University of Missouri-Kansas City, Kansas City, Missouri.

Abstract

The Global Initiative for Asthma (GINA) was established in 1993 and publishes a yearly global strategy to improve asthma awareness, prevention and management of asthma worldwide, based on a review of the most updated evidence. The current 2024 GINA update advises that all adults and adolescents with asthma receive inhaled corticosteroid (ICS)-containing medication and should not be treated with short acting beta agonist (SABA) alone. The 2024 GINA strategy divides treatment into two 'Tracks": Track 1 (preferred Track), the reliever is as-needed combination low dose ICS-formoterol; Track 2 uses SABA as the reliever along with a separate ICS inhaler. The updates also stress the importance that individuals with asthma should have a written asthma action plan, and asthma management should be tailored to the individual to help reduce the occurrence of serious exacerbations, fatalities, and hospitalizations.

Introduction

Asthma is the most prevalent chronic non-communicable condition impacting over 260 million individuals globally. In the United States, asthma prevalence is 7.9% with higher prevalence among individuals residing in areas with lower annual household incomes. According to the Global Burden of Disease report, asthma contributes to 42,000 deaths annually worldwide.[1] Avoidable factors, such as under-prescription of inhaled glucocorticoids or inadequate access to medical care, contributes to the majority of asthma-related deaths. This overview delves into the goals and components of asthma management, applicable to adult populations and reviews the Global Initiative for Asthma (GINA) 2024 guidelines.

According to GINA, asthma is defined as a heterogeneous disease characterized by chronic airway inflammation. Patients have recurrent respiratory symptoms including shortness of breath, wheezing, chest tightness, coughing, and fatigue which limits expiratory airflow. Spirometry with before and after bronchodilator administration, peak expiratory flow (PEF) measurement, and flow-volume loop helps further assist in asthma diagnosis and management. A scooped, concave shape of the expiratory segment of the flow-volume loop indicates intrathoracic airflow obstruction, a characteristic feature of asthma and other obstructive lung conditions. Normal pulmonary function tests can be seen in patients with asthma, especially when patients is otherwise asymptomatic. However,

some asthma patients experience persistent airflow limitation regardless of symptomatology, often associated with long-standing, poorly controlled disease.

After diagnosis, there are two primary goals of treatment. Symptom control focuses on reducing symptoms, limiting sleep disturbance, and minimizing limitations in daily life. Risk reduction focuses on maintaining normal lung function, preventing exacerbations or death, and minimizing medication side effects. Asthma Control Test (ACT) is a standard assessment that evaluates the effectiveness of current asthma management (Figure 1). If inadequately controlled, treatment should be escalated through a "step up" therapy. Well controlled asthma patients experience symptoms requiring quick-reliever medication on less than two days/week, nighttime awakenings less than two nights/month, maintain lung function or forced expiratory volume in 1 second (FEV1) within normal range (or 20% of personal best value), and encounter no more than one exacerbation/year necessitating urgent care or oral glucocorticoids.

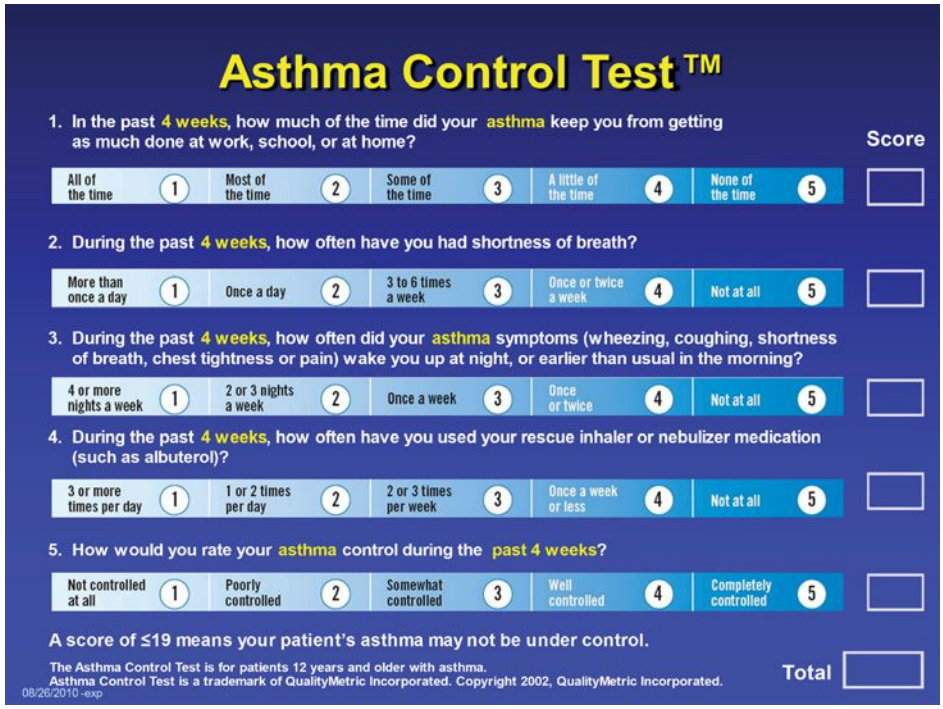


Figure 1. Asthma Control Test

Regular utilization of SABA, even for a duration as short as one to two weeks, can lead to detrimental effects such as beta-receptor downregulation, diminished broncho-protection, and rebound hyper-responsiveness. Increased SABA usage correlates with adverse clinical outcomes; dispensing three or more SABA inhalers, annually is linked with a heightened risk of exacerbations, while dispensing twelve or more SABA inhalers annually significantly elevates the risk of mortality.

Tract 1

For this reason, studies that looked at as-needed-only low dose ICS-formoterol compared with the former "standard" as-needed SABA only treatment. Two studies showed the risk of severe exacerbations was reduced by 60-64% in those that used as-needed ICS-formoterol in Steps 1-2 of the Track 1 of GINA Guidelines versus as-needed SABA (Figure 2).[2, 3] GINA now advises that all adults and adolescents with asthma should have access to ICS-containing inhalers (e.g., budesonide-formoterol 80 mcg-4.5 mcg or 160 mcg-4.5 mcg), administering one to two inhalations as needed for asthma symptoms to diminish the occurrence of serious exacerbations, fatalities, hospitalizations, and exacerbations necessitating oral steroid treatment.[4, 5]

The step-up therapy outlined in the GINA guidelines involves gradual increase in medication dosage or type to achieve better asthma control (Figure 1).[4] If asthma symptoms persist, therapy is escalated by transitioning to low-dose maintenance ICS-formoterol (Step 3), then gradually progressing to medium-dose maintenance ICS-formoterol (Step 4). Steps 3-5 include Single Maintenance and Reliever Therapy (SMART), with ICS-formoterol used as both a maintenance and reliever inhaler help to reduce severe exacerbations compared with ICS or ICS-LABA plus SABA reliever.[4] If symptoms persistent to Stage 5, additional long-acting muscarinic antagonist (LAMA) and biologic agents may be introduced. The primary aim is to attain and sustain asthma control using the minimal necessary medication.[4, 5]

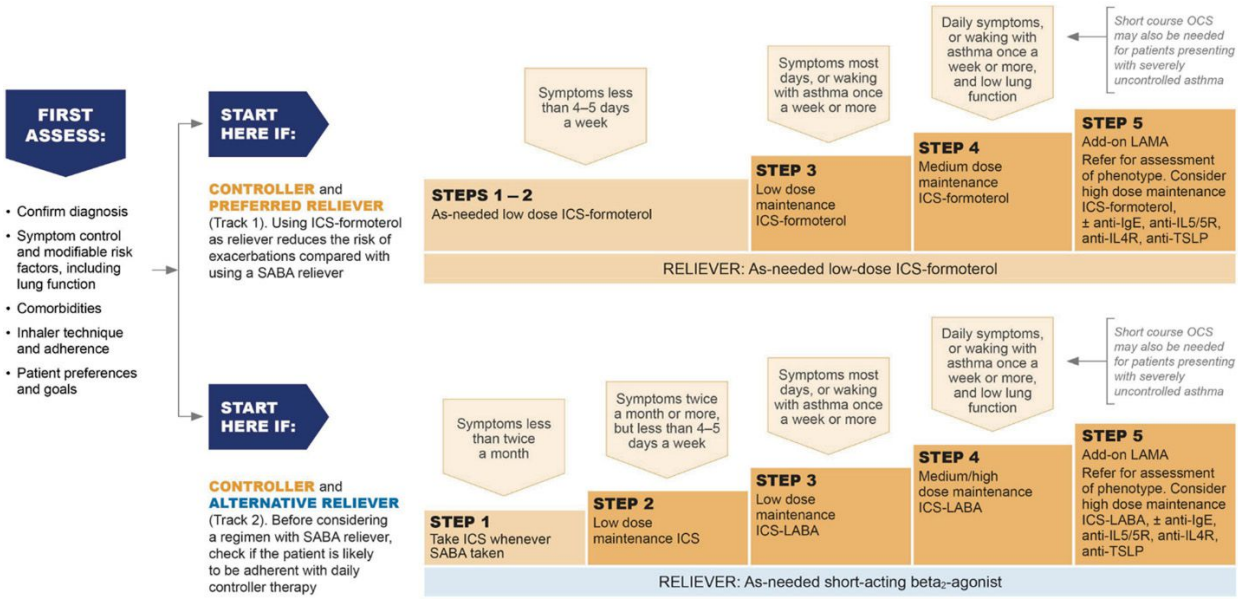


Figure 2. Steps in GINA Guidelines

Track 2

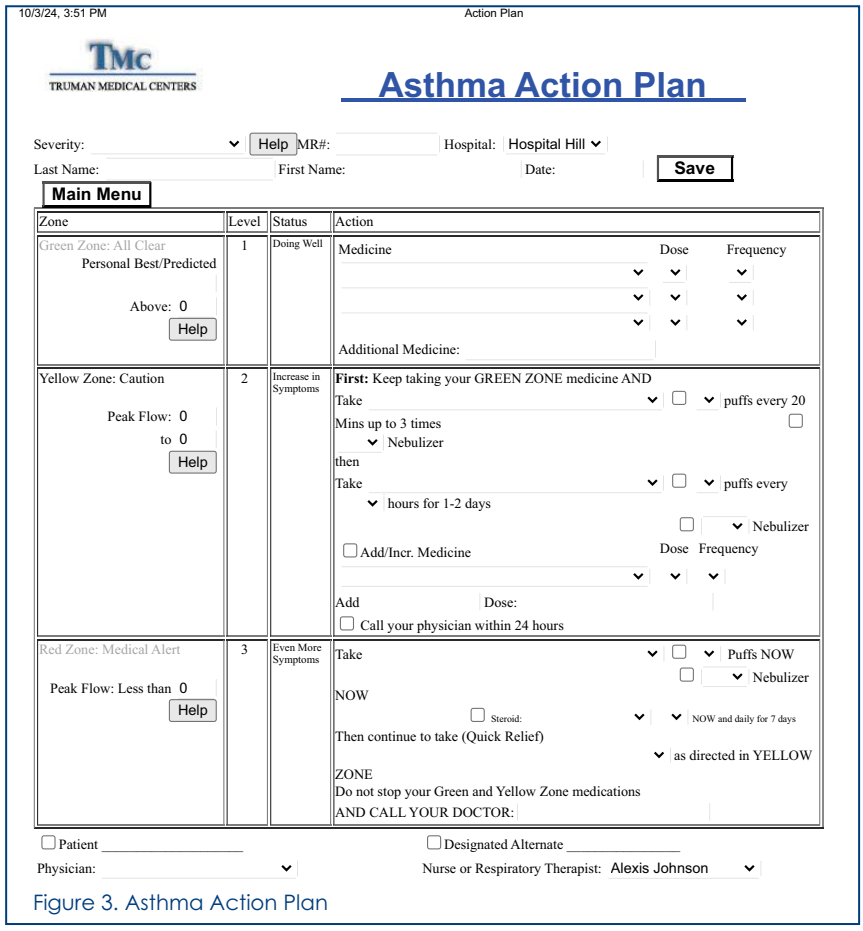
An alternative approach, Track 2 (Figure 2), involves taking an ICS containing medication whenever short-acting beta-agonist (SABA) is used, and gradually escalating to low-dose maintenance ICS (Step 2).[4] The BEST study looked at 445 patients over six months, and showed the mean number of exacerbations per patient per year was lower in the combined ICS-SABA group compared to as needed SABA alone.[6] Most recently, in the study Albuterol-Budesonide Fixed Dose Combination Rescue Inhaler for Asthma, the hazard ratio for probability of severe exacerbations was 0.73 (95% CI 0.61-0.88) with higher-dose of as-needed albuterol-budesonide compared with as-needed albuterol alone.[7] The evidence continues to point to access to an ICS containing inhaler for rescue, whether that be in the ICS-LABA formulation or ICS-SABA or ICS plus SABA.[4, 5] Steps 3-5 of Track 2 follow Track 1 with regards to the up titration of controller medications and eventual addition of biologic agents.[4]

Conclusion

SMART (Single Inhaler Maintenance and Reliever Therapy) for asthma offers the advantage of simplifying the treatment regimen by using a single inhaler for both maintenance and reliever medication, which may improve adherence and provide quick symptom relief. However, it carries the risk of overuse of the reliever component, limited availability of suitable combination inhalers, and potential for confusion in medication use, and may not be suitable for all patients.

Most insurance companies only allow for one ICS-LABA inhaler per month, which may be problematic for patients using this as SMART therapy.

Patients with frequent symptoms run the risk of running out of their ICS-LABA inhaler early in the month resulting in no maintenance and reliever therapy available until the following month. Patients with intermittent or mild persistent asthma using their ICS-LABA as needed less than 120 inhalations per month are good candidates for SMART therapy. Patients with moderate or severe asthma have an increased risk of running out of their ICS-LABA inhaler and should generally use their ICS-LABA twice daily with rescue use of albuterol or the recently approved albuterol-budesonide inhaler.


10/3/24, 3:51 PM Action Plan

TMC TRUMAN MEDICAL CENTERS

Asthma Action Plan

Severity: Help MR#: Hospital: Hospital Hill

Last Name: First Name: Date: Save

Main Menu

Zone	Level	Status	Action
Green Zone: All Clear Personal Best/Predicted Above: 0 Help	1	Doing Well	Medicine Dose Frequency Additional Medicine:
Yellow Zone: Caution Peak Flow: 0 to 0 Help	2	Increase in Symptoms	**First:** Keep taking your GREEN ZONE medicine AND Take puffs every 20 Mins up to 3 times Nebulizer then Take puffs every hours for 1-2 days Nebulizer Add/Incr. Medicine Dose Frequency Add Dose: Call your physician within 24 hours
Red Zone: Medical Alert Peak Flow: Less than 0 Help	3	Even More Symptoms	Take Puffs NOW Nebulizer NOW Steroid: NOW and daily for 7 days Then continue to take (Quick Relief) as directed in YELLOW ZONE Do not stop your Green and Yellow Zone medications AND CALL YOUR DOCTOR:

Patient Designated Alternate

Physician: Nurse or Respiratory Therapist: Alexis Johnson

Figure 3. Asthma Action Plan

Regardless of the Track used, patients require a tailored "asthma action plan," or a documented guide that furnishes them with instructions to adhere to at home (Figure 3). This aids in clarifying medication schedules, assisting patients in recognizing deteriorations in asthma control, and directing treatment modifications based on alterations in symptoms, as well as home measurements of peak expiratory flow (PEF). It should undergo review and refinement during subsequent follow-up appointments. Highlighting the patient's individual goals is crucial for improving adherence.

Asthma management should be focused on maximizing symptom control and mitigating likelihood of flare ups while reducing the adverse effects of medications. Well-managed asthma allows individuals to lead active lives and it involves educating patients, reducing exposure to triggers, monitoring symptoms and lung function, and administering appropriate treatments. GINA 2024 guidelines emphasize the importance of switching from single SABA use to early ICS-formoterol (or ICS plus SABA) use for the reliever medication to prevent exacerbations and diminish the occurrence of serious exacerbations, fatalities, hospitalizations, and exacerbations necessitating oral steroid treatment. Optimal asthma management requires a multifaceted approach, addressing clinical, social, and environmental factors to improve outcomes and enhance quality of life.

References

1. Braman SS. The Global Burden of Asthma. Chest. 2006;130(1):4S12S. doi:https://doi.org/10.1378/chest.130.1_suppl.4s
2. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma. New England Journal of Medicine. 2018;378(20):1865-1876. doi:https://doi.org/10.1056/nejmoa1715274
3. Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma. New England Journal of Medicine. 2019;380(21):2020-2030. doi:https://doi.org/10.1056/nejmoa1901963
4. World Asthma Day 2024. Global Initiative for Asthma - GINA. Accessed April 28, 2024. https://ginasthma.org/world-asthma-day-2024/#:~:text=Asthma%20is%20one%20of%20the
5. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. European Respiratory Journal. 2019;53(6):1901046. doi:https://doi.org/10.1183/13993003.01046-2019
6. Papi A, Canonica GW, Maestrelli P, et al. Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma. New England Journal of Medicine. 2007;356(20):2040-2052. doi:https://doi.org/10.1056/nejmoa063861
7. Papi A, Chipps BE, Beasley R, et al. Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. New England Journal of Medicine. 2022;386(22). doi:https://doi.org/10.1056/nejmoa2203163

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Lung Cancer in Missouri

by David Roelofsz, MD & Garrett Rampon, MD

Lung cancer remains one of the most commonly diagnosed forms of cancer and is the leading cause of cancer related deaths in Missouri and the US.



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Abstract

Lung Cancer remains one of the leading causes of cancer related diagnoses and deaths in Missouri and across the United States. It is a major source of morbidity, mortality, and economic impact in Missouri. Over the past several years, major insights to the underlying risk factors of lung cancer have been discovered. Lung cancer screening has evolved and there are new updates to guideline recommendations on screenings. Here we outline the epidemiology and etiology of lung cancer, mitigation strategies for risk factor reduction, and review updates to lung cancer screening recommendations.

Epidemiology and Etiology

Lung cancer is the leading cause of cancer death in the United States, accounting for an estimated 127,070 deaths in 2023, representing 20.8% of all cancer associated deaths per the National Cancer Institute SEER database. It has the third highest incidence of cancer related diagnoses, compromising 12.2% of all cancer diagnoses, trailing only breast and prostate. Prognosis after diagnosis is poor, with the five-year relative survival at only 25.4%. The factors which contribute the largest to prognosis are subtype of lung cancer (small cell vs. non-small cell) and stage at time of diagnosis.

In Missouri, lung cancer is the most common non-skin cancer and is the leading cause of cancer related deaths. According to the American Lung Association, in 2023, Missouri had a rate of new lung cancer diagnosis of 68.4 per 100,000 which is significantly higher than the national rate of 54.6. Missouri ranked forty-third among all states in new diagnoses, placing it in "below average tier." Life expectancy following diagnosis is also below average, raking twenty-seventh among the 42 states with survival data.[2]

Encouragingly, Missouri is considered "top tier" by the American Lung Association in terms of access to treatment with only 15.4% of cases receiving no treatment after diagnosis, putting the state at fourth in the nation for available access to treatment.[2] Additionally, Missouri has fewer racial and ethnic disparities than most states. The rate of new lung cancer cases for black individuals is significantly higher in Missouri than the US average (73.3 vs. 56.3) and is higher than new cases among white individuals in Missouri (69.1). Yet rates of early diagnosis and five-year survival rate is not significantly different between black and white individuals in Missouri. Other racial and ethnic disparities can be found in detail on the American

Lung Association website, www.lung.org/research/state-of-lung-cancer/states/missouri.[2]

The role of genetic variants and their association with the development of lung cancer remains poorly understood. Numerous genome-wide association studies have been performed and several candidate genes have been identified for close association with the development of lung cancer in both smokers and non-smokers including APEX1, AXIN2, and EGFR,[3-5] however the specific role of genetic mutations, single nucleotide polymorphisms, and tumor microenvironment epigenetics in the development of lung cancer remains an area of ongoing research. The primary understood etiology of lung cancer remains environmental exposure. The strongest ties include tobacco, radon, and air pollution.[3,6]

Tobacco Use

Tobacco use is the single greatest risk factor for lung cancer. It is implicated in an estimated 85-90% of all lung cancer cases. Smoking induces a series of mutational changes over time due both to known carcinogens and reactive oxygen species in tobacco as well as upregulation of the inflammatory cascade leading to deregulated cells, cytokine release, and production of growth factors. The result is substantial DNA mutations occurring a rate of roughly one genetic mutation every 15 cigarettes smoked.[5,7] Environmental tobacco smoke, or second-hand smoke, is also identified as a significant risk factor for the development of lung cancer.[8]

Smoking cessation should be strongly recommended to all patients who use tobacco. Cessation of tobacco should be discussed at every encounter, even if the patient has previously indicated they do not wish to stop smoking. Screening, brief intervention, and referral to treatment (SBIRT) practices were initially developed to aid in tobacco and alcohol cessation, and is an evidence based and billable strategy to assist in cessation.[9] SBIRT utilizes a screening tool to assess use, and if positive, a brief intervention to discuss cessation is undertaken. If the patient shows an interest in cessation, treatment options are discussed.

There are multiple strategies to promote the cessation of tobacco use. These include behavioral changes, i.e., counseling either in person or via telephone, self-help materials, etc., nicotine replacement therapy (NRT) including patches, lozenges, gum, inhalers, or nasal sprays, as well as pharmaceuticals. Varenecline, a selective norepinephrine reuptake inhibitor, and buproprion, a norepinephrine-dopamine reuptake inhibitor, are the only Federal Drug Association approved medications with this indication.

The United States Preventive Services Task Force recommends behavioral interventions with or without medication assistance. If NRT is utilized, they recommend combination of two types of NRT.[10] The American Thoracic Society recommendations of initiating pharmacologic treatment for smoking cessation include a strong recommendation to use varenicline over buproprion or NRT alone, including patients with comorbid psychiatric conditions. Combination varenicline and NRT is recommended over varenicline alone.[11]

The safety of electronic cigarettes, or vaping, for tobacco cessation is not well understood. There is a lack of long-term safety data and evidence of significant short term lung injury including the electronic cigarette or vaping associate acute lung injury which can cause acute hypoxemic respiratory failure and death.[12]

Radon

Radon is a naturally occurring radioactive gas released by decay of uranium-238. It is invisible, odorless, tasteless, and is usually present as a gas. It can collect in water if there are radon deposits in wells or nearby natural water sources and can be found virtually anywhere. It becomes dangerous by inhaling radon as it concentrates indoors, which can occur via cracks in foundation, via building materials, or in contaminated water sources. It is the dominant source of exposure to ionizing radiation in most countries.[13] The mechanism of radon and lung cancer carcinogenesis is primarily due to the emission of alpha particles which induce direct damage to respiratory tract epithelium, resulting in DNA double-strand breaks, translocations, deletions and microRNA dysregulation.[14] Indoor radon was declared a human carcinogen by the World Health Organization in 1987 and the US signed the Indoor

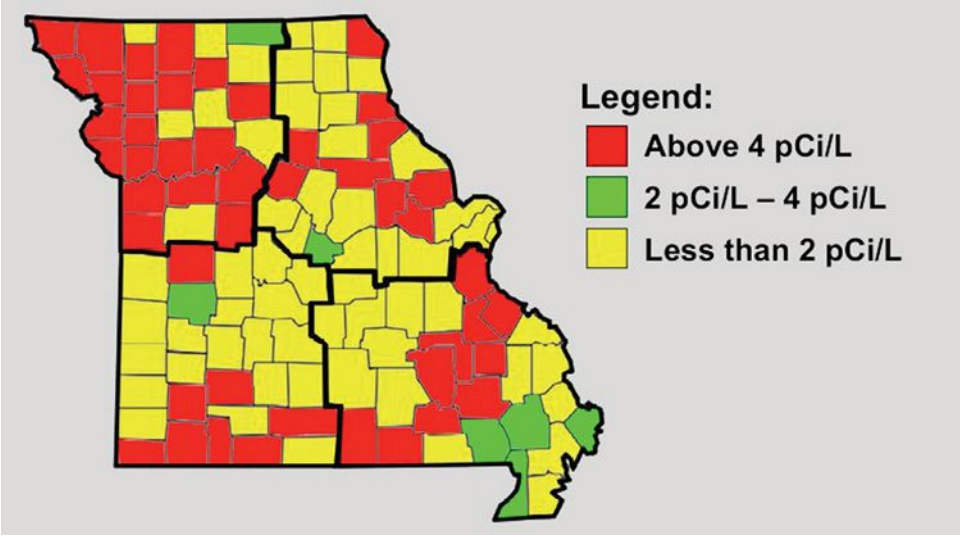


Figure 1: Missouri Radon Levels Map. Quantified averaged radon test results by county from 2005-2022. Data as reported by Missouri Department of Health and Senior Services. Figure reproduced with permission from the Hope Light Foundation (https://www.hopelightproject.com/about-us.html).

Radon Abatement Act in 1988 establishing a long-term goal of reducing indoor radon exposure.[15]

Radon is the second leading cause of lung cancer behind tobacco and is responsible for approximately 3-14% of lung cancer cases.[16] It affects both smokers and non-smokers alike.[17] Home radon testing is recommended by the Environmental Protection Agency (EPA) and the Centers for Disease Control if radon levels have never been tested, after renovations, when preparing to buy or sell a home, or if there is increased time spent in the lower levels. In Missouri, there are very few statewide policies on radon testing. There are no statewide standards in effect and no credentialing requirements service buildings for radon testing or contracting work. There is no homebuyer protection requirement for radon, no radon system requirements for newly constructed homes, and no testing requirements for schools despite 33% of buildings exceeding the EPA upper limit threshold of 4 pCi/L (Figure 1).[18] If elevated, the EPA recommends contacting a qualified radon reduction contractor to lower the building's radon level to acceptable levels. Radon testing kits are available for free to Missouri residents through the Missouri Department of Health & Senior Services (https://health.mo.gov/living/environment/radon/).

There are an estimated 850 annual radon-induced lung cancer cases resulting in nearly $350 million in total medical and economic costs in the state of Missouri.[18]

Environmental Hazards

A wide range of occupational and environmental exposures have been linked to the development of lung cancer. Inhalational carcinogens are prevalent in occupations with known hazards such as radioactive ores including uranium and inhaled chemicals including arsenic, beryllium, cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers, which all been linked to the development of lung cancer.[12] Those that perform construction, factory, coal, or shipyard work, or those that are exposed to solvents (including those commonly associated with painting), are at increased risk for lung cancers due to undue exposure to these hazards.[19-22]

Air pollution represents a significant risk of pulmonary malignancy to the general public [23,24] specifically with exposures to environmental particulate matter measuring <2.5µm ($PM_{2.5}$).[25,26] $PM_{2.5}$ is a complex collection of pollutants released from both natural and human activities including volcanoes, wildfires, vehicle emissions, solid fuel and biomass burning, industrial discharge, and agricultural byproducts.[27] $PM_{2.5}$ levels contribute substantially to the global burden of diseases including ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, lung cancer, and lower respiratory infections, and caused an estimated 4.2 million deaths worldwide in 2015 representing the fifth highest risk factor for death behind high blood pressure, smoking, high fasting plasma glucose, and high total

cholesterol.[28] Numerous cohort studies worldwide have noted a dose-dependent relationship between $PM_{2.5}$ levels and the risk of developing lung cancer, with evidence of a risk threshold of annual mean concentration of 10 μg/m^3.[29-31]

Air monitoring is required by the United States Clean Air Act. Missouri operates approximately 50 air monitoring sites across the state with 15 sites monitoring for particulate matter including $PM_{2.5}$ and PM_{10} to ensure the state adheres to the National Ambient Air Quality Standards for Particulate Matter. On February 7, 2024, the EPA finalized a rule to reduce PM2.5 annual mean levels from 12.0μg/m^3 to 9.0 μg/m^3.

Lung Cancer Screening

In 2011, the results of the National Lung Cancer Screening Trial were published.[32] This study enrolled 53,454 patients randomized to low dose lung cancer screening computerized tomography (LDCT) vs. single-view chest radiography. LDCT intervention was associated with a relative reduction in mortality from lung cancer by 20.0%. Results were replicated in the NELSON trial, which utilized slightly different inclusion criteria and LDCT metrics, that showed a 24% reduction in the LDCT group.[33]

Following these landmark studies, nearly all major thoracic, oncological, and medical societies including the American Cancer Society, the American College of Chest Physicians, Centers for Medicare and Medicaid Servies (CMS), American Academy of Family Physicians, and the USPSTF all recommend LDCT screening for high risk individuals.[34-38]

LDCT is recommended for individuals ages 50-80, with a 20 pack-year smoking history, and who currently smoke or have quit within the last 15 years. It should be noted that the CMS excludes individuals beyond the age of 77.[36] Additionally, this group should include those who do not have signs or symptoms of lung cancer and should not include those who have previously had lung cancer.[38] People should not be screened if they have serious medical problems which will likely limit how long they live.

If a lesion is found on LDCT, the risk of malignancy can be assessed using The American College of Radiology Lung CT Screening Reporting and Data System (Lung-RADS).[39] The Lung-RADS scoring system assigns a score ranging from 1 (either no nodules or definitely benign nodules) to 4b (highly concerning). The interpreting radiologist should also incorporate corresponding management recommendations including repeating imaging at a specified interval or additional work up including positron emission tomography scan or tissue biopsy.

Following passage of the Affordable Care Act, low dose lung cancer screening is covered fully by private insurers, and Medicare.[40] Medicaid coverage is state dependent, with Missouri Medicaid covering LDCT testing completely.[2]

Despite the safety, efficacy, and accessibility of LDCT for lung cancer screening, rates of screening remain poor. Nationwide, only 5.8% of eligible patients undergo screening.[41]

Conclusion

Lung cancer remains one of the most commonly diagnosed forms of cancer and is the leading cause of cancer related deaths in Missouri and the US. Risk factors for developing lung cancer include environmental factors such as tobacco smoke, radon gas exposure, air pollution, as well as possible genetic causes. Mitigation of risk factors is essential for improving lung cancer rates, and physicians and health care providers should be prepared to engage patients in smoking cessation counselling utilizing societal guidelines to maximize cessation success. Lung cancer screening with low dose CT scans for high-risk persons significantly reduces mortality and is covered by private insurances, Medicare, and Missouri Medicaid, and should be considered in all persons who quality.

References

1. National Institute of Health. Surveillance, Epidemiology, and End Results (SEER)Program Cancer Stat Facts. Accessed 30 March 2024, https://seer.cancer.gov/statfacts/html/common.html
2. American Lung Association. State of Lung Cancer | Missouri. Accessed 27 March 2024, 2024. https://www.lung.org/research/state-of-lung-cancer/states/missouri
3. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. Sep 25 2008;359(13):1367-80. doi:10.1056/NEJMra0802714
4. de Alencar VTL, Formiga MN, de Lima VCC. Inherited lung cancer: a review. Ecancermedicalscience. 2020;14:1008. doi:10.3332/ecancer.2020.1008
5. Yoshida K, Gowers KHC, Lee-Six H, et al. Tobacco smoking and somatic mutations in human bronchial epithelium. Nature. Feb 2020;578(7794):266-272. doi:10.1038/s41586-020-1961-1
6. Alduais Y, Zhang H, Fan F, Chen J, Chen B. Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment.

Medicine (Baltimore). Feb 22 2023;102(8):e32899. doi:10.1097/MD.0000000000032899
7. Alexandrov LB, Ju YS, Haase K, et al. Mutational signatures associated with tobacco smoking in human cancer. Science. Nov 4 2016;354(6312):618-622. doi:10.1126/science.aag0299
8. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. Jan 8 2011;377(9760):139-46. doi:10.1016/S0140-6736(10)61388-8
9. Agerwala SM, McCance-Katz EF. Integrating screening, brief intervention, and referral to treatment (SBIRT) into clinical practice settings: a brief review. J Psychoactive Drugs. Sep-Oct 2012;44(4):307-17. doi:10.1080/02791072.2012.720169
10. Siu AL, Force USPST. Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. Oct 20 2015;163(8):622-34. doi:10.7326/M15-2023
11.Leone FT, Zhang Y, Evers-Casey S, et al. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. Jul 15 2020;202(2):e5-e31. doi:10.1164/rccm.202005-1982ST
12. Salzman GA, Alqawasma M, Asad H. Vaping Associated Lung Injury (EVALI): An Explosive United States Epidemic. Mo Med. Nov-Dec 2019;116(6):492-496.
13. Pershagen G, Akerblom G, Axelson O, et al. Residential radon exposure and lung cancer in Sweden. N Engl J Med. Jan 20 1994;330(3):159-64. doi:10.1056/NEJM199401203300302
14. Robertson A, Allen J, Laney R, Curnow A. The cellular and molecular carcinogenic effects of radon exposure: a review. Int J Mol Sci. Jul 5 2013;14(7):14024-63. doi:10.3390/ijms140714024
15. Riudavets M, Garcia de Herreros M, Besse B, Mezquita L. Radon and Lung Cancer: Current Trends and Future Perspectives. Cancers (Basel). Jun 27 2022;14(13)doi:10.3390/cancers14133142
16. World Health Organization. WHO handbook on indoor radon : a public health perspective. World Health Organization,; 2009:1 electronic resource (xiv, 94 pages). https://hdl.loc.gov/loc.gdc/gdcebookspublic.2021763117
17. Centers for Disease Control and Prevention. Radon and Your Health. Accessed 27 March 2024, 2024. http://www.cdc.gov/nceh/features/protect-home-radon/index.html
18. American Association of Radon Scientists and Technologists. Indoor Enviornments Association: The Radon Report Card: Risk and Response | Missouri. 2024. Accessed 1 April 2024. https://aarst.org/Report-Cards/MO-Report-Card.html
19. Ge C, Peters S, Olsson A, et al. Diesel Engine Exhaust Exposure, Smoking, and Lung Cancer Subtype Risks. A Pooled Exposure-Response Analysis of 14 Case-Control Studies. Am J Respir Crit Care Med. Aug 1 2020;202(3):402-411. doi:10.1164/rccm.201911-2101OC
20. Ge C, Peters S, Olsson A, et al. Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks. A Pooled Analysis of Case-Control Studies. Am J Respir Crit Care Med. Aug 1 2020;202(3):412-421. doi:10.1164/rccm.201910-1926OC
21. Christiani DC. Combating environmental causes of cancer. N Engl J Med. Mar 3 2011;364(9):791-3. doi:10.1056/NEJMp1006634
22. Espina C, Porta M, Schuz J, et al. Environmental and occupational interventions for primary prevention of cancer: a cross-sectorial policy framework. Environ Health Perspect. Apr 2013;121(4):420-6. doi:10.1289/ehp.1205897
23. Pope CA, 3rd, Burnett RT, Turner MC, et al. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. Environ Health Perspect. Nov 2011;119(11):1616-21. doi:10.1289/ehp.1103639
24. Cohen AJ, Pope CA, 3rd. Lung cancer and air pollution. Environ Health Perspect. Nov 1995;103 Suppl 8(Suppl 8):219-24. doi:10.1289/ehp.95103s8219
25. Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. Nature. Apr 2023;616(7955):159-167. doi:10.1038/s41586-023-05874-3
26. Wu X, Zhu B, Zhou J, Bi Y, Xu S, Zhou B. The epidemiological trends in the burden of lung cancer attributable to PM(2.5) exposure in China. BMC Public Health. Apr 15 2021;21(1):737. doi:10.1186/s12889-021-10765-1
27. Nan N, Yan Z, Zhang Y, Chen R, Qin G, Sang N. Overview of PM(2.5) and health outcomes: Focusing on components, sources, and pollutant mixture co-exposure. Chemosphere. May 2023;323:138181. doi:10.1016/j.chemosphere.2023.138181
28. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet. May 13 2017;389(10082):1907-1918. doi:10.1016/S0140-6736(17)30505-6
29. Bai L, Shin S, Burnett RT, et al. Exposure to ambient air pollution and the incidence of lung cancer and breast cancer in the Ontario Population Health and Environment Cohort. Int J Cancer. May 1 2020;146(9):2450-2459. doi:10.1002/ijc.32575
30. Gharibvand L, Shavlik D, Ghamsary M, et al. The Association between Ambient Fine Particulate Air Pollution and Lung Cancer Incidence: Results from the AHSMOG-2 Study. Environ Health Perspect. Mar 2017;125(3):378-384. doi:10.1289/EHP124
31. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol. Aug 2013;14(9):813-22. doi:10.1016/S1470-2045(13)70279-1
32. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. Aug 4 2011;365(5):395-409. doi:10.1056/NEJMoa1102873
33. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. Feb 6 2020;382(6):503-513. doi:10.1056/NEJMoa1911793
34. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. May 2019;69(3):184-210. doi:10.3322/caac.21557
35. Mazzone PJ, Silvestri GA, Souter LH, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. Chest. Nov 2021;160(5):e427-e494. doi:10.1016/j.chest.2021.06.063
36. Centers for Medicare & Medicaid Services. Screening for lung cancer with low dose computed tomography (LDCT) (CAG-00439R). Accessed 1 April 2024, 2024. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=304
37. American Academy of Family Physicians. AAFP updates recommendation on lung cancer screening. Accessed 1 April 2024, 2024. https://www.aafp.org/news/health-of-the-public/20210406lungcancer.html
38. Jonas DE, Reuland DS, Reddy SM, et al. Screening for Lung Cancer With Low-Dose Computed Tomography: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. Mar 9 2021;325(10):971-987. doi:10.1001/jama.2021.0377
39. Christensen J, Prosper AE, Wu CC, et al. ACR Lung-RADS v2022: Assessment Categories and Management Recommendations. Chest. Mar 2024;165(3):738-753. doi:10.1016/j.chest.2023.10.028
40. American Cancer Society. Costs and Insurance Coverage for Cancer Screening. Accessed 1 April 2024, 2024. https://www.cancer.org/cancer/screening/cancer-screening-costs-insurance-coverage.html
41. American Lung Association. State of Lung Cancer. 2022. https://www.lung.org/getmedia/647c433b-4cbc-4be6-9312-2fa9a449d489/solc-2022-print-report.pdf

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Sarcoidosis: A Review of the Guidelines and What's To Come

by Timothy Kable, MD, Samuel DuMontier, DO & Christopher Streiler, MD

Though the etiology and pathophysiology of sarcoidosis remains elusive there are concise, yet comprehensive, guidelines released by multiple societies. These can guide physicians in the diagnosis and management of sarcoidosis.



Timothy Kable, MD, and Samuel DuMontier, DO, are Pulmonary and Critical Care Fellows and Christopher Streiler, MD, (pictured), is an Assistant Professor; all are in Department of Pulmonary and Critical Care Medicine, University Health Hospital, University of Missouri - Kansas City, Kansas City, Missouri.

Abstract

Sarcoidosis is a disease hallmarked by granulomatous inflammation of nearly all organ systems. Though it has been widely recognized for over 100 years, much remains unknown about the etiology and pathophysiology of the disease. Due in part to this is ambiguity, diagnosis and treatment, algorithms have been difficult to create and even harder to develop a strong evidence base for. In this article, we attempt to consolidate the guidelines, recommendations, and algorithms provided by multiple societies across the US and abroad. We have assembled these into a concise quick-reference format article for those looking for a cohesive approach to the diagnosis and management of sarcoidosis, including when it doesn't respond to initial therapy. We also delve into a new and promising treatment that is in the investigation pipeline, but not yet ready for implementation.

Introduction

Sarcoidosis was first described in 1877 and remains a challenging diagnosis for physicians to this day.[1] This is primarily due to the ambiguity of a disease process that encompasses a multitude of symptoms involving multiple organs affected by the formation of non-caseating granulomas. Although our understanding of the disease process has grown, the exact etiology of the disease and a standardized diagnostic algorithm has not been established. The first guideline appeared in a joint statement by the American Thoracic Society, European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) in 1999 with further recommendations added in 2014. Most recently, the American Thoracic Society in 2020 and European Respiratory Society 2021 (ATS 2020/ERS 2021) have constructed a set of guidelines facilitating a practical approach to the diagnose and of sarcoidosis.

Sarcoidosis: Making the Diagnosis

Three major criteria are essential to diagnosing sarcoidosis. The first criterium is the patient exhibiting compatible clinical and radiographic features. Sarcoidosis is a multi-system granulomatous disease process with symptoms ranging from singular and nonspecific to complex and multifactorial. Fatigue, fever, cough, weight loss and chest pains are typical pulmonary symptoms, but extra-thoracic manifestations are also often present. In the US, women and Black people are at higher risk of developing

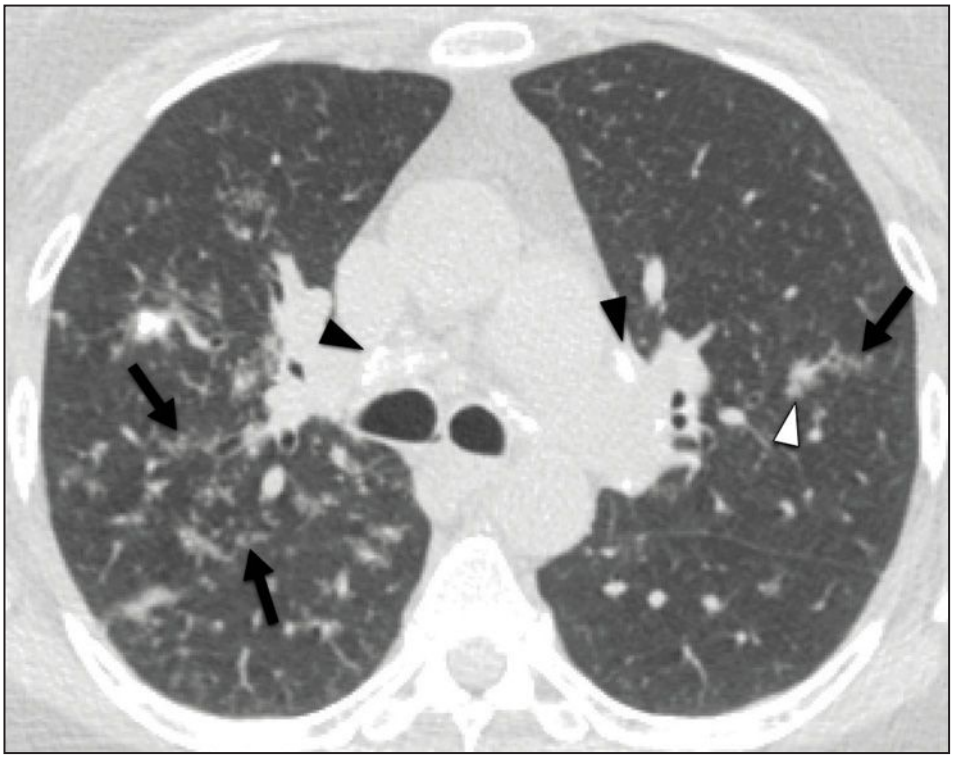


Figure 1. Axial CT image of the chest in a 60-year-old female with biopsy-proven sarcoidosis demonstrates the characteristic imaging features with numerous perilymphatic nodules (black arrows), some of which coalescence to form the so-called "galaxy sign" (white arrowhead), as well as calcified mediastinal and hilar lymph nodes (black arrowheads).

the disease between the ages of 20 to 60 years old. Black women were found to have four-fold increased risk of developing sarcoidosis than white women.[2] Additionally, Black people tend to experience symptoms earlier, roughly by 10 years, and have more advanced extra-thoracic disease states.[3]

Historically, bilateral hilar adenopathy has been the predominant radiographic feature supporting the diagnosis of sarcoid found initially on chest radiograph.[4] However, sarcoidosis can affect the lung parenchyma resulting in interstitial lung disease and potential fibrosis which portray a multitude of different radiographic patterns (Figure 1). The Scadding staging system for pulmonary sarcoidosis was originally proposed in 1960s and has since been modified.[4] Stage 0 has no adenopathy or pulmonary infiltrates present on imaging. Stage 1 consists of hilar and mediastinal adenopathy alone without pulmonary parenchymal infiltrates. Stage 2 has both adenopathy and pulmonary infiltrates present. Stage 3 has pulmonary infiltrates without lymph node involvement and stage 4 indicates presence of pulmonary fibrosis[4].

More recently, Anderson et al. have recognized high resolution computed tomography (HRCT) phenotypical patterns distinct to pulmonary sarcoidosis.[5] Members of the Fleischner Society, World Association of Sarcoidosis and other Granulomatous Disorders, and assorted chest physicians and thoracic radiologists concluded in a consensus study that HRCT should be performed at baseline in patients with sarcoidosis. Distinct HRCT phenotypes were broken down to non-fibrotic and fibrotic features. Defining features of non-fibrotic pulmonary disease consists of nodules, consolidations and ground-glass opacifications that can be standalone or in combination. Nodules were well defined in a peri-lymphatic distribution most commonly bronchovascular, peri-fissural, or subpleural. Larger nodules with numerous circulating micronodules colloquially known as "galaxy sign" can be seen as well. Reticulations with or without dense parenchymal opacifications, cysts or cavitations and large bronchocentric masses typically represent fibrotic disease. Fibrotic changes are typically upper-lobe predominant. Honeycombing is rarely seen.[5]

The second criterium for establishing diagnosis are one or more tissue samples with non-caseating granulomas present (Figure 2).

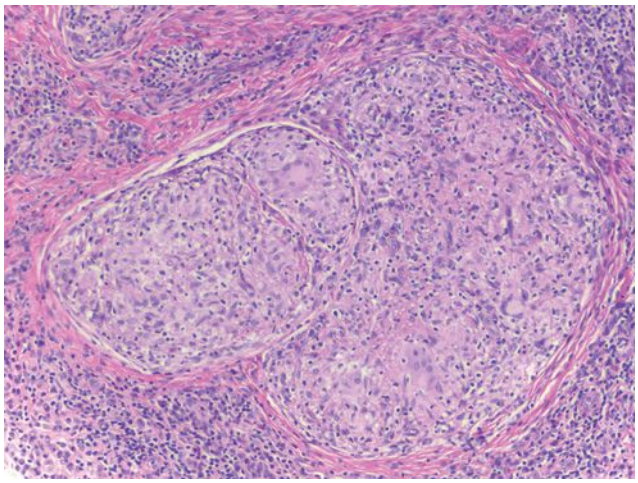


Figure 2. Microscopic Image of Non-Caseating Granuloma

These well-formed granulomas of sarcoidosis are different in appearance from the poorly formed granulomas of hypersensitivity pneumonitis or other conditions. There are several syndromes considered pathognomonic for sarcoidosis. Presence of these conditions obviates the need for biopsy.[6] The pathognomonic syndromes include Lofgren syndrome, Heerfordt syndrome, and lupus pernio. Lofgren syndrome typically occurs in third and fourth decades of life and consists of acute onset of fever, hilar adenopathy, erythema nodosum and/or arthropathy.[7] Heerfordt syndrome primarily consists of acute extrapulmonary manifestations that includes a blend of uveitis (most commonly anterior), parotid gland involvement, and facial nerve pals.[8] Lastly, Lupus Pernio is a cutaneous form of sarcoid that predominantly affects African Americans and females and is described as a "red to violaceous indurated lesions affecting the nose, cheeks, perioral areas, and forehead."

For patients who have identified hilar adenopathy but are asymptomatic it is important to note both the risk and benefits of biopsy and likelihood of alternative etiologies as hilar adenopathy alone is typically self-limiting disease.[6] Ultimately, guidelines do not recommend for or against lymph node sampling for asymptomatic patients. For patients who have suspected sarcoid without high probability clinical features and lymphadenopathy present, tissue sampling is essential in confirming the diagnosis. Endobronchial ultrasound (EBUS) directed lymph node sampling over mediastinoscopy is the recommended initial approach. EBUS guided lymph node sampling provides high yield results and is less invasive than mediastinoscopy.[6] Transbronchial needle aspiration (TBNA) is a reasonable alternative if EBUS is not available although diagnostic yield is not as high.

Endobronchial biopsies (EBB) and bronchoalveolar lavage (BAL) for CD4/CD8 cell counts and degree of lymphocytosis may also aid clinicians in their "sarcoid hunt," the colloquialism pulmonary proceduralists use to refer to bronchoscopies evaluating for sarcoidosis. Sarcoidosis typically features lymphocytosis and a lower percentage of other cell types in contrast to other inflammatory lung conditions. A CD4:CD8 ratio > 3.5 has been shown to have high specificity but low sensitivity for sarcoidosis.[9] Sarcoidosis can affect the central airways warranting an EBB. Possible airway abnormalities encountered include cobble stoning, nodularity, plaques, increased vascularity and thickened mucosa.[10] Surgical biopsies are rarely indicated beyond the aforementioned multimodal endoscopic approach.

The third criterium is to rule out other disease processes as sarcoidosis is somewhat a diagnosis of exclusion. It is essential to rule out other infections which include mycobacterium tuberculosis nontuberculous mycobacterium, atypical and fungal (histoplasma, blastomycosis). Inflammatory lung diseases (eosinophilic lung disease, hypersensitivity pneumonitis), malignancies (Hodgkin or non-Hodgkin lymphoma), and other granulomatous diseases (Granulomatosis Polyangiitis and Eosinophilic Granulomatosis with Polyangiitis) can appear similar to sarcoidosis. It is not imperative to definitively rule out every alternative diagnosis during sarcoidosis workup unless clinically reasonable.

Pulmonary function testing (PFT) is typically performed but can vary widely and should not play a role in the diagnosis of sarcoidosis though it is helpful from a prognostic standpoint. It is estimated that 10-30% of patients with sarcoidosis will have a normal PFT. Patterns of abnormality can vary as well. Restriction due to parenchymal involvement and obstruction due to airway involvement can occur separately and concomitantly. Diffusing capacity may also be decreased due to parenchymal involvement.

Six-minute walk distance can also be used prognostically and to assess response of treatment. It is additionally helpful in determining exertional hypoxemia.[11]

Sarcoidosis: The Treatment

When deciding whether to initiate treatment of sarcoidosis, the physician must consider two questions. Does this patient's disease status represent a current or future threat to organ function or loss of life? Does this patient have symptoms that affect their quality of life in a way that is unacceptable to them? If the answer to either question is yes, then treatment should be discussed and initiated.

The aforementioned ERS guidelines offer excellent treatment algorithms based on which organ system(s) is involved. The first line of therapy for all organ systems, with exception of skin, is systemic steroids with prednisone. While there has been a long-standing recommendation of the starting dose being 0.3-0.6 mg/kg of IBW, more recent data has caused a shift in the guidelines. The current recommendation is to initiate prednisone at a dose of 20 mg per day.[12] This dose is typically continued for one to three months and is then reassessed clinically. At that time point, the dose can be titrated down if patient is clinically improved and a discussion is had to facilitate shared decision making. If there is a good clinical response, steroids can be titrated down with a goal of 5-10 mg per day. Steroids should generally be continued for a period of at least six months to one year prior to discontinuation.

If there are significant glucocorticoid side effects, continued disease, or relapse then therapy should be transitioned to a second-line therapy. Though there are several reasonable choices, the agent with the most robust evidence base is methotrexate. This statement is made with the caveat that much of the data would be considered "weak" when compared to treatment regimens of other disease processes.

Methotrexate is an inhibitor of dihydrofolic acid reductase and inhibits purine and thymidylic acid synthesis ultimately interfering with DNA synthesis. Methotrexate is typically dosed weekly at 10-25 mg. It is imperative to also prescribe supplemental folic acid to avoid side effects and toxicity. Folic acid can be given 1 mg daily except for the day methotrexate is also taken or it can be given 5 mg the day following the methotrexate dose. Contraindications are chronic kidney disease, hepatic impairment, and pregnancy. Common side effects are fatigue, anemia, gastrointestinal symptoms, and renal/liver impairment.

Methotrexate has been shown to be effective for sarcoidosis and can reduce markers of pulmonary inflammatory disease such as BAL lymphocytosis and macrophage TNF release.[13] Additionally, there was response/improvement shown across multiple organ systems, not just in pulmonary disease. Furthermore, there are data supporting methotrexate in regard to multiple patient centered outcomes such as increasing forced vital capacity and being able to markedly reduce steroid dosing.[14]

Due to its supporting data as well as long history of use in sarcoidosis, methotrexate is widely considered to be the second-line agent of choice in steroid refractory or steroid intolerant disease. It is typically well tolerated and not cost prohibitive. If patients develop intolerable gastrointestinal side effects, a subcutaneous weekly injection of methotrexate with a 1:1 dose conversion can be considered. Lab monitoring is warranted throughout the duration of treatment to monitor for bone marrow suppression and renal/hepatic impairment.

If sarcoidosis continues to negatively impact a patient's quality of life or threatens organ function despite glucocorticoid therapy and methotrexate there are other treatment options available. Azathioprine, leflunomide and mycophenolate mofetil have all been shown to be effective at treating pulmonary sarcoidosis.[12] Generally, one of these medications is initiated if the patient has a contraindication to methotrexate, such as renal or hepatic function impairment.[12] Most of the data investigating these medications comes from retrospective cohort studies. Azathioprine was shown to be as effective as methotrexate in treating pulmonary sarcoidosis and had similar steroid sparing potency.[15] Side effects of azathioprine include dyspepsia, oral ulcers, myalgias, jaundice and blurred vision. Compared to methotrexate, azathioprine has higher rates of opportunistic infections. It is also important to measure thiopurine S-methyltransferase (TPMT) levels prior to initiation of azathioprine. Those with

TPMT deficiency are at higher risk of developing toxicity. Leflunomide was shown to be well tolerated in patients with sarcoidosis and appeared as effective as methotrexate.[16] Major side effects include nausea, leukopenia, and hepatotoxicity. Mycophenolate has some benefit to those who were intolerant to previous steroid sparing agents.[17] Side effects to monitor for include diarrhea, leukopenia, and vomiting. Mycophenolate also carries an increased risk of infection when compared to both azathioprine and methotrexate.

For patients with ongoing disease, the next step in therapy is the addition of a biologic agent such as TNF-α inhibitors infliximab (Remicade) or adalimumab (Humira). Both agents have been shown to be effective options for treatment of sarcoidosis, though Infliximab is more widely used and has more supporting data.[12] Infliximab was shown to have a statistically significant improvement in forced vital capacity (FVC) compared to placebo in a double-blind, randomized control trial.[18] This result has been replicated in several other studies. Infliximab also has been shown to decrease maximum SUV uptake on FDG-PET.[19] That same study also demonstrated that patients with high maximum SUV uptake on FDG-PET appeared more likely to respond to infliximab therapy. This result suggests that FDG-PET may be beneficial in therapeutic decision making for patients with complex sarcoidosis. Adalimumab has not been studied as extensively as Infliximab. In a small open-label trial, adalimumab demonstrated a reduction in immunosuppressive therapy as well as an increase in both FVC and 6-minute walk time.[20]

Both infliximab and adalimumab are contraindicated in patients with severe congestive heart failure, prior malignancy, demyelinating neurologic disease, and active tuberculosis. As such, you must screen for mycobacterium tuberculosis prior to initiating either of these medications.[11] Side effects of these medications include abdominal pain, nausea, diarrhea, dyspepsia, headache, rash, pruritis, pharyngitis, sinusitis, and sore throat. Infusion reactions, including anaphylaxis can occur with infliximab. Injection site reactions can occur in those taking adalimumab. Overall, adalimumab is less toxic than infliximab and generally better tolerated.[11] Infliximab is a recombinant DNA-derived chimeric IgG monoclonal antibody protein that contains both murine and human components that inhibit TNF-α. As such, patients can develop antibodies (human anti-chimeric antibodies) against infliximab which lowers the drug efficacy and causes infusion reactions.[19] To reduce the risk of developing antibodies, patients are generally started on other immunosuppression medications such as methotrexate at a low dose. Adalimumab should be considered in these patients that have been treated successfully with infliximab but have developed antibodies.[11]

For those with continued disease burden, further therapeutic options are limited. Rituximab is generally considered the next line of therapy for refractory sarcoidosis, however data supporting its use is scarce.[11] An open-label phase I/II trial showed an inconsistent response to the medication for patients with pulmonary sarcoidosis.[21] Ten patients were included in this study. Five patients and had an increase in FVC > 5% predicted and five patients had an increase in their 6-minute walk distance of >30m (some only improved FVC or 6-min walk distance). A more recent study showed rituximab was generally well tolerated and led to a decrease in maximum FDG uptake on FDG PET/CT in patients with cardiac sarcoidosis, however this was a small retrospective study that included only seven patients.[22]

There are numerous ongoing trials of new agents to treat refractory sarcoidosis. One of the more promising investigational therapies is efzofitimod, which is a novel immunomodulator. Efzofitimod selectively binds to neuropilin-2 which is upregulated on immune cells in response to lung inflammation.[23] The medication is administered intravenously, typically every four weeks. Early studies of the medication demonstrated that increasing doses of efzofitimod appeared to lead to a reduction in daily steroid dosing.[23] In a double-blind, placebo-controlled study evaluating ascending doses of efzofitimod, it demonstrated a reduction in daily steroid use when compared to placebo at all three doses studied. There was also a dose-dependent but non-significant trend toward improved lung function. The most common side effects of the medication were cough, wheezing,

dyspnea, and upper respiratory tract infection. These side effects were not dose dependent, were typically mild in severity and did not limit treatment duration. Overall, the medication was tolerated at all doses with no unexpected adverse events[2,4] These findings further support the need for future prospective trials evaluating efzofitimod use in pulmonary sarcoidosis.

Conclusion

Though the etiology and pathophysiology of sarcoidosis remains elusive there are concise, yet comprehensive, guidelines released by multiple societies. These can guide physicians in the diagnosis and management of sarcoidosis. Diagnosis centers around a pathologic diagnosis within the appropriate clinical setting or certain pathognomonic syndromes. Management centers around immunosuppression, first with prednisone and then with second- and third-line agents if needed. Additionally, there are promising medications in the therapeutic pipeline as well. It is the authors' hope that this review provides a quick reference for sarcoidosis management and points you towards other sources of evidence and expert opinion-based guidelines.

References

1. Kashyap S, Bhardwaj M. New sarcoidosis guidelines: Are we near to perfection? Lung India. May-Jun 2022;39(3):217-219. doi:10.4103/lungindia.lungindia_159_22
2. Dumas O, Abramovitz L, Wiley AS, Cozier YC, Camargo CA, Jr. Epidemiology of Sarcoidosis in a Prospective Cohort Study of U.S. Women. Ann Am Thorac Soc. Jan 2016;13(1):67-71. doi:10.1513/AnnalsATS.201508-568BC
3. Rybicki BA, Major M, Popovich J, Jr., Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. Feb 1 1997;145(3):234-41. doi:10.1093/oxfordjournals.aje.a009096
4. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med. Mar 1 2011;183(5):573-81. doi:10.1164/rccm.201006-0865CI
5. Desai SR, Sivarasan N, Johannson KA, et al. High-resolution CT phenotypes in pulmonary sarcoidosis: a multinational Delphi consensus study. Lancet Respir Med. Dec 14 2023;doi:10.1016/S2213-2600(23)00267-9
6. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. Apr 15 2020;201(8):e26-e51. doi:10.1164/rccm.202002-0251ST
7. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. Clin Rev Allergy Immunol. Aug 2015;49(1):63-78. doi:10.1007/s12016-014-8450-y
8. Denny MC, Fotino AD. The Heerfordt-Waldenstrom syndrome as an initial presentation of sarcoidosis. Proc (Bayl Univ Med Cent). Oct 2013;26(4):390-2. doi:10.1080/08998280.2013.11929014
9. Costabel U, Bonella F, Ohshimo S, Guzman J. Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. Semin Respir Crit Care Med. Aug 2010;31(4):404-8. doi:10.1055/s-0030-1262207
10. Livi V, Sivokozov I, Annema JT, et al. High-Definition Videobronchoscopy for the Diagnosis of Airway Involvement in Sarcoidosis: The Enhance Sarcoidosis Multicenter Study. Chest. Nov 2023;164(5):1243-1252. doi:10.1016/j.chest.2023.04.034
11. Yao Q, Ji Q, Zhou Y. Pulmonary Function in Pulmonary Sarcoidosis. J Clin Med. Oct 24 2023;12(21)doi:10.3390/jcm12216701
12. Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. Dec 2021;58(6) doi:10.1183/13993003.04079-2020
13. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. Thorax. Aug 1999;54(8):742-6. doi:10.1136/thx.54.8.742
14. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med. Apr 24 1995;155(8):846-51.
15. Vorselaars ADM, Wuyts WA, Vorselaars VMM, et al. Methotrexate vs azathioprine in second-line therapy of sarcoidosis. Chest. Sep 2013;144(3):805-812. doi:10.1378/chest.12-1728
16. El Jammal T, Jamilloux Y, Gerfaud-Valentin M, Valeyre D, Seve P. Refractory Sarcoidosis: A Review. Ther Clin Risk Manag. 2020;16:323-345. doi:10.2147/TCRM.S192922
17. Hamzeh N, Voelker A, Forssen A, et al. Efficacy of mycophenolate mofetil in sarcoidosis. Respir Med. Nov 2014;108(11):1663-9. doi:10.1016/j.rmed.2014.09.013
18. Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. Oct 1 2006;174(7):795-802. doi:10.1164/rccm.200603-402OC
19. Vorselaars AD, Crommelin HA, Deneer VH, et al. Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. Eur Respir J. Jul 2015;46(1):175-85. doi:10.1183/09031936.00227014
20. Sweiss NJ, Noth I, Mirsaeidi M, et al. Efficacy Results of a 52-week Trial of Adalimumab in the Treatment of Refractory Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. Apr 18 2014;31(1):46-54.
21. Sweiss NJ, Lower EE, Mirsaeidi M, et al. Rituximab in the treatment of refractory pulmonary sarcoidosis. Eur Respir J. May 2014;43(5):1525-8. doi:10.1183/09031936.00224513
22. Elwazir M, Krause ML, Bois JP, et al. Rituximab for the Treatment of Refractory Cardiac Sarcoidosis: A Single-Center Experience. J Card Fail. Feb 2022;28(2):247-258. doi:10.1016/j.cardfail.2021.07.008
23 .Walker G, Adams R, Guy L, et al. Exposure-response analyses of efzofitimod in patients with pulmonary sarcoidosis. Front Pharmacol. 2023;14:1258236. doi:10.3389/fphar.2023.1258236
24. Culver DA, Aryal S, Barney J, et al. Efzofitimod for the Treatment of Pulmonary Sarcoidosis. Chest. Apr 2023;163(4):881-890. doi:10.1016/j.chest.2022.10.037

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Insomnia in Adults in the Primary Care Clinic Setting

by Jason Zweig, MD, Ashraf Gohar, MD & Abid Bhat, MD

Insomnia remains a complex and burdensome disease, common in the general population and easily mistaken for other disease states. Due to the complexity of the disorder, these processes can be difficult to manage in the primary care setting.



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Abstract

Insomnia is one of the most common sleep concerns raised by patients both to primary care as well as sleep specialists. Chronic insomnia has a lifetime prevalence of approximately 30% in the general population, resulting in roughly $100 billion dollars healthcare expenditures annually. Given the complexity of insomnia this can become burdensome for primary care providers. In this article we will highlight the main issues and how to manage these individuals in the primary care clinic.

Introduction

Insomnia is defined as a persistent difficulty to fall or maintain sleep and linked with dissatisfaction, concern, or perceived daytime impairment.[1] There are three subtypes of insomnia, often overlooked or under-treated, affecting all ages and being disruptive on mental as well as physical health. Treatment requires a collaborative effort between the patient and physician. We will discuss the impact on health, definition, subtypes, manifestations, testing, and treatment for insomnia.

Impact on Health

Chronic Insomnia, untreated or unrecognized, can have detrimental effects on mental and physical health, with an increased risk of depression, suicide and other psychiatric disorders.[2] Patients with insomnia with short sleep duration are at increased risk for developing hypertension and impaired sleep events can also adversely impact patient's perception of pain.[3,4] This can cause patients with chronic pain as well as fibromyalgia to have a predisposition to developing insomnia as well. It has also been shown that patients with objective short sleep duration are associated with high risk of diabetes and mortality.[5]

Subtypes and Definitions

Due to difficulty of initiation or maintenance of sleep, patients with insomnia frequently perceive daytime impairment (i.e. fatigue, decreased mood, irritability, general malaise, or cognitive impairment).[1] Currently insomnia has been subcategorized into three subtypes by International Classification of Sleep Disorders 3rd edition Text Revision (ICSD-3-TR): chronic insomnia disorder, short term insomnia disorder, and other insomnia disorder.



Figure 1. Chronic insomnia affects about 10% of the population more common with female subjects and individuals with medical, psychiatric, substance abuse disorders, advanced age and lower socioeconomic status.

Chronic Insomnia

Chronic insomnia affects about 10% of the population more common with female subjects and individuals with medical, psychiatric, substance abuse disorders, advanced age and lower socioeconomic status (Figure 1).[1,6,7] To establish the diagnosis, criteria A-F must be met.[8]

A) One of the following must be present: difficulty initiating sleep, difficulty maintaining sleep, final awakening earlier than desired, resistance to going to bed on an appropriate schedule, or difficulty sleeping without caregivers presence or intervention (in adults with cognitive dysfunction).

B) The patient or caregiver notices at least one of the following in relation to night time sleeping difficulty: 1) fatigue, 2) impaired attention, concentration or memory, 3) impaired social, family, occupational, or academic performance, 4) mood disturbance or irritability, 5) subjective daytime sleepiness, 6) behavioral problems (e.g. hyperactivity, impulsivity, aggression), 7) reduced motivation/energy/initiative, 8) proneness for errors/accidents, 9) concerns about/dissatisfaction with sleep.

C) Reported sleep/wake complaints cannot be explained purely by inadequate opportunity or inadequate circumstances for sleep.

D) The sleep disturbance and associated daytime symptoms occur ≥ three times per week.

E) Symptoms have been present for ≥3 months. (Although some patients with chronic insomnia may show recurrent episodes lasting for several weeks at a time over several years but not meeting the three months in each time)

F) The sleep disturbance and associated daytime symptoms are not solely due to another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

There are some essential features for chronic insomnia that help delineate individuals with insomnia versus unrealistic expectations about sleep and they are as follows.[8] Sleep onset insomnia if it takes >30 minutes to fall asleep. Sleep maintenance insomnia if the period of wakefulness during sleep is >30 minutes or, early morning awakenings typically >30 minutes before desired rising time as well as an overall reduction in total sleep time.

Short term insomnia disorder is acute insomnia is also a relatively common disorder. In adults the one year prevalence is 15-20% and it's more common in women and older individuals.[8] The main difference obviously is the duration, acute <3 months. In acute insomnia, the patient usually can identify the inciting event or circumstance that became the catalyst for onset.

The last subtype of insomnia is "Other Insomnia Disorder," reserved for individuals who have difficulty

either starting or maintaining sleep but don't meet the full criteria for short or chronic insomnia disorder.[8] This may be assigned to an individual on a provisional basis when further information is needed to be obtained to establish a diagnosis. This diagnosis should be used scarcely given its non-specific name.

Differential Diagnosis

There are several disorders that can mimic insomnia making it difficult to differentiate the true cause when a proper history and physical is overlooked. Such disorders include but not limited to: Circadian rhythm sleep wake disorders, excessive time in bed, short sleeper, sleep disruptive environmental circumstances, chronic insufficient sleep syndrome, narcolepsy, sleep related breathing disorders, and movement disorders.

There are several different Circadian rhythm sleep-wake disorders (CRSWD) that can mimic insomnia. Four of them may mimic chronic and two mimic short term insomnia disorder. The mimickers of chronic insomnia are delayed sleep wake phase disorder (DSWPD), advanced sleep wake phase disorder (ASWPD), irregular sleep wake rhythm disorder (ISWRD), and non-24-hour sleep wake rhythm disorder (N24SWD).

DSWPD is a sleep initiation problem typically seen in teenagers and young adults. These individuals consistently have sleep initiation that is later than desired, or due to social norms, required timing.[9] This is due to a delayed endogenous circadian rhythm. Patients with DSWPD are able to fall asleep with less difficulty and acquire a normal duration of sleep, if they're allowed to sleep on their preferred time, and feel rested and productive throughout their day.

On the opposite side of the spectrum is ASWPD that may be mistaken as sleep maintenance insomnia. Patients with ASWPD will have a consistent earlier than desired sleep initiation timing and will wake up earlier than social normal due to their endogenous circadian rhythm being more advanced.[10] Their total sleep time is sufficient and are able to carry out their daily activities without difficulties.-

ISWRD is a CRSWD in which there is lack of clearly defined circadian rhythm of sleep and wake.[11] In these individuals the sleep wake pattern is temporally disorganized with significant variability of sleep and wake episodes throughout the 24 hour cycle leading to fragmented sleep wake episodes.[11] These individuals will have their longest sleep episode < 4 hours. They nap throughout the day, total sleep time through the day may be normal for the given age.

N24SWD is a CRSWD where the intrinsic circadian pacemaker is not attuned to a 24-hour light-dark cycle.[12] Patients typically display sleep wake patterns that have a progressive delay or advancement depending on the length of time than their endogenous circadian rhythm.[12] Given this pattern it can cause an individual to have sleep onset or sleep maintenance insomnia. It can also cause the patient to be hypersomnolent. This is typically seen in blind individuals and rarely in sighted individuals. The cause for this CRSWD in sighted individuals is still unknown. For this disorder, a diagnosis requires a 14 day sleep diary/actigraphy documenting progressively shifting sleep wake times.[12]

CRSWD mimickers of acute insomnia include Shift work disorder and jet lag caused by a mismatch between the endogenous circadian rhythm and desired or required sleep wake schedule. These then cause one to complain about their sleep as their inner circadian rhythm has been manipulated for certain needs required at that time.

There are two other factors/disorders that are related to environmental or social events that mimic insomnia. Environmental changes can disrupt sleep, including noise, light, extreme temperatures and safety, ex: watching TV, working on computers, reading in bed, due to light from electronic devices reaching the retina inhibiting melatonin release.[13] This type of behavior conditions the brain to not associate the bed as a place of rest. Patients will report that the "mind is racing" when not using electronic devices. In addition, concerns for one's safety will also heightene a sense of arousal, inhibiting sleep.

The other disorder is Chronic insufficient sleep syndrome where there is inadequate sleep duration secondary to work, personal requirements or social/recreational schedules. This will lead to daytime sleepiness and fatigue, however given sufficient sleep time, they are able to initiate and maintain sleep without difficulty for normal duration.[14]

Other normal variants of sleep schedules are individuals with excessive time spent in bed and short sleepers. These individuals may express prolonged sleep latency or long periods of wakefulness during the night without complaints of insomnia or daytime impairment.[8] In adults, without cognitive impairments,

this is most common in non-complaining individuals who allocate more time in bed than required. Unemployed individuals could be at risk of developing inefficient sleep habits by spending excessive time in bed, as they lack a structuring activity.[15] Short sleepers are individuals who commonly obtain <6 hours of sleep and have no sleep/wake complaints or daytime dysfunction.[16] For these individuals the short average sleep period is not from intentional prolonged sleep restriction but rather their constitutional disposition for reduced sleep requirement.[16]

There are multiple disorders that cause or mimic insomnia if not properly evaluated. These disorders include, but not limited to: sleep-related breathing disorders, movement disorders, chronic pain with fibromyalgia, and narcolepsy. With sleep related breathing disorders, most commonly obstructive sleep apnea (OSA), there can be frequent night time awakenings, mimicking sleep maintenance insomnia, due to the fragmented sleep occurring with the arousals after obstructive events. These can fully awaken patients making it difficult/frustrating for the patient regain sleep. Movement disorders such as restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) can lead to insomnia. RLS is a sensorimotor disorder in which the individual will complain of a strong, irresistible urge to move the limbs. The sensations occur predominantly in the evening with inactivity.[17] Resolution of the symptoms when moving or walk around is a hallmark feature. The term RLS is a misnomer as some patients will also describe some arm sensations.[17] These sensations make it difficult for individuals to fall asleep for which patients present as sleep initiation insomnia. PLMD is characterized by periodic episodes of repetitive, stereotype limb movements during sleep which then leads to clinical sleep disturbance or daytime impairment that cannot be explained by another sleep disorder or etiology. This can lead to frequent awakening during the night mimicking sleep maintenance insomnia. In patients who have under-treated chronic pain or fibromyalgia, insomnia will occur 50-80% of the time.[4] Under-treated pain or uncontrolled fibromyalgia can lead to sleep initiation insomnia. Narcolepsy, a rare central disorder of hyper-somnolence, can also be mistaken for insomnia. Narcolepsy can be mistaken for sleep maintenance insomnia as these patients have high arousal states when asleep causing fragmentation and frequent nocturnal awakenings.

Testing

Routine and detailed testing is not indicated in the evaluation of insomnia unless required to exclude other sleep disorders based on history or exam. A useful tool to assist in differentiating sleep disorders and insomnia includes a two-week sleep diary.[2] Using sleep diaries can also help differentiate whether the individual has a CRSWD as well as possible habits that are perpetuating their symptoms, such as drinking caffeine at night. Another beneficial tool is actigraphy, a device that is typically worn on the wrist and detects motion. Lack of movement suggests sleep and useful in individuals, not sure or unable to recall their sleep pattern.[18] With concerns of insomnia, polysomnography (PSG) is indicated when the history suggest an underlying sleep disorder such as OSA or PLMs. In lab PSGs are indicated. In regard to a multiple sleep latency test (MSLT) this test is only indicated if the individual has hypersomnolence for who narcolepsy is of concern.[18] With insomnia, the history is paramount in differentiating the problem. See Figure 2 for a list of questions that can help differentiate the type and underlying cause to their sleep difficulty.

Management

The goal in the treatment of insomnia is to improve the patients experience in initiating and maintaining sleep, improving the quality of life without introducing unnecessary harm.[18] When insomnia is due to an underlying medical condition, treating that condition is the first step. If there is no responsible underlying medical or psychiatric condition, the first line treatment is always to ensure proper sleep hygiene, cognitive behavioral therapy, followed by pharmacological therapy.

Sleep hygiene should be assessed whenever an individual has a complaint about their sleep quality. The environment is a dark, quiet, cool room in a safe environment, void of distractions and used only for sleep and intimacy. Patients should be discouraged from naps, avoid late consumption of caffeine, alcohol or smoking or exercise prior to intended sleep.[18] A sleep schedule should also be established for continuity.

Cognitive Behavioral Therapy for Insomnia (CBT-I) is considered the first line of treatment.[19] CBT-I is a multi-component treatment that targets behavioral, cognitive, and physiological factors that perpetuate insomnia and aims to modify and alter maladaptive behaviors and distorted beliefs about sleep

Figure 2.

Questions that can help differentiate the type and underlying cause to their sleep difficulty.



1. How long have you had insomnia?
2. Anything specific started the insomnia?
3. Stresses, medications?
4. What time do you go to bed?
5. Are you sleepy when you go to bed?
6. How long does it take you to fall asleep?
7. What do you do during this time?
8. Anything prevent you from falling asleep?
9. Racing mind, noises, leg symptoms, other?
10. Do you wake up in the middle of the night?
11. What wakes you up?
12. How long do you take to fall asleep?
13. What time do you wake up in the morning?
14. Do you wake up with an alarm or by yourself?
15. Do you take naps and how long?
16. Do you drink any caffeine, alcohol, or drugs?
17. Do you currently or have you taken any medications for insomnia?

and insomnia.[19] CBT-I is led by trained therapist that covers stimulus control, sleep restriction, relaxation techniques, cognitive therapy, and sleep hygiene education.[19] This form of therapy can be delivered in multiple formats such as face to face, tele-visit, or group therapy. CBT-I has been shown to improve sleep as efficacious as medication in the short term but its effects are more sustainable in the long term.[19] One study showed that between 70-80% of patients had improvement in their insomnia, 50% achieved clinically meaningful outcomes (sleep latency was < 30 minutes, and reduction in hypnotic use) and 33% became good sleepers after undergoing CBT-I.[20,21] CBT-I has also been shown to help individuals slow or reverse cortical gray matter atrophy in patients with comorbid fibromyalgia.[4] CBT-I has also been found to be beneficial for individuals with insomnia with comorbid conditions such as depression, post-traumatic stress disorder (PTSD), anxiety, alcohol dependence, chronic pain, and cancer.[19] Benefits from CBT-I compared to medications is an elimination of dependency on "medication" and avoiding potential drug side effects.

Hypnotic medications can improve sleep only modestly with the evidence of low quality and 60% of the benefit attributed to a placebo effect.[18,22] Five classes of medications are approved by the FDA to be used for insomnia. Some assist with sleep onset, others for sleep maintenance or both. Examples are Benzodiazepine receptor agonists (Z-drugs), Orexin receptor antagonists, Melatonin receptor agonists, Tricyclic antidepressants, and Benzodiazepines.

Benzodiazepine receptor agonists (Z-drugs) used for insomnia are Zolpidem, Zaleplon, and Eszopiclone that attach to the GABA receptor.[23] A black box warning exist on these agents due to case reports of complex sleep behaviors, including sleepwalking, driving, cooking and sexual acts during sleep. Eszopiclone and Zolpidem are approved to treat both sleep onset and maintenance insomnia.[22] Zaleplon is recommended only for sleep onset insomnia.

Orexin receptor antagonists can be used in insomnia by blocking the Orexin receptor. There are currently three FDA approved Orexin receptor antagonists: Suvorexant, Lemborexant, and Daridorexant.[24] These medications are contraindicated in patients with narcolepsy. These three medications are used to treat sleep maintenance insomnia and do not have a limit on duration of use.[18]

The third class is melatonin receptor agonists such as Ramelteon a synthetic tricyclic analog of melatonin and binds to MT_1 and MT_2 receptors in the suprachiasmatic nucleus.[23] Ramelteon is used to treat sleep onset insomnia.[18]

The fourth class of medications are Tricyclic antidepressants, such as Doxepin, has a high affinity for H1 receptor (approximately 100 times more than that of nor-epinephrine and serotonin receptors) which given the antagonism in the TMN nucleus inhibits the arousal pathway thus producing its hypnotic action.[25] Doxepin is indicated for sleep maintenance insomnia as the onset of the medication is slow and the duration of the effects are long.[18] Frequently in the primary care setting Trazodone is given for insomnia due to the sedating side effects. However, the risk/benefit assessment suggest greater harm and its use should be discouraged.[22]

The last class of medication is benzodiazepines, two of which are Temazepam and Triazolam. They work by binding to the GABA receptors and cause release of the inhibitory neurotransmitter GABA which then induces sedative and hypnotic effect.[23] Both of these medications are indicated for sleep onset insomnia but only Temazepam is indicated for the treatment of sleep maintenance insomnia as well. While considered safer, recommendations remain for a limited period of use to avoid dependency.

Conclusion

Insomnia remains a complex and burdensome disease, common in the general population and easily mistaken for other disease states. Due to the complexity of the disorder, these processes can be difficult to manage in the primary care setting. Referral to a sleep medicine specialist may be warranted in patients with insomnia, who do no not respond to basic behavioral therapy and have persistent and distressing symptoms.

References

1. Levenson JC, Kay DB, Buysse DJ. The pathophysiology of insomnia. Chest. 2015;147(4).
2. Schutte-Rodin SL, Broch L, Buysee D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of Clinical Sleep Medicine. 2008;4(5).
3. Dai Y, Chen B, Chen L, et al. Insomnia with objective, but not subjective, short sleep duration is associated with increased risk of incident hypertension: the Sleep Heart Health Study. Journal of Clinical Sleep Medicine. 2023;19(8).
4. McCrae CS, Mundt JM, Curtis AF, et al. Gray matter changes following cognitive behavioral therapy for patients with comorbid fibromyalgia and insomnia: A pilot study. Journal of Clinical Sleep Medicine. 2018;14(9).
5. Fernandez-Mendoza J, Vgontzas AN. Insomnia and its impact on physical and mental health. Curr Psychiatry Rep. 2013;15(12).
6. Bonnet MH, Burton GG, Arand DL. Physiological and medical findings in insomnia: Implications for diagnosis andcare. Sleep Med Rev. 2014;18(2).
7. Baglioni C, Regen W, Teghen A, et al. Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies. Sleep Med Rev. 2014;18(3).
8. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd, Text revision ed. Darien, IL: American Academy of Sleep Medicine; 2023.
9. Saxvig IW, Pallesen S, Wilhelmsen-Langeland A, Molde H, Bjorvatn B. Prevalence, and correlates of delayed sleep phase in high school students. Sleep Med. 2012;13(2).
10. Curtis BJ, Ashbrook LH, Young T, et al. Extreme morning chronotypes are often familial and not exceedingly rare: The estimated prevalence of advanced sleep phase, familial advanced sleep phase, and advanced sleep-wake phase disorder in a sleep clinic population. Sleep. 2019;42(10).
11. Zee PC, Vitiello M V. Circadian Rhythm Sleep Disorder: Irregular Sleep Wake Rhythm. Sleep Med Clin. 2009;4(2):213-218.
12. Auger RR, Burgess HJ, Emens JS, Deriy L V., Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). an update for 2015. Journal of Clinical Sleep Medicine. 2015;11(10).
13. Caddick ZA, Gregory K, Arsintescu L, Flynn-Evans EE. A review of the environmental parameters necessary for an optimal sleep environment. Build Environ. 2018;132.
14. Mader EC, Mader ACL, Singh P. Insufficient Sleep Syndrome: A Blind Spot in Our Vision of Healthy Sleep. Cureus. 2022. doi:10.7759/cureus.30928
15. Greissl S, Mergl R, Sander C, Hensch T, Engel C, Hegerl U. Is unemployment associated with inefficient sleep habits? A cohort study using objective sleep measurements. J Sleep Res. 2022;31(3).
16. Skiba V, Hershner S. Short Sleeper. AASM Sleep Education.
17. Nanayakkara B, Di Michiel J, Yee BJ. Restless legs syndrome. Aust J Gen Pract. 2023;52(9).
18. Sutton EL. Insomnia. Ann Intern Med. 2021;174(3).
19. Chan NY, Chan JWY, Li SX, Wing YK. Non-pharmacological Approaches for Management of Insomnia. Neurotherapeutics. 2021;18(1).
20. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. Nonpharmacologic treatment of chronic insomnia. Sleep. 1999;22(8).
21. Morin CM, Jarrin DC. Epidemiology of Insomnia. Sleep Med Clin. 2022;17(2).
22. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American academy of sleep medicine clinical practice guideline. Journal of Clinical Sleep Medicine. 2017;13(2).
23. Brunton L, Chabner B, Knollman B. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition.; 2011. http://books.google.de/books/about/Goodman_and_Gilman_s_The_Pharmacological.html?id=e_yAOpyyaowC&pgis=1. Accessed May 3, 2015.
24. Monkemeyer N, Thomas S V., Hilleman DE, Malesker MA. Insomnia Treatment Update with a Focus on Orexin Receptor Antagonists. US Pharmacist. 2022;47(5).
25. Katwala J, Kumar AK, Sejpal JJ, Terrence M, Mishra M. Therapeutic rationale for low dose doxepin in insomnia patients. Asian Pac J Trop Dis. 2013;3(4).

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Non-CPAP Therapies for Obstructive Sleep Apnea in Adults

by Rayyan Abid, Lawrence Zhang, MD & Abid Bhat, MD

The "one-size-fits-all" approach of CPAP therapy is no longer the most effective treatment plan for most patients.



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Abstract

Obstructive sleep apnea (OSA) is a widespread sleep disorder characterized by repeated collapse of the upper airway during sleep, resulting in disruption of sleep. This condition is linked to a host of symptoms, including excessive daytime sleepiness, cardiovascular disorders, and a variety of other comorbidities. Continuous positive airway pressure (CPAP) is, by far, the most common treatment for OSA, and has long served as the standard treatment for most patients. However, CPAP therapy has a variety of limitations, including low adherence, and the heterogenous presentation of OSA. Thus, there exists an increasing need for alternative therapies for OSA. Some of these include lifestyle modifications, positional therapy, mandibular advancement devices, upper airway surgery, pharmacological therapies, and hypoglossal nerve stimulation. Because OSA presents heterogeneously, effective treatment for most patients would likely include a combination of these treatments.

Introduction

Obstructive sleep apnea (OSA) is a common disease defined by repeated episodes of partial or complete upper airway collapse during sleep, leading to cyclic intermittent hypoxia, intrathoracic pressure swings, and sleep fragmentation.[1] This can result in excessive daytime sleepiness, increased risk of hypertension, coronary artery disease, metabolic disease, cognitive impairment, reduced quality of life, and increased risk for motor vehicle accidents.[2] Studies suggest that sleep-disordered breathing can be detected in 9-38% of the general adult population.[3] Moreover, as rates of obesity have increased, occurrence of sleep apnea in patients has increased by 14-55% over the last 20 years depending on severity, gender, and age group.[4] While obesity is the most common risk factor associated with OSA, other common risk factors include family history, male gender, use of alcohol and opiates, and craniofacial abnormalities.

However, recent research has recognized that OSA is a highly heterogenous disorder presenting with a variety of clinical and physiological phenotypes.[5] Each patient may present with different risk factors, clinical presentation, and potential prognoses. Thus, traditional "one size fits all" continuous positive airway pressure (CPAP) therapy must be reevaluated. While its effectiveness is typically high, low long-term compliance and a lack of patient-specific care ensure its net effects remain insufficient.[6] This review aims to provide an overview of

Table 1. Non-CPAP therapies for the treatment of Obstructive Sleep Apnea

	Advantages	Disadvantages
Positional therapy	Affordable for a substantial proportion of patients	Less efficacious versus PAP Potential to cause back discomfort
Mandibular advancement devices	Good acceptance and adherence	Residual apnea-hypopnea events are frequent. Long-term dental alterations
Negative pressure therapies	More effective for mild to moderate OSA	Dental or oral discomfort
Pharmacotherapy	Desire from many patients for a nondevice treatment	Not currently approved
Hypoglossal nerve stimulator	Minimal input required after placement Encouraging results from recent studies	High upfront cost

common alternatives to CPAP therapy that can help physicians best tailor the treatment to their patients' unique clinical phenotypes (Table 1) These treatments include lifestyle modification, positional therapy, maxillofacial surgery, hypoglossal nerve stimulation, and pharmacological solutions. While personalized treatments for patients will likely involve some combination of these therapies, this review will discuss each of them individually.

Lifestyle Modification

Obesity is the most prevalent risk factor for developing OSA and yields the greatest reversal of symptoms if reduced. Fat deposition associated with obesity typically obstructs upper airway anatomy, and other neurological factors like depressed neuromuscular control of the upper airway can also cause OSA.[7] Numerous epidemiological studies have shown that weight gain is the strongest predictor of OSA as up to 60% of obese patients suffer from the disease.[8] Moreover, a longitudinal study in the Wisconsin Sleep Cohort indicated that a 10% increase in weight was observed to be associated with a 32% increase in patients' apnea-hypopnea index (AHI).[9] Thus, weight loss should be considered as a first-line treatment for overweight and obese patients afflicted with OSA. Weight loss has been shown to decrease the apnea-hypopnea index, improve sleep architecture, and decrease daytime somnolence.[10] Exercise may also reasonably improve OSA even in the absence of significant weight. [11] Although limited data indicates that CPAP therapy may be associated with weight gain, studies suggest that the initial improvement in AHI achieved through weight loss can persist for a number of years in spite of regaining weight.[12,13]

Reduction of alcohol consumption and smoking must also be discussed. Cigarette smoking may increase the risk of OSA by altering sleep architecture, upper airway neuromuscular function, arousal mechanisms, and upper airway inflammation.[14] Alcohol not only increases the frequency of apneas and hypopneas during sleep but also prolongs their duration by delaying arousal. Similarly, Yang et al. found a direct correlation between drinking cessation and reduced OSA risk, especially in females.[15]

Positional Therapy

Positional OSA (POSA) is defined by as having an AHI at least twice as high in the supine position as other positions. By this definition, nearly half of OSA patients experience some form of POSA.[16] The "tennis ball" technique is a form of positional therapy that involves strapping a bulky item to the back of the patient during sleep. While this treatment has proven to be effective in reducing sleep time in the supine position, long term compliance is extremely low with less than 10% of patients continuing use 30 months after prescription.[17] Similarly, this technique is not recommended for patients who struggle with any shoulder problem or other physical disability that impairs their ability to sleep in the lateral position. Novel positional therapy solutions include devices worn on the neck or chest that can correct the supine sleeping position with a subtle vibration alarm or stimulus to the body.[18] In the first month of treatment, over 75% of patients used these devices for at least four hours a night for at least five days a week. However, long-term compliance of these novel treatments has yet to be

studied and other long-term complications are not yet known. Positional therapy is more effective in younger and less obese patients, and not appropriate for all OSA sufferers.[19]

Oral Advancement Devices

Oral advancement devices (OADs) aim to reposition craniofacial or oral structures to increase pharyngeal airway space and reduce airway collapse. Some appliances work by suspending the tongue in an anterior position in the mouth. Lazard et al. showed that a tongue-retaining device could reduce mean AHI from 38 to 14.[20] The most common and widely researched OADs are mandibular advancement devices (MADs). The aim of MADs is to advance the mandible relative to the maxilla to enlarge and stabilize the upper airway. Moreover, the MAD resists the downward rotation of the mandible and associated mandibular retrusion during sleep, compromising upper airway flow.[21]

While MADs typically yield lesser effects to AHI than CPAP, Sutherland et al. showed that approximately two-thirds of patients experience a greater than 50% reduction in AHI with more than a third achieving complete AHI normalization.[22] A custom, tailor-made devices should be preferred over non-custom devices, and patients should check in regularly with their sleep physician and a qualified dentist to ensure continued efficacy. To avoid costs and time constraints, some patients may prefer to use self-molded devices that are submerged in warm water and bitten into by the patient to create a mold of their teeth. While these thermoplastic devices may be readily available at outpatient clinics, they are often less tolerated than customized MADs and yield low tolerance.[23] Thus, custom titratable MADs are typically the most effective form of treatment. These two-piece devices cover the lower and upper teeth, allowing for titration, a gradual modification of the mandible through incremental advancements.[24] Due to the progressive nature of this therapy, the protrusion can be tailored to each patient. While AHI reduction associated with MADs is often incomplete, therapy adherence is higher than in CPAP. Patients often find that MADs are more comfortable, quieter, and more mobile than CPAP machines. Although severe OSA is not typically considered a good indicator for MAD treatment, Byun et al. showed a decrease in AHI of 64% after a month of treatment with especially significant results in patients with low BMIs.[25] Similarly, an individual patient meta-analysis found that, although titratable MADs were less effective than CPAP at reducing AHI, both devices yielded similar results for major subjective outcomes like daytime sleepiness and quality of life. Polysomnography showed that both treatments improved sleep architecture with increases in both N3 and rapid eye movement (REM) sleep.[26] Because MADs can yield similar relief to CPAP on average, studies tend to show that patient preference and adherence are higher in MADs.

There exists little evidence regarding the effects of MADs on cardiovascular and metabolic health. Short-term randomized controlled trials report no effect on rates of hypertension or endothelial functions.[27] Long-term interventional randomized trials are necessary to determine the impact of MADs on respiratory events, cardiovascular events, and other forms of mortality. A variety of factors contribute to limiting the application of MADs in clinical practice. For over a third of patients, dental issues like insufficient maximum protrusive distance, a lack of teeth, and temporomandibular joint pain rule out MADs as a potential treatment.[28] Even for patients who are viable candidates for titratable MADs, follow-ups are typically required every six months to ensure prevention of dental side effects like tooth movements or bite changes. Similarly, a reduction in efficacy can occur if the mandible is advanced too far forward, shifting the airway from a wide to more narrow lateral diameter. Moreover, the exact clinical characteristics that suggest MADs as an effective therapy have not yet been determined. Currently, some accepted characteristics associated with favorable outcomes for MAD therapy include non-severe OSA, lower BMI, and younger age.[29] Thus, there exists a need for studies validating potential clinical indicators for MADs and determining the exact location of airway obstruction during sleep. Vroegop et al. used drug-induced sleep endoscopies (DISE) to find that tongue base collapse is a likely indicator of MAD effectiveness and complete lateral oropharyngeal collapse and complete collapse of the airway at the palatal level do not elicit responses from MADs.[30,31] Moreover, patients with lower airway collapsibility overall tend to respond more strongly to MADs.

Upper Airway Surgery

Upper airway surgery aims to improve anatomy to prevent pharyngeal collapse. The widely used form of upper airway surgery for OSA is uvulopalatopharyngoplasty (UPPP). UPPP reduces pharyngeal collapse and increases the retropalatal lumen volume through removal of the uvula and

Table 2. Hypoglossal nerve stimulation indications and contraindications

Indications	Contraindications
Apnea-hypopnea index of 15-100 events per hour	> 25% central or mixed apneic events on sleep study
Body mass index < 40	Concentric collapse on drug-induced sleep endoscopy
Failure of or intolerant to positive pressure therapy	Pre-existing condition that comprises neurological control of the upper airway
Antero-posterior collapse on drug induced sleep endoscopy	Pregnancy or planning to become pregnant
	Require magnetic resonance imaging (in some cases)

soft palate. This procedure is often accompanied by a tonsillectomy. A meta-analysis by Stuck et al. showed that UPPP in adult OSA patients yielded a significant decrease in AHI with an average AHI difference of 18.59 following surgery.[32] UPPP also yielded a significant decrease in daytime sleepiness based on the Epworth Sleepiness Scale. However, UPPP typically leads to rhinolalia, dysphagia, nasopharyngeal regurgitation, soft palatal edema, velopharyngeal insufficiency, and abnormal scarring with velopharyngeal stenosis. Given the variety of complications associated with UPPP, palatal surgery has been expanded to methods that do not require total ablation. Instead, lateral pharyngoplasty has become an increasingly common treatment for OSA.[33] One such method of palatal surgery is barbed reposition pharyngoplasty (BRP). Vicini et al. showed that BRP presents a safer and potentially more effective form of treating pharyngeal obstruction.[34] Pang et al introduced another form of palatal surgery with expansion sphincter pharyngoplasty (ESP).[35] Retrospective comparison studies analyzing UPPP, BRP, and ESP have established that BRP and ESP are typically as effective in terms of AHI with fewer postoperative complications than UPPP.[36] Radiofrequency thermotherapy (RFTT) can be used in combination with UPPP if a patient has a hypertrophic tongue. A retrospective study done by Plzak et al. showed that RFTT combined with UPPP successfully reduced severe OSA in 51.7% of patients as opposed to a success rate of 41.9% for patients treated with UPPP alone.[37] Maxillo-mandibular advancement (MMA) surgery has also been shown to be an effective treatment, with an initial improvement in 80% of patients, and is more successful in patients with lower BMI, younger age and with a higher AHI. [38,39]

Hypoglossal Nerve Stimulation

Hypoglossal nerve stimulation (HNS) is a novel approach to treating upper airway collapse. During sleep, it is common for muscle tone in the upper airway to decrease slightly. However, for individuals afflicted with OSA, this can often lead to narrowing or total collapse of the upper airway. Thus, studies have turned to HNS as a potential method of mitigating this patency. The hypoglossal nerve is comprised of exclusively motor fibers, innervating the genioglossus muscle bilaterally, and the genioglossus is the primary pharyngeal dilator muscle. Electrical stimulation of the hypoglossal nerve thus causes the tongue to protrude and stiffens the anterior pharyngeal wall, significantly increasing the diameter of the upper airway.

The HNS was approved by the FDA based on the findings in the Stimulation Therapy for Apnea Reduction (STAR) trial.[40] The primary outcome of this prospective trial of 126 patients included AHI and oxygen desaturation index. Secondary outcomes included quality of life measured by Functional Outcomes of Sleep Questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS). Patient demographics included mean age of 54.5 years, 83% male gender, mean BMI 28, and average baseline AHI of 34/hr. These patients had tried conventional OSA therapy including CPAP but could not tolerate it. There was a 68% reduction in the AHI (29 to 9 per hour) and a 70% reduction in the ODI (25.4 to 7.4 per hour). HNS is associated with high adherence and durable benefits up to 5 years, consisting of improvements in the ESS, FOSQ and reduced AHI.[41,42] All patients who are being evaluated for HNS are required to have drug-induced sleep endoscopy (DISE) and must show palatal collapse in an antero-posterior pattern. Concentric collapse is considered a contraindication to the HNS procedure.[43]

The indications and contraindications are also listed in Table 2. Although HNS has been approved for adults age 22 year or older, the 2023 FDA update has included patients ages 18 to 21, and pediatric patients with Down syndrome ages 13 to 18 and an AHI 10 to 50 who are not candidates for adenotonsillectomy, and who have failed positive airway pressure therapy.[44] The main adverse effects of HNS include incision discomfort, temporary tongue weakness, headaches, risk of infection to the incision site, and discomfort from the electrical stimulation. The ongoing TESLA trial will assess transcutaneous electrical stimulation of the upper airway dilator muscles and will determine whether electrical stimulation can be a treatment modality for a wide range of patients with OSA.[45]

Pharmacological Therapy

Anti-depressants like Fluoxetine are potential pharmacological solutions to increasing the patency of upper airway muscles during sleep. Because sleep-dependent serotonin delivery is responsible for stimulating upper airway dilator motor neurons, SSRIs have been studied as a method of treating OSA. Hanzel et al. found that mean AHI decreased from 57 to 34 events per hour in patients treated with Fluoxetine.[46] Recent studies have aimed to target upper airway dilator motor neurons using nonandrogenic and muscarinic agents in concert. An ongoing trial of Atomoxetine plus Oxybutynin combination has been shown to reduce OSA severity by improving upper airway collapsibility, increasing breathing stability, and augmenting the threshold for arousal in OSA. These effects lead to a reduction in the AHI and an increased genioglossal muscle responsiveness. [47] A meta-analysis done by Lee et al. found a significant decrease in AHI of 9.03 events per hour. [48] This combination also appeared to improve oxygen saturation and decreased hypoxic burden, likely due to a significant reduction in tongue collapsibility. However, Lee et al. also reported several side effects associated with this combination of agents, including fatigue, dryness of mouth, erectile dysfunction, and urinary hesitation. The combination therapy seems promising but is not currently available.

Negative Pressure Therapy

The iNAP device applies negative pressure through an intraoral interface held in place with a flange that fits between the teeth and the lips. It improves the retropalatal airway size by displacing the anterior-superior segment of the tongue forward and the soft palate anteriorly and superiorly.[49] In a systematic review, only 25% to 37% of patients had at least a 50% reduction in the AHI and a residual AHI of 10 or less. [50] The baseline severity of OSA did not correlate with success. The Winx device consists of a mouthpiece that works by establishing a vacuum in the oral cavity which pulls the uvula and soft palate forward thereby increasing the pharyngeal airway lumen. Based on the limited data obtained from a cohort of 63 patients who tried the Winx device, 20 showed a clinically important response, dropping the mean AHI index by greater than 50%, and lowering Epworth Sleepiness Scores from 12.1 to 8.6.[51]The long-term acceptance and adherence to the negative pressure therapy devices remains to be established.

Conclusion

Personalized medicine has become increasingly prevalent in sleep medicine, and this trend is reflected in potential treatments of OSA. The "one-size-fits-all" approach of CPAP therapy is no longer the most effective treatment plan for most patients. While CPAP is undoubtedly effective for a significant number of those afflicted with OSA, clinicians may not relieve their patients of all obstructive events during sleep with CPAP alone. Therapies like lifestyle modification, positional therapies, oral advancement devices, upper airway surgeries, hypoglossal nerve stimulation, and pharmacological therapies each provide unique advantages that, in tandem, may be more effective at treating OSA than CPAP therapy alone. However, because these therapies each provide unique advantages, further challenges for clinicians include finding the most effective combination of therapies for each unique presentation of OSA.

References

1. Balachandran JS, Patel SR. Obstructive sleep apnea. Annals of internal medicine. 2014;161(9):ITC1-15.
2. Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. Nature Reviews Disease Primers. 2015/06/25 2015;1(1):15015.
3. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Medicine Reviews. 2017;34:70-81.
4. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology. 2013;177(9):1006-1014.
5. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea – New pathways for targeted therapy. Sleep Medicine Reviews. 2018/02/01/ 2018;37:45-59.
6. Collard P, Pieters T, Aubert G, et al. Compliance with nasal CPAP in obstructive sleep apnea patients. Sleep medicine reviews. 1997;1(1):33-44.
7. De Sousa A, Cercato C, Mancini M, et al. Obesity and obstructive sleep apnea-hypopnea syndrome. Obesity Reviews. 2008;9(4):340-354.
8. Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and

insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med. Mar 1 2002;165(5):677-82.
9. Peppard PE, Young T, Palta Met al. Longitudinal study of moderate weight change and sleep-disordered breathing. Jama. 2000;284(23):3015-3021.
10. Smith PL, Gold AR, Meyers DA et al. Weight loss in mildly to moderate obese patients with obstructive sleep apnea. Ann Intern Med. 1985 Dec;103(6 (Pt 1)):850-855.
11. Iftikhar IH, Kline CE, Youngstedt SD. Lung. 2014;192(1):175-184.
12. Quan SF, Budhiraja R, Clark DP et al. Impact of treatment with continuous positive airway pressure (CPAP) on weight in obstructive sleep apnea.
13. Kuna Samuel T, Reboussin DM, Borradaile KE, et al. SLEEP. 2013;36(5):641-649.
14. Krishnan V, Dixon-Williams S, Thornton JD. Where there is smoke… there is sleep apnea: exploring the relationship between smoking and sleep apnea. Chest. 2014;146(6):1673-1680.
15. Yang S, Guo X, Liu W, et al. Alcohol as an independent risk factor for obstructive sleep apnea. Irish Journal of Medical Science 2022;191(3):1325-1330.
16. Oksenberg A, Arons E, Radwan H, et al. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic and multiple sleep latency test data. Chest. 1997;112(3):629-639.
17. Bignold JJ, Deans-Costi G, Goldsworthy MR, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. Journal of clinical sleep medicine. 2009;5(5):428-430.
18. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. Journal of clinical sleep medicine. 2015;11(2):139-147.
19. Oksenberg A, Silverberg D, Offenbach D et al. Positional therapy for obstructive sleep apnea patients: a 6-month follow-up study. Laryngoscope. 2006; 116:1995-2000.
20. Lazard DS, Blumen M, Lévy P, et al. The tongue-retaining device: efficacy and side effects in obstructive sleep apnea syndrome. Journal of Clinical Sleep Medicine. 2009;5(5):431-438.
21. Basyuni S, Barabas M, Quinnell T. An update on mandibular advancement devices for the treatment of obstructive sleep apnoea hypopnoea syndrome. Journal of thoracic disease. 2018;10(Suppl 1):S48.
22. Sutherland K, Cistulli PA. Oral appliance therapy for obstructive sleep apnoea: state of the art. Journal of clinical medicine. 2019;8(12):2121.
23. Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. American journal of respiratory and critical care medicine. 2008;178(2):197-202.
24. Dieltjens M, Vanderveken OM, Van de Heyning PH, et al. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. Sleep medicine reviews. 2012;16(2):177-185.
25. Byun J-I, Kim D, Ahn S-J, et al. Efficacy of oral appliance therapy as a first-line treatment for moderate or severe obstructive sleep apnea: a Korean prospective multicenter observational study. Journal of clinical neurology (Seoul, Korea). 2020;16(2):215.
26. Trzepizur W, Cistulli PA, Glos M, et al. Health outcomes of continuous positive airway pressure versus mandibular advancement device for the treatment of severe obstructive sleep apnea: an individual participant data meta-analysis. Sleep. 2021;44(7).
27. Yamamoto U, Nishizaka M, Tsuda H, et al. Crossover comparison between CPAP and mandibular advancement device with adherence monitor about the effects on endothelial function, blood pressure and symptoms in patients with obstructive sleep apnea. Heart and vessels. 2019;34:1692-1702.
28. Petit F-X, Pépin J-L, Bettega G, Sadek H, et al. Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. American Journal of Respiratory and Critical Care Medicine. 2002;166(3):274-278.
29. Sutherland K, Takaya H, Qian J, et al. Oral appliance treatment response and polysomnographic phenotypes of obstructive sleep apnea. Journal of Clinical Sleep Medicine. 2015;11(8):861-868.
30. Vroegop AV, Vanderveken OM, Verbraecken JA. Drug-induced sleep endoscopy: evaluation of a selection tool for treatment modalities for obstructive sleep apnea. Respiration. 2020;99(5):451-457.
31. Op de Beeck S, Dieltjens M, Verbruggen AE, et al. Phenotypic labelling using drug-induced sleep endoscopy improves patient selection for mandibular advancement device outcome: a prospective study. Journal of Clinical Sleep Medicine. 2019;15(8):1089-1099.
32. Stuck B, Ravesloot MJ, Eschenhagen T, et al. Uvulopalatopharyngoplasty with or without tonsillectomy in the treatment of adult obstructive sleep apnea. 2018;50:152-165.
33. Cammaroto G, Stringa LM, Iannella G, et al. Manipulation of lateral pharyngeal wall muscles in sleep surgery: a review of the literature. International Journal of Environmental Research and Public Health. 2020;17(15):5315.
34. Vicini C, Hendawy E, Campanini A, et al. Barbed reposition pharyngoplasty (BRP) for OSAHS: a feasibility, safety, efficacy and teachability pilot study."We are on the giant's shoulders". European Archives of Oto-Rhino-Laryngology. 2015;272:3065-3070.
35. Pang KP, Vicini C, Montevecchi F, et al. Long-term Complications of Palate Surgery: A Multicenter Study of 217 Patients. The Laryngoscope. 2020;130(9):2281-2284.
36. Rashwan MS, Montevecchi F, Cammaroto G, et al. Evolution of soft palate surgery techniques for obstructive sleep apnea patients: A comparative study for single-level palatal surgeries. Clinical Otolaryngology. 2018;43(2):584-590.
37. Plzak J, Zabrodsky M, Kastner J, Betka J, Klozar J. Combined bipolar radiofrequency surgery of the tongue base and uvulopalatopharyngoplasty for obstructive sleep apnea. Archives of Medical Science. 2013;9(6):1097-1101.
38. Zaghi S, Holty JE, Certal L et al. Maxillomandibular advancement for treatment of obstructive sleep apnea: a meta-analysis. JAMA Otolaryngol Head Neck Surg. 2016;142(1):58-66.
39. Holty JE, Guilleminault C. Maxillomandibular advancement for treatment of obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev. 2010;14(5):287-97.
40. Strollo PJ Jr, Soose RJ, Maurer JT et al; Star Trial Group. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med. 2014;370(2):139-149.
41. Thaler E, Schwab R, Maurer J et al. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. Laryngoscope 2020;130(5):1333-1338.
42. Woodson BT, Strohl KP, Soose RJ et al. Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. Otolaryngol Head Neck Surg 2018; 159(1):194-202.
43. Vanderveken OM, Maurer JT, Hohenhorst W et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. J Clin Sleep Med. 2013;9(5):433-438.
44. US Food and Drug Administration. Inspire upper airway stimulation. Approval June 8, 2023. https://www.fda.gov/medical-devices-recently-approved-devices/inspire-upper-airway-stimulation-p 130008s090. Accessed February 18, 2024.
45. Pengo MF, Xiao S, Ratneswaran C et al. Randomized sham-controlled trial of transcutaneous electrical stimulation in obstructive sleep apnea. Thorax 2016; 71:923-931.
46. Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest. 1991;100(2):416-421.
47. Taranto-Montemurro L, Messineo L, Sands Saet al. The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity. A randomized, placebo-controlled, double-blind crossover trial. Am j Respir Crit Care Med. 2019; 199:1267-76.
48. Lee Y-C, Lu C-T, Chuang L-P, et al. Pharmacotherapy for obstructive sleep apnea-A systematic review and meta-analysis of randomized controlled trials. Sleep Medicine Reviews. 2023:101809.
49. Schwab RJ, Kim C, Siegel L et al. Examining the mechanism of action of a new device using oral pressure therapy for the treatment of obstructive sleep apnea. Sleep 2014;37(7):1237-1247.
50. Nigam G, Pathak C, Riaz M. Effectiveness of oral pressure therapy in obstructive sleep apnea: a systematic analysis. Sleep Breath 2016;20(2):663-671.
51. Colrain IM, Black J, Siegel LC et al. A multicenter evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. Sleep Med 2013;14(9):830-837.

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Management of Visually Significant Vitreous Opacities

by Nikki Gill, MD & Ajay Singh, MD

Visually significant floaters can pose a significant burden on patients. With advances in imaging and surgical instrumentation, there are now more definitive options to diagnose and treat these patients.



Nikki Gill, MD, is starting ophthalmology residency at the University of Missouri – Kansas City School of Medicine and **Ajay Singh, MD**, (pictured), is affiliated with the University of Kansas School of Medicine and the Kansas City VA Medical Center, Kansas City, Missouri.

Abstract

Visual floaters can significantly affect quality of vision. Although these opacities are visible on ophthalmoscopy, objectively measuring severity has been difficult. The standard approach has been to monitor individuals for complications rather than treating the floaters. With advances in surgical instrumentation and techniques, ophthalmologists have multiple options for treating visually significant floaters, most commonly pars plana vitrectomy and laser vitreolysis. This article aims to review the literature discussing methods for diagnosing and treating floaters.

Introduction

Visually significant vitreous opacities, commonly referred to as floaters, can frequently impact a patient's quality of life. One survey sent to smartphone users reported that 76% of respondents reported floaters, 33% of whom had noticeable visual impairment.[1] While this cannot be applied to the general population due to the selection bias of a smartphone survey selecting younger patients, it still shows the possibly high incidence of floaters.

The most common cause of floaters are primary vitreous opacities. These are caused by the degeneration of the vitreous gel structure leading to liquefaction of the vitreous body and aggregation of vitreous collagen fibers. This occurs with increasing age or earlier in patients with high myopia. Other common causes of visually significant floaters include posterior vitreous detachment (PVD), diabetic vitreopathy, and inflammation involving the posterior segment of the eye.[2,3] Floaters may not impair visual acuity, but they can cause a decrease in contrast sensitivity and induce scattering of light. Both of these changes lead to subjective visual impairment.[2] Patients often report difficulty with vision in bright light and trouble reading.[4] The term myodesopsia – derived from Greek (myioides = flylike and opsis = vision) – describes the fragmented vision experienced by patients with floaters.[2]

Diagnosis

Despite the significant impact of vitreous opacities on vision, they are difficult to measure objectively. Floaters can be visible on fundoscopic exams, but their size or location does not always correlate with the severity of symptoms. Several imaging methods are used to document opacities.

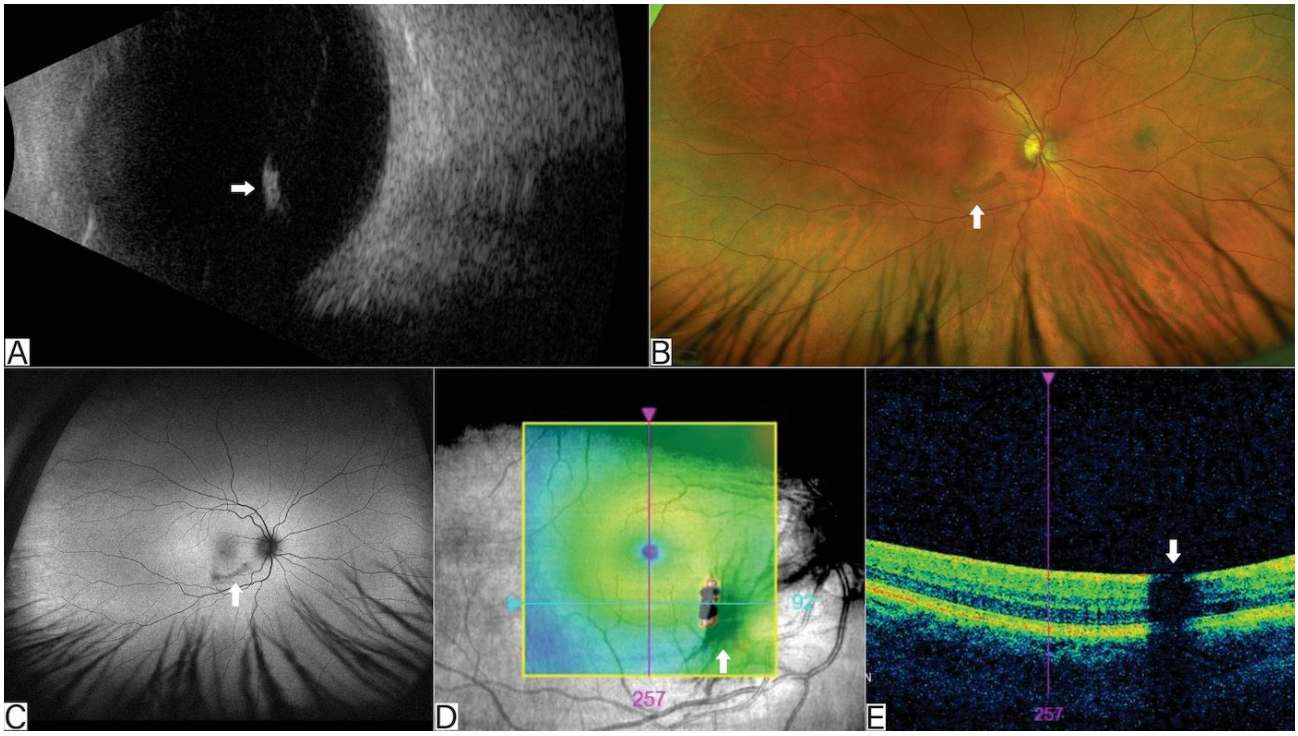


Figure 1. (A) B-scan ultrasound of PVD (arrow) with vitreous opacity, (B) color photograph of vitreous opacity, seen as hyperpigmented consolidation anterior to the retina (arrow), (C) fundus autofluorescence showing hypo-autofluorescent artifact (arrow) from vitreous opacity, (D) obscuration on OCT near-infrared reflectance from opacity (arrow), (E) OCT section of retina with shadow (arrow) of vitreous opacity.

Optical coherence tomography (OCT) can help clinicians identify the presence of vitreous opacities.[3,5] However, it is better at identifying floaters closer to the retina than those in the central or anterior vitreous. Central vitreous opacities are typically the source of floater phenomena.[3]

Ophthalmic ultrasound, or B-scan, allows the visualization of the entire vitreous body. It can detect degeneration in the vitreous, often represented by a heterogenous appearance of the posterior segment. B-scan is also used to identify a PVD. Opacities can be more accurately identified using quantitative ultrasound. This technique involves layering multiple ultrasound frames into one image, like CT or MRI. Then, a computer algorithm determines specific regions of interest (ROI) and measures the energy, mean, and percentage of ROI occupied by opacities. Compared to other imaging modalities, this method correlates better with diminished contrast sensitivity and quality of life in these patients.[6]

Another imaging modality for floaters is infrared confocal scanning laser ophthalmoscopy (SLO). SLO has been shown to accurately grade the severity of opacities based on their size and proximity to the macula.[7] SLO also provides a more dynamic view of anterior floaters not often detected by OCT. Additionally, a positive correlation exists between patients' symptoms and the severity of opacities on SLO.[8]

Most commonly, these opacities can be documented with a wide-field color fundus photo (Optos plc., Marlborough, MA, USA), B-scan ultrasound, and near-infrared on OCT (Zeiss, Hebron, KY, USA) as shown in Figure 1.

Management of Vitreous Opacities

Many physicians take a conservative approach to managing vitreous opacities since they are sometimes difficult to appreciate objectively and visual acuity is often unchanged. This approach entails regular monitoring for retinal detachments (RDs) or breaks but no other intervention.[9] Two forms of intervention are currently utilized. Pars plana vitrectomy (PPV) and Neodymium:yttrium-aluminum-garnet (nd:YAG) laser vitreolysis.

More recently, PPV for symptomatic floaters – colloquially termed "floaterectomy" – has become more accepted in the retina community.[10] Arguments against PPV include the general risk of the surgery, unrealistic patient expectations and possible ridicule by the retina community.[11]

Pars Plana Vitrectomy Technique

PPV is a surgical procedure utilized to remove vitreous gel. Although the procedure has been performed for over forty years, the instrumentation has improved significantly over the past two decades. In this procedure, the light source, infusion cannula, and vitreous cutter are inserted through the pars plana portion of the eye. This approach prevents any injury to the retina and the natural lens. Currently, common instrumentation sizes used are 23, 25 or 27 gauge.

Small gauge vitrectomy instruments with high cut rates of vitreous may be less likely to cause intraoperative complications.[12] The surgeon may or may not induce a posterior vitreous detachment (PVD). The induction of a PVD manually separates the vitreous gel from its attachment to the underlying retina resulting in more complete removal of vitreous.

Risks

The most common risk of PPV is the accelerated rate of cataract formation in phakic eyes. In multiple studies, approximately half of the otherwise healthy phakic eyes needed cataract extraction within five years following PPV.[12] Limited or core vitrectomy without PVD induction preserves retrolental vitreous and may decrease the risk of early cataract formation or slow its progression. The risk of needing cataract extraction in these cases is approximately 20% within 12 months of the PPV.[13]

Postoperative RD is a less common complication of PPV. Intraoperative iatrogenic retinal tears can cause an RD necessitating further surgery. PVD induction may result in retinal tear formation, thereby increasing the risk of RD.[12] There is also an increased risk in cases with larger gauge instruments or lower cut rates.[12] Reports of retinal tears after elective PPV range from 3-16% of cases.[14,15] The rate of RD is approximately 2%.[16]

Other infrequent postoperative complications associated with elective PPV are vitreous hemorrhage, macular edema, glaucoma, or endophthalmitis. These collectively occur in less than 5% of cases.

Benefits

The primary benefit of PPV for symptomatic floaters is a qualitative improvement in vision. As floaters do not dramatically impact visual acuity, most studies do not show a significant improvement in this outcome.[17,18] However, patients report subjective improvement in vision and performance of daily activities, leading to an enhanced quality of life.[19,20] Postoperatively, patients report high satisfaction.[19,21] These outcomes are similar regardless of surgical technique.

Patients also experience objective improvements, especially of contrast sensitivity function.[21,22] This can be measured with the Freiburg Acuity Contrast Test after patients adapt to a dark environment. This test requires patients to read dark grey letters on a lighter grey background, and the letters progressively get lighter in color. The amount of contrast sensitivity function can be measured with the Weber index, which calculates the difference in luminance between the letter and the background. These measurements can be used to compare pre-operative and post-operative function.

Quantitative ultrasound can confirm elective PPV's beneficial outcomes.[21] This can be done pre-operatively to detect the vitreous heterogeneity, but it should also be done post-operatively to ensure the removal of opacities. Vitreous echodensity typically diminishes after PPV, allowing confirmation of removal.

Nd:YAG Laser Vitreolysis

Laser vitreolysis is an alternative treatment for vitreous opacities. This method to treat vitreous opacities is cost-effective and minimally invasive compared to PPV, also decreasing the risk of postoperative infection.

YAG laser vitreolysis aims to disrupt a single large opacity into smaller fragments, reducing the size of the floater's shadow on the retina. For multiple opacities, the laser is directed at the posterior hyaloid face, allowing the vitreous to collapse and reconfigure in the inferior pole.[23] Typically, the ideal opacities to target are those in the central part of the vitreous cavity, away from the retina and retrolental region. The reported improvement of subjective visual function ranges from 50 to 70%.[24,25] Most patients experience moderate symptom improvement and fewer report complete resolution.

Similar to PPV, the main complications of YAG laser vitreolysis are retinal tears and breaks, acceleration of cataract formation, and development of open-angle glaucoma.[26–28] While there have been few reported cases of adverse events, most findings are from small-scale trials or case reports. More investigation is needed on the best technique and indication for YAG laser vitreolysis.

Conclusion

Visually significant floaters can pose a significant burden on patients. With advances in imaging and surgical instrumentation, there are now more definitive options to diagnose and treat these patients. Although these interventions are not without risks, the benefits may outweigh the risks for many patients, warranting thorough discussions on a case-by-case basis.

References

1. Webb BF, Webb JR, Schroeder MC, North CS. Prevalence of vitreous floaters in a community sample of smartphone users. Int J Ophthalmol. 2013;6(3):402-405. doi:10.3980/j.issn.2222-3959.2013.03.27
2. Sebag J. Vitreous and Vision Degrading Myodesopsia. Prog Retin Eye Res. 2020;79:100847. doi:10.1016/j.preteyeres.2020.100847
3. Milston R, Madigan MC, Sebag J. Vitreous floaters: Etiology, diagnostics, and management. Surv Ophthalmol. 2016;61(2):211-227. doi:10.1016/j.survophthal.2015.11.008
4. Hahn U, Krummenauer F, Ludwig K. 23G pars plana vitrectomy for vitreal floaters: prospective assessment of subjective self-reported visual impairment and surgery-related risks during the course of treatment. Graefes Arch Clin Exp Ophthalmol. 2018;256(6):1089-1099. doi:10.1007/s00417-018-3979-8
5. Ruminski D, Sebag J, Toledo RD, et al. Volumetric Optical Imaging and Quantitative Analysis of Age-Related Changes in Anterior Human Vitreous. Invest Ophthalmol Vis Sci. 2021;62(4):31. doi:10.1167/iovs.62.4.31
6. Mamou J, Wa CA, Yee KMP, et al. Ultrasound-based quantification of vitreous floaters correlates with contrast sensitivity and quality of life. Invest Ophthalmol Vis Sci. 2015;56(3):1611-1617. doi:10.1167/iovs.14-15414
7. Son G, Sohn J, Kong M. Acute symptomatic vitreous floaters assessed with ultra-wide field scanning laser ophthalmoscopy and spectral domain optical coherence tomography. Sci Rep. 2021;11(1):8930. doi:10.1038/s41598-021-88371-9
8. Garcia-Aguirre G, Henaine-Berra A, Salcedo-Villanueva G. Visualization and Grading of Vitreous Floaters Using Dynamic Ultra-Widefield Infrared Confocal Scanning Laser Ophthalmoscopy: A Pilot Study. J Clin Med. 2022;11(19):5502. doi:10.3390/jcm11195502
9. Broadhead GK, Hong T, Chang AA. To Treat or Not to Treat: Management Options for Symptomatic Vitreous Floaters. Asia-Pac J Ophthalmol Phila Pa. 2020;9(2):96-103. doi:10.1097/APO.0000000000000276
10. Staff B. Retina Surgeons Share Their Treatment Preferences. Published November 10, 2022. Accessed July 17, 2023. https://www.reviewofophthalmology.com/article/retina-surgeons-share-their-treatment-preferences
11. Cohen MN, Rahimy E, Ho AC, Garg SJ. Management of Symptomatic Floaters: Current Attitudes, Beliefs, and Practices Among Vitreoretinal Surgeons. Ophthalmic Surg Lasers Imaging Retina. 2015;46(8):859-865. doi:10.3928/23258160-20150909-11
12. Zeydanli EO, Parolini B, Ozdek S, et al. Management of vitreous floaters: an international survey the European VitreoRetinal Society Floaters study report. Eye. 2020;34(5):825-834. doi:10.1038/s41433-020-0825-0
13. Yee KMP, Tan S, Lesnik Oberstein SY, et al. Incidence of Cataract Surgery after Vitrectomy for Vitreous Opacities. Ophthalmol Retina. 2017;1(2):154-157. doi:10.1016/j.oret.2016.11.012
14. Dysager DD, Koren SF, Grauslund J, Wied J, Subhi Y. Efficacy and Safety of Pars Plana Vitrectomy for Primary Symptomatic Floaters: A Systematic Review with Meta-Analyses. Ophthalmol Ther. 2022;11(6):2225-2242. doi:10.1007/s40123-022-00578-9
15. Tan HS, Mura M, Oberstein SYL, Bijl HM. Safety of Vitrectomy for Floaters. Am J Ophthalmol. 2011;151(6):995-998. doi:10.1016/j.ajo.2011.01.005
16. Mura M, Barca F, Dell'Omo R, Nasini F, Peiretti E. Iatrogenic retinal breaks in ultrahigh-speed 25-gauge vitrectomy: a prospective study of elective cases. Br J Ophthalmol. 2016;100(10):1383-1387. doi:10.1136/bjophthalmol-2015-307654
17. Lin Z, Zhang R, Liang QH, et al. Surgical Outcomes of 27-Gauge Pars PLana Vitrectomy for Symptomatic Vitreous Floaters. J Ophthalmol. 2017;2017:5496298. doi:10.1155/2017/5496298
18. Fink S, Kumar JB, Cunningham MA. Small-Gauge Pars Plana Vitrectomy for Visually Significant Vitreous Floaters. J Vitreoretin Dis. 2021;5(3):247-250. doi:10.1177/2474126420961736
19. Morris RE. Vitreous Opacity Vitrectomy (VOV): Safest Possible Removal of "Floaters." Clin Ophthalmol Auckl NZ. 2022;16:1653-1663. doi:10.2147/OPTH.S361557
20. Reference 20: Waseem TC. Pars Plana Vitrectomy for Symptomatic Vitreous Floaters: Another Look. Int J Ophthalmol Clin Res. 2021;8(1). doi:10.23937/2378-346X/1410124
21. Sebag J, Yee KMP, Nguyen JH, Nguyen-Cuu J. Long-Term Safety and Efficacy of Limited Vitrectomy for Vision Degrading Vitreopathy Resulting from Vitreous Floaters. Ophthalmol Retina. 2018;2(9):881-887. doi:10.1016/j.oret.2018.03.011
22. Sebag J, Yee KMP, Wa CA, Huang LC, Sadun AA. Vitrectomy for floaters: prospective efficacy analyses and retrospective safety profile. Retina Phila Pa. 2014;34(6):1062-1068. doi:10.1097/IAE.0000000000000065
23. Delaney YM, Oyinloye A, Benjamin L. Nd:YAG vitreolysis and pars plana vitrectomy: surgical treatment for vitreous floaters. Eye. 2002;16(1):21-26. doi:10.1038/sj.eye.6700026
24. Ludwig GD, Gemelli H, Nunes GM, Serracarbassa PD, Zanotele M. Efficacy and safety of Nd:YAG laser vitreolysis for symptomatic vitreous floaters: A randomized controlled trial. Eur J Ophthalmol. 2021;31(3):909-914. doi:10.1177/1120672120968762
25. Nunes GM, Ludwig GD, Gemelli H, Zanotele M, Serracarbassa PD. Long-term evaluation of the efficacy and safety of Nd:YAG laser vitreolysis for symptomatic vitreous foaters. Arq Bras Oftalmol. Published online September 23, 2022:S0004-27492022005010216. doi:10.5935/0004-2749.2021-0395
26. Hahn P, Schneider EW, Tabandeh H, Wong RW, Emerson GG. Reported Complications Following Laser Vitreolysis. JAMA Ophthalmol. 2017;135(9):973-976. doi:10.1001/jamaophthalmol.2017.2477
27. Sun IT, Lee TH, Chen CH. Rapid Cataract Progression after Nd:YAG Vitreolysis for Vitreous Floaters: A Case Report and Literature Review. Case Rep Ophthalmol. 2017;8(2):321-325. doi:10.1159/000477159
28. de Vries E, Faraj C, Gerbrandy F, Hulsman C. Secondary open-angle glaucoma following YAG-laser vitreolysis. BMJ Case Rep. 2022;15(4):e248937. doi:10.1136/bcr-2022-248937

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The Status of Cadaver-Based Anatomy Instruction in Missouri Medical Schools

by J. Patrick Brooks, MD & Carlton Homan, BS

The allopathic and osteopathic medical schools of Missouri continue to place a strong emphasis on cadaver-based anatomical instruction, mostly by cadaveric dissection.



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Abstract

Cadaveric dissection has been a foundational principle of medical anatomic education for the last 400 years, yet medical anatomy course hours have been drastically reduced in the last decades. With this course reduction and the availability of other modalities for anatomic instruction, the physician may question the current role of cadavers in medical anatomy courses. This study aims to evaluate the role cadaveric dissection plays in anatomy programs in allopathic and osteopathic medical schools in Missouri and compare course hours to the national trend. Ongoing challenges are reviewed, including the international shortage of qualified cadaveric anatomists.

Introduction

The use of human cadavers in anatomic education has been a cornerstone of medical education since the inception of Medicine. Andreas Vesalius (1514 – 1564) is known for his landmark treatise *De Humani Corporis Fabrica* and its detailed illustrations characteristic of the Renaissance (Figure 1). The source of this substantial leap in anatomical knowledge was his personal labors in dissection of human cadavers, work that was previously relegated to barber-surgeons.[1] Advanced anatomical knowledge comes from dissection. This foundational principle of medical education has lasted many hundreds of years (Figure 2).

While gross anatomy remains important in medical education, it has been the victim of the time crunch borne by the vast increase in knowledge of other biomedical sciences seeking their own claims on classroom time. A series of reports in the last three decades provided numerous recommendations for medical education curricula reform. These recommendations included the integration of the basic sciences with clinical education, integration of clinical experience at all levels, emphasis on self-directed learning, and individualization of the learning process.[2] Anatomy lecture and lab hours were progressively reduced. Teaching was to become less compartmentalized. The progressive decrease in instructional time for gross anatomy over the last several decades has been well documented (Figure 3).[3, 4-9] The most drastic decrease, noted in 1975, prompted the authors to proclaim, "the amount of detail in many courses in gross regional anatomy has now decreased below the safety level."[5]

With this decline in the time allotted to the study of anatomy in medical school, and particularly the decline in laboratory time, a number of other advances in alternative anatomical pedagogical techniques arose. As computers became more powerful, anatomical



Figure 1. Frontispiece to De Humani Corporis Fabrica, Andreas Vesalius, 1543, revealing a bearded Vesalius dissecting a corpse.
Source: Wikipedia

computer-assisted learning (CAL) programs flourished. Computerized anatomy visualization systems such as Anatomage were developed that display images of life-sized cadavers for touchscreen "dissections" through the layers. Synthetic cadavers are available, free of formaldehyde vapors. With the high cost of cadaver lab buildings, the labor of cadaveric preservation, and cadavers' variance from lifelike colors and textures, perhaps this centuries-old technique is becoming obsolete.

Purpose of this Study

This study aims to evaluate the role cadaveric dissection plays in anatomy programs in allopathic and osteopathic medical schools in Missouri. The importance of cadaveric anatomy in these programs will be compared to alternative pedagogical techniques. Assessing the ongoing decline in anatomic instruction, Missouri medical anatomy course hours will be compared to available national data.

Methods

This study was approved by the Missouri State University Institutional Review Board (#IRB-FY2021-16). A faculty member was contacted by email from each of the four allopathic and three osteopathic Missouri medical schools' anatomy departments. Surveys were conducted by email or phone, as to the faculty member's preference. Initial questions focused on the use of cadavers versus alternate teaching methods. The study was then expanded to review instructional hours in typical anatomy lecture and lab courses, and student-to-faculty teaching ratios. The answers and opinions are to be presented in aggregate. The results will be compared with available data from the most recent national survey.

Results

An anatomy faculty member at each of the seven Missouri medical school anatomy departments was contacted to discuss the use of cadavers in their 2019 courses. All seven programs reported use of cadavers as their primary teaching modality in the anatomy lab; none reported any decrease in the usage of cadavers in the last decade. Six of the seven schools taught primarily by student-performed dissection. Prosected (previously dissected) cadaveric specimens were used sparingly in four of these schools for focused areas. One school reported anatomy lab instruction entirely with prosected cadavers throughout the school's history, while being quick to point out that they recognized the value of a dissection-based curriculum and therefore offer dissection electives. Alternating dissection, wherein student groups take turns participating in laboratory dissection, was used in four programs to make the best use of the decreasing laboratory time. Two anatomy programs integrated their anatomy courses with the schedule of other first year basic and clinical science courses, and one considered their course to be partially integrated. Of the four programs employing a traditional stand-alone regional anatomy course, one was considering integration in the near future. No school reported any difficulty with cadaver shortages. All schools considered the use of cadavers to be cost-effective, with an estimated cost of $1,500 to acquire a cadaver from a university with a donor body program in 2019. Only one school had an Anatomage table (estimated cost $77,000) (Figure 4), which was used in the lecture hall. No school had a synthetic cadaver (estimated cost $40,000). No school had a mandated emphasis on CAL instruction, although there was general agreement that it can augment cadaver-based learning. Five of the seven programs noted a general shortage of qualified anatomists to teach cadaver-based anatomy. Regarding the foreseeable future of medical



Figure 2. Medical students conducting a dissection at the Woman's College of Pennsylvania, Philadelphia, PA, Circa 1880.
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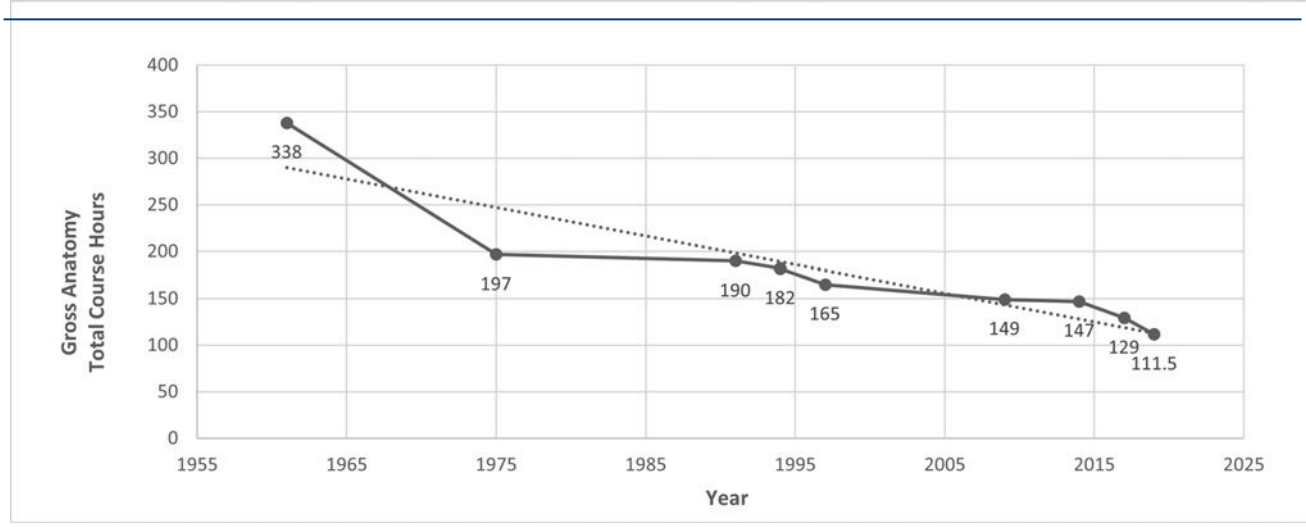


Figure 3. The trend in Medical School gross anatomy total course hours. Recent decreases in course hours may in part reflect some schools' integration of anatomy teaching into other courses. Data abstracted from prior reviews.2,4-9 The final data point represents the averages of Missouri medical anatomy programs in this study.

anatomy instruction in Missouri, all seven programs expected their anatomy education to remain centered on the use of cadavers.

After a recovery period following the COVID-19 pandemic, the seven medical schools in Missouri were surveyed regarding their 2019 course hours of instruction in gross anatomy lecture, lab, neuroanatomy, and embryology. Survey techniques included electronic communication with members of the anatomy faculty. When faculty were unavailable, medical students were contacted for a review of their course syllabi to allow a sampling of a majority of the programs. Responses were

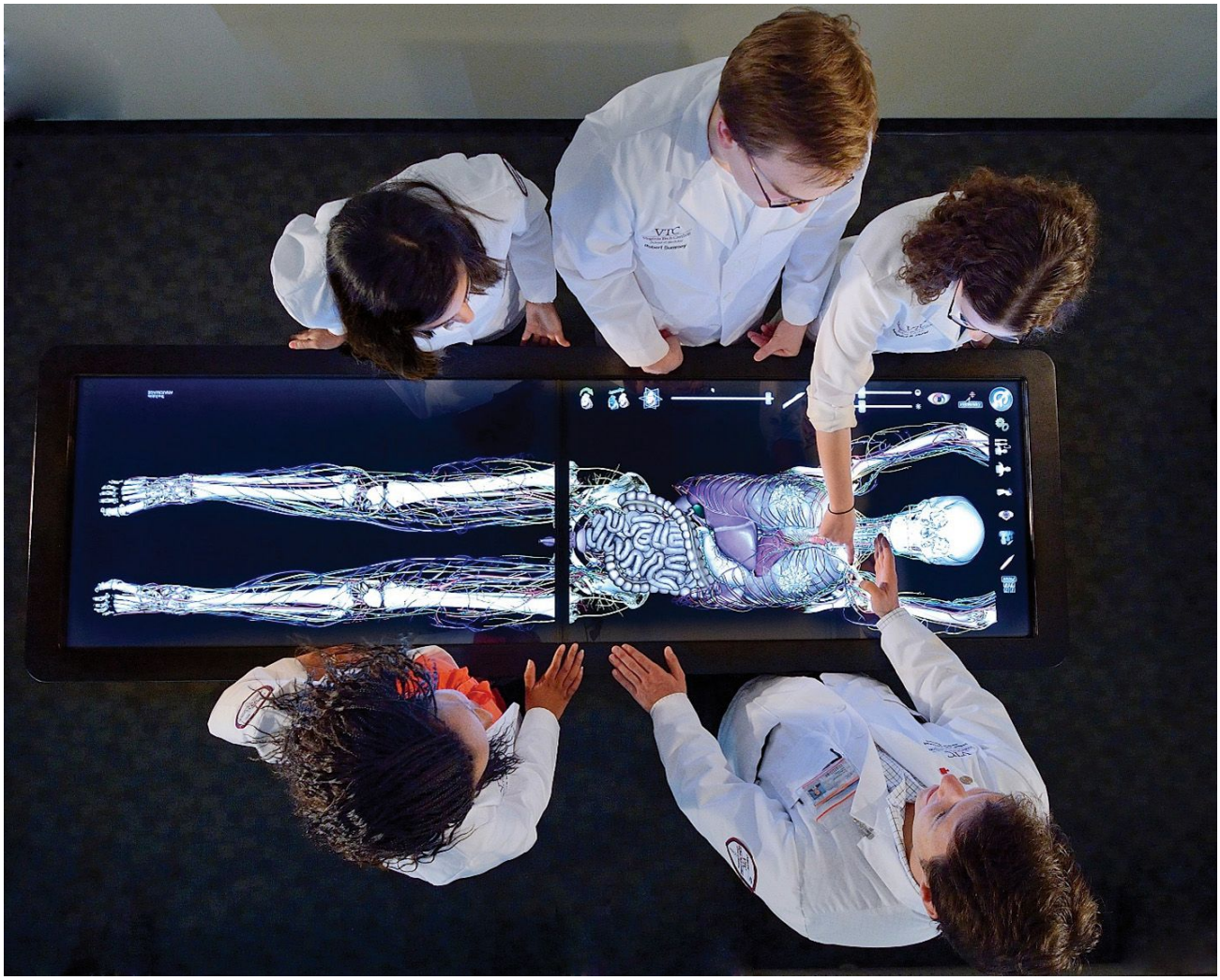


Figure 4. Anatomage table in the virtual anatomy lab at the Virginia Tech Carilion School of Medicine.
Source: https://news.vt.edu/articles/2014/02/022714-vtc-anatomytable.html

obtained from five out of seven programs, three from faculty and two from medical students. Embryology data was the exception, with only four programs responding. All responses included a mix of allopathic and osteopathic programs. The course hour totals are displayed in ranges and averages (Table 1). Data on student to faculty ratio within the gross anatomy lab was obtained as well. Wide ranges were reported, from 21:1 up to 62:1. Average student to faculty ratios were 42.8:1 (SD +/- 18.3). This data does not include graduate students' instruction in the labs, which was significant especially in programs with higher ratios.

Discussion

Gross human anatomy has classically been taught in the first year of the medical curriculum with other basic sciences, and remains a foundational subject in medical education. When postgraduate residency program directors of various specialties were asked to rank the importance of basic sciences within medical education, gross anatomy came out on top.[3] After completion of residency training in Germany, the physicians ranked gross anatomy only behind internal medicine when grading the relevance of all their prior medical school subjects.[10]

All Missouri medical schools continue to emphasize the importance of gross anatomy as well as cadaveric laboratory instruction, with each still employing cadaveric teaching as their primary mode of experiential learning. Six of the seven anatomy departments prioritized the traditional pedagogic technique of cadaveric dissection and planned to do so in the future.

Table 1. Survey results of Missouri medical anatomy course hours.

	Gross Anatomy Lecture	Gross Anatomy Lab	Neuroanatomy Lecture	Neuroanatomy Lab	Embryology
Range	12 – 80 hrs	32 – 105 hrs	8 – 68 hrs	9 – 20 hrs	1 – 21 hrs
Mean (SD)	48.7 hrs (22.3)	62.8 hrs (28.5)	24.3 hrs (21.8)	13.0 hrs (4.3)	9.8 hrs (10.3)

Alternating dissection, used in four of six dissection-based Missouri courses, allows all students to experience dissection within the confines of limited course hours.

A 2006 publication emphasized the importance of dissection in medical anatomy courses with a discussion of the five dissection-based US programs who abandoned dissection, with each resuming dissection soon thereafter.[11] Two returned to dissection due to poor performance of their students in their clinical clerkships. One of those schools found that prosections were not cost-effective, presumably because faculty needed remuneration for the tedious process previously done by students. One school returned to dissection due to concerns of preparedness of their students and concerns about the appearance to the accreditation board. In two other schools, the students chose to return to dissecting. The most recent national survey using 2017 data revealed that all 66 responding medical anatomy programs continued to use cadavers, with 44 relying completely on student performed dissection, 19 using a combination of prosection and dissection, and only three using entirely prosected specimens.[9]

One in seven Missouri schools used a computerized anatomy visualization system such as Anatomage, similar to the 11% national usage rate. Although CAL is increasingly used in anatomical education nationally, it has generally been in a supportive role rather than a replacement for dissection[12-18] in agreement with the responses from the Missouri anatomists. Historically, students most often preferred cadaveric instruction to CAL.[19-21] A review of radiologic imaging shows global support for its enhancement of the quality and efficiency of human anatomy instruction.[22] By 2017, US medical school anatomy laboratories included the use of computed tomography, computer stations, and virtual/video dissections in roughly half of the schools.[23]

Medical students have been asked about preferences in teaching methods. When comparing dissection, prosection with demonstration, didactic teaching only, models, CAL, and living anatomy with radiologic studies, students preferred cadaveric dissection as the method of teaching to achieve the full set of course goals.[24] Students and expert anatomists have also found dissection to be the most "fit for purpose" to achieve relevant learning, gain three-dimensional appreciation of human anatomy, and achieve the widest range of course aims.[25] The advantages of cadaveric dissection are reviewed in detail in an invited argument: "cadavers, like patients, are three dimensional beings; touch-mediated perception reinforces learning and is not currently well simulated elsewhere; anatomic variability is introduced; eye hand coordination is developed by the use of clinically relevant instruments; peer learning/teaching/teamwork is developed; and the concept of death and dying are introduced."[26]

With the national trend in the reduction in anatomic teaching, the average teaching hours from Missouri medical schools for each 2019 course were compared to the most recent national survey of 2017[9] data using a one sample Z-test (Figure 5). No statistically significant differences in course hours of instruction were noted between the two groups, although total neuroanatomy hours approached statistical significance (p=0.071). With wide variability in Missouri neuroanatomy teaching and national neuroanatomy data varying tremendously (from four to 200 hours of instruction), sampling errors are possible in each group.

Although integration of anatomy with other basic sciences courses has been recommended for many years,[3] the process requires significant time, work, planning, and organization.[19] Nationally, only 6% of anatomy courses are delivered as stand-alone courses (no connection with other concurrently taught disciplines). This is a rapidly changing metric, as only 53% of US anatomy programs reported integration in the national survey four years earlier.[8] While four of seven Missouri programs reported no integration for this study's survey, one was considering integration. This metric is likely closer to the national trend at this time.

When comparing Missouri medical school cadaveric anatomy teaching to the national averages,

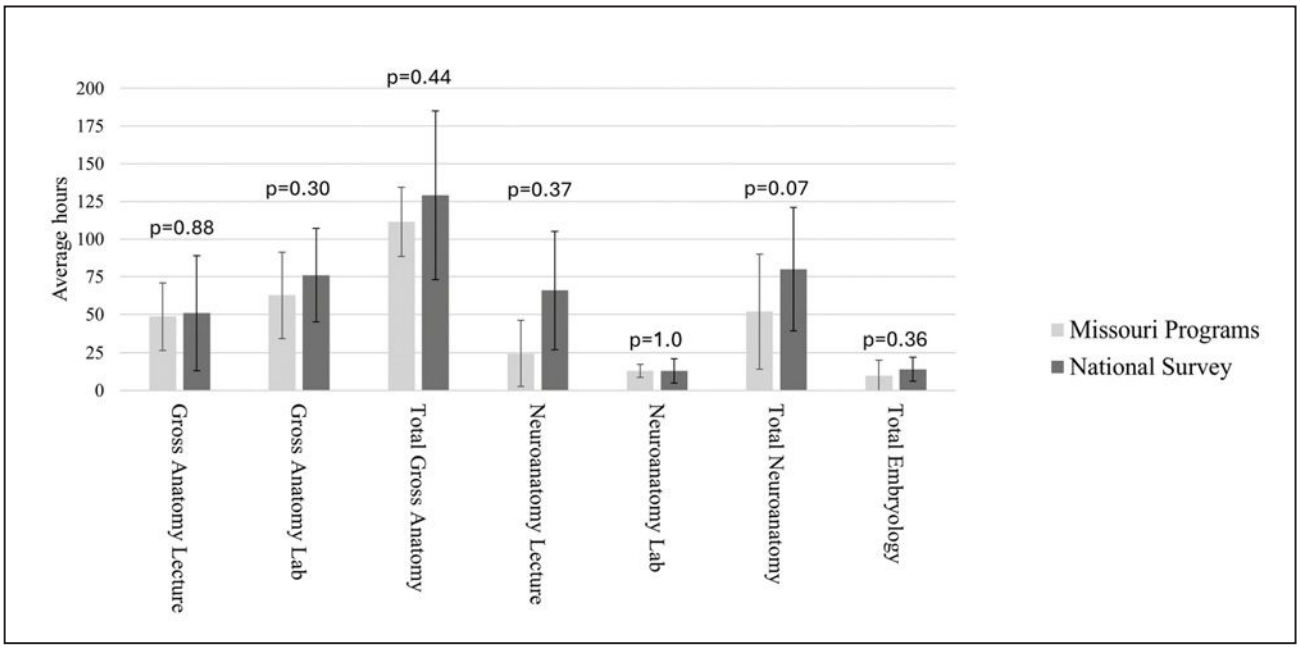


Figure 5. Average Missouri medical anatomy course hours from 2019, compared to 2017 national data.[9]

the most significant difference is found in laboratory student to faculty ratios. Missouri medical school gross anatomy labs averaged 41.8 students per faculty (SD +/- 18.3), while the national average is 19:1 (no standard deviation provided).[9] Comparing these ratios with a one-sample, two tailed t-test revealed a significant difference, p=0.029. Two Missouri programs with higher student to faculty ratios extensively supplement their laboratory faculty with graduate students (not included in faculty numbers) who dedicate an entire year to anatomy instruction. This allows them to meet teaching obligations with fewer faculty, an important consideration given the status of faculty availability.

Qualified anatomy instructors are in short supply internationally. Over 65% of anatomy departmental leaders in the US, Canada, and the European Union anticipate moderate to great difficulty hiring anatomy educators.[27] The number of anatomy educator job postings in US medical schools more than doubled from 21 postings in 2017 to 52 postings in 2018. Twenty-one percent of these postings were never filled. Student enrollment in allopathic and osteopathic medical schools has risen significantly since 2002, increasing by 11,477 students, a 59% increase.[28] The number of graduating US anatomists with a doctorate (PhD) has decreased over 50 years to a low of eight graduates in 2017.[29] Additional health career programs compete for these anatomy instructors, with 58 new physician assistant programs opening in the US between 2020 to 2023 (Figure 6).[30] The average age of anatomy faculty is advancing in parallel with the advancing age of US physicians. A survey on projected anatomy faculty plans estimates the rate of faculty retirements at 40 per year.[31] When compared to the projection of 22 anatomy PhD graduates per year,[29] this shortage of anatomists will certainly continue.

Paralleling the data on student to faculty teaching ratios in Missouri anatomy programs, five of the seven departments interviewed for this article sensed this shortage of available cadaveric anatomy faculty in response to the survey. In the last six months, six medical schools in Missouri alone posted openings for anatomy faculty. Degree requirements for anatomy faculty openings typically list "Doctoral degree: PhD, MD, or DO". In 2019, 11% of full time US medical school anatomy faculty held an MD degree.[32] While some programs do not list faculty members online, physicians can be found in at least four medical school anatomy departments in Missouri.

Several reports discuss the opinions of clinicians, graduate medical education program directors, and graduating medical students all agreeing that the recent course reductions and limited clinical correlations have resulted in inadequately prepared graduates.[2,33-36] In response to course hour reductions, several anatomy programs describe positive outcomes from their novel incorporation of clinical concepts within their anatomy courses.[37-40] Medical students strongly support this



Figure 6. Physician Assistant students in the Graduate Anatomy Dissection Lab, Missouri State University, Springfield, Missouri.

content in the first year anatomy course, and 91% agree these clinical examples provide motivation to learn anatomy.[41] A physician looking for a new challenge can fill a position of need in a medical anatomy program and bring unparalleled clinical knowledge and experience to the course.

Limitations of this Study

Survey studies are limited by incomplete response rates, which can introduce nonresponse bias. Response rates for the Missouri data were 100% regarding cadaveric usage questions, and 71.4% for most data on hours of instruction. Obtaining national data regarding medical anatomy programs is more challenging, with the most recent national survey obtaining a 61% response rate for 2017 data.[9] That publication also discusses the challenges of calculating and reporting instructional hours for various courses as contributing to lower response rates on this subject.

The transition from the first round of cadaveric usage questions to the course hours survey coincided with the COVID-19 pandemic. The challenges of cadaveric instruction during the pandemic are outside the scope of this study, yet the turmoil of recovering from pandemic course changes led to delays and a lower response rate. Certain aspects of anatomic instruction may have changed for some institutions between 2019 and the time of manuscript submission, although no program anticipated any movement away from the use of cadavers. For comparison, the Cleveland Clinic group has authored the last three sequential national studies, the most recent using 2017 data, as was used for comparisons in this manuscript.[7-9] Based on these prior publication dates, any potential national follow up study is delayed further than their prior intervals, possibly related to similar challenges in data gathering related to pandemic recovery.

Conclusion

The allopathic and osteopathic medical schools of Missouri continue to place a strong emphasis on cadaver-based anatomical instruction, mostly by cadaveric dissection. None of the newer teaching modalities are poised to take over. Instructional hours for the various anatomic subspecialties in Missouri medical anatomy programs are on par with national trends, which have decreased to a level concerning to many anatomists and physicians. Both locally and internationally, the shortage of cadaveric anatomy faculty is the biggest challenge for the future of medical anatomy instruction. Physicians, with training in cadaveric anatomy (likely exceeding current course durations) and unparalleled clinical knowledge could bridge these challenges, should they have interest in transitioning to a teaching role.

References

1. Ghosh SK. Human cadaveric dissection: a historical account from ancient Greece to the modern era. Anat Cell Biol. 2015;48(3):153-169.
2. Drake RL. A retrospective and prospective look at medical education in the United States: trends shaping anatomical sciences education. J Anat. 2014;224(3):256-260.
3. Cottam WW. Adequacy of medical school gross anatomy education as perceived by certain postgraduate residency programs and anatomy course directors. Clin Anat. 1999;12(1):55-65.
4. Eldred E, Eldred B. Supply and demand for faculty in anatomy. J Med Educ. 1961;36:134-147.
5. Sinclair D. The two anatomies. Lancet. 1975;1(7912):875-878.
6. Collins TJ, Given RL, Hulsebosch CE, Miller BT. Status of gross anatomy in the U.S. and Canada: Dilemma for the 21st century. Clin Anat. 1994;7:275-296.
7. Drake RL, McBride JM, Lachman N, Pawlina W. Medical education in the anatomical sciences: the winds of change continue to blow. Anat Sci Educ. 2009;2(6):253-259.
8. Drake RL, McBride JM, Pawlina W. An update on the status of anatomical sciences education in United States medical schools. Anat Sci Educ. 2014;7(4):321-325.
9. McBride JM, Drake RL. National survey on anatomical sciences in medical education. Anat Sci Educ. 2018;11(1):7-14.
10. Pabst R, Rothkötter HJ. Retrospective evaluation of undergraduate medical education by doctors at the end of their residency time in hospitals: consequences for the anatomical curriculum. Anat Rec. 1997;249(4):431-434.
11. Rizzolo LJ, Stewart WB. Should we continue teaching anatomy by dissection when...? Anat Rec B New Anat. 2006;289(6):215-218.
12. Gunderman RB, Wilson PK. Viewpoint: exploring the human interior: the roles of cadaver dissection and radiologic imaging in teaching anatomy. Acad Med. 2005;80(8):745-749. Kaye A, Miranda M, Jones T. The Donor Letter Project: Learning Professionalism and Fostering Empathy in an Anatomy Curriculum. J Med Humanit. 2019;40(4):607-612.
13. Ghosh SK. Cadaveric dissection as an educational tool for anatomical sciences in the 21st century. Anat Sci Educ. 2017;10(3):286-299.
14. Tam MD, Hart AR, Williams S, Heylings D, Leinster S. Is learning anatomy facilitated by computer-aided learning? A review of the literature. Med Teach. 2009;31(9):e393-e396.
15. Battulga B, Konishi T, Tamura Y, Moriguchi H. The effectiveness of an interactive 3-dimensional computer graphics model for medical education. Interact J Med Res. 2012;1(2):e2. Published 2012 Jul 9.
16. Saltarelli AJ, Roseth CJ, Saltarelli WA. Human cadavers Vs. multimedia simulation: A study of student learning in anatomy. Anat Sci Educ. 2014;7(5):331-339.
17. Biasutto SN, Caussa LI, Criado del Río LE. Teaching anatomy: cadavers vs. computers?. Ann Anat. 2006;188(2):187-190.
18. Houser JJ, Kondrashov P. Gross Anatomy Education Today: The Integration of Traditional and Innovative Methodologies. Mo Med. 2018;115(1):61-65.
19. Estai M, Bunt S. Best teaching practices in anatomy education: A critical review. Ann Anat. 2016;208:151-157.
20. Jeyakumar A, Dissanayake B, Dissabandara L. Dissection in the Modern Medical Curriculum: An Exploration into Student Perception and Adaptions for the Future. Anat Sci Educ. 2020;13(3):366-380.
21. Azer SA, Eizenberg N. Do we need dissection in an integrated problem-based learning medical course? Perceptions of first- and second-year students. Surg Radiol Anat. 2007;29(2):173-180.
22. Grignon B, Oldrini G, Walter F. Teaching medical anatomy: what is the role of imaging today?. Surg Radiol Anat. 2016;38(2):253-260.
23. McBride JM, Drake RL. Longitudinal cohort study on medical student retention of anatomical knowledge in an integrated problem-based learning curriculum. Med Teach. 2016;38(12):1209-1213.
24. Kerby J, Shukur ZN, Shalhoub J. The relationships between learning outcomes and methods of teaching anatomy as perceived by medical students. Clin Anat. 2011;24(4):489-497.
25. Patel KM, Moxham BJ. The relationships between learning outcomes and methods of teaching anatomy as perceived by professional anatomists. Clin Anat. 2008;21(2):182-189.
26. Granger NA. Dissection laboratory is vital to medical gross anatomy education. Anat Rec B New Anat. 2004;281(1):6-8.
27. Wilson AB, Kaza N, Singpurwalla DJ, Brooks WS. Are Anatomy PhDs Nearing Extinction or Adapting to Change? United States Graduate Education Trends in the Anatomical Sciences. Anat Sci Educ. 2021 Jul;14(4):432-439. doi: 10.1002/ase.2013. Epub 2020 Sep 28. PMID: 32812707.
28. AAMC. 2021. Association of American Medical Colleges. AAMC Medical School Enrollment Survey: 2020 Results. Association of American Medical Colleges, Washington, DC. URL: https://www.aamc.org/media/9936/download [accessed 13 Feb 2024].
29.Wilson AB, Notebaert AJ, Schaefer AF, Moxham BJ, Stephens S, Mueller C, Lazarus MD, Katrikh AZ, Brooks WS. A Look at the Anatomy Educator Job Market: Anatomists Remain in Short Supply. Anat Sci Educ. 2020 Jan;13(1):91-101. doi: 10.1002/ase.1895. Epub 2019 Jun 12. PMID: 31095899.
30.APC-PA. 2024. Accreditation Review Commission on Education for the Physician Assistant. ARC-PA accre4dited PA programs. Accreditation review Commission on Education for the Physician Assistant, Inc. Suwanee, GA. URL: http://www.arc-pa.org/accreditation/accredited-programs/ [accessed 13 Feb 2024]
31. Edwards DN, Meyer ER, Brooks WS, Wilson AB. Faculty retirements will likely exacerbate the anatomy educator shortage. Anat Sci Educ. 2023;16(4):618-628. doi:10.1002/ase.2217
32. AAMC Faculty Roster, December 31, 2019 snapshot, as of December 31, 2019.
33. Waterston SW, Stewart IJ. Survey of clinicians' attitudes to the anatomical teaching and knowledge of medical students. Clin Anat. 2005;18(5):380-384.
34. Prince KJ, Scherpbier AJ, van Mameren H, Drukker J, van der Vleuten CP. Do students have sufficient knowledge of clinical anatomy? Med Educ. 2005;39(3):326-332.
35. Fitzgerald JE, White MJ, Tang SW, Maxwell-Armstrong CA, James DK. Are we teaching sufficient anatomy at medical school? The opinions of newly qualified doctors. Clin Anat. 2008;21(7):718-724.
36. Fillmore EP, Brokaw JJ, Kochhar K, Nalin PM. Understanding the current anatomical competence landscape: Comparing perceptions of program directors, residents, and fourth-year medical students. Anat Sci Educ. 2016;9(4):307-318.
37. Haubert LM, Jones K, Moffatt-Bruce SD. Surgical clinical correlates in anatomy: design and implementation of a first-year medical school program. Anat Sci Educ. 2009 Nov-Dec;2(6):265-72. doi: 10.1002/ase.108. PMID: 19764083.
38. Rizzolo LJ, Rando WC, O'Brien MK, Haims AH, Abrahams JJ, Stewart WB. Design, implementation, and evaluation of an innovative anatomy course. Anat Sci Educ. 2010 May-Jun;3(3):109-20. doi: 10.1002/ase.152. PMID: 20496432.
39. Zill SN. Rethinking gross anatomy in a compressed time frame: Clinical symptoms, not case studies, as the basis for introductory instruction. Clin Anat. 2021 Jan;34(1):57-70. doi: 10.1002/ca.23645. Epub 2020 Jul 20. PMID: 32628297; PMCID: PMC7754134.
40. Keim SA, Harmon DJ, Martindale JR, et al. Essential anatomy for core clerkships: A clinical perspective. Anat Sci Educ. 2023 Sep-Oct;16(5):943-957. doi: 10.1002/ase.2272. Epub 2023 Apr 11. PMID: 36929575.
41. Moxham BJ, Shaw H, Crowson R, Plaisant O. The Future of Clinical Anatomy. Eur J Anat. 2011;15(1): 29-46.

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The Role of Pharmacy Benefit Managers and Skyrocketing Cost of Medications

by Suzanne G. Bollmeier, PharmD & Scott Griggs, PhD, PharmD

UNIVERSITY OF HEALTH SCIENCES & PHARMACY

Pharmacy Benefit Managers do hold a valuable place in the delivery of healthcare to patients. However, without reform, their practices are harming the healthcare arena and the patients they serve.



Suzanne G. Bollmeier, PharmD, FCCP, BCPS, AE-C, (pictured), is Professor, Pharmacy Practice; and Scott Griggs, PhD, PharmD is Associate Professor, Pharmacy Administration, St. Louis College of Pharmacy, University of Health Sciences and Pharmacy, St. Louis, Missouri.

Abstract

This article reviews how pharmacy benefit managers (PBMs) play a role in the delivery of modern healthcare services. A discussion regarding the lack of transparency regarding PBM services, consolidation of the market and vertical integration, as well as a typical flow of payments related to medications is provided. Authors review what higher drug costs are doing to patients, and provide an overview of what is happening to fight these trends.

Introduction

Pharmacy benefit managers (PBMs) like Express Scripts®, CVS Caremark®, and OptumRx® claim to lower drug prices for patients. Perversely, PBMs are driving up the costs of healthcare and prescriptions. This manuscript will take an in depth look at PBMs including their functions in the healthcare system and their roles in determining the cost of medications.

What is a Pharmacy Benefit Manager?

Pharmacy benefit managers (PBM) play a significant role in the delivery of pharmacy services. PBMs (Table 1) act as an intermediary (or middle-man) between pharmacies, insurance companies or employers, and drug manufacturers.[1] (Figure 1). In 2023, the three largest PBMs combined to account for approximately 80% of the equivalent prescription drug claims (PBM market share) in the US.[2,3]

How Did PBMs Start?

Pharmacy benefit managers got their start in the US in the 1960s when large insurance companies started offering a drug benefit.[1,5] As early as 1966, a democratic Senator from Illinois, Paul Douglas, wanted to add a prescription drug benefit to Medicare and introduced an amendment to a Social Security bill.[6] While the Douglas amendment was later deleted from the bill, it soon became the norm that third-party payers (private companies, nonprofit firms, and government programs) would cover prescriptions on behalf of employees and retirees.[7] These plan sponsors subsequently hired an outside company, a prescription benefit manager (what would later become PBMs), to help manage the overall costs of the program and help organize a network that would accept their enrollees prescription coverage benefits.[7] The original

Table 1. Three Largest PBMs in the United State[2,3]

CVS Caremark® (part of CVS Health)	Express Scripts® (part of Cigna)	OptumRx® (part of United Health Group)

intent in hiring these PBMs was to help insurance companies keep the cost of prescription drugs contained.

PBMs Role in Delivering Pharmacy Services Has Expanded

In the 1970s, PBMs began to take on other roles in the management and dispensing of medications. They started to adjudicate (i.e., electronically process) drug claims. To adjudicate a drug claim in a pharmacy today means that pharmacies determine patient eligibility for the medication in real-time. The pharmacy submits patient, medication, and insurance information to the PBM online; the pharmacies are then notified of the formulary status of that claim (i.e., a prescription drug), whether accepted or rejected, by the PBM. If accepted, pharmacies can then be assured they will be reimbursed for the medication prior to it being dispensed to the patient. Claims may also be denied or declined in real-time. If denied, the drug is not covered, and the PBM will not be reimbursing the dispensing pharmacy for this medication. Prescription claims may also be reversed by the pharmacy. This is typically carried out if the prescription item is not picked up by the patient and returned to the pharmacy's inventory.[8]

In addition to adjudicating prescription claims, PBMs have other roles in the delivery of pharmacy services as well. The PBM will establish the plan's formulary, negotiate pricing and rebates with drug manufacturers, and set up the network of pharmacies that policy holders can use.[9] (Figure 2). For example, members of the plan may only be able to utilize one large pharmacy chain, such as Walgreens, for their pharmacy needs and/or a mail order pharmacy. This means that if the patient were to try to get a medication filled at a Medicine Shoppe, the drug would not be covered or the patient would pay a higher copay, simply because this pharmacy is out-of-network.

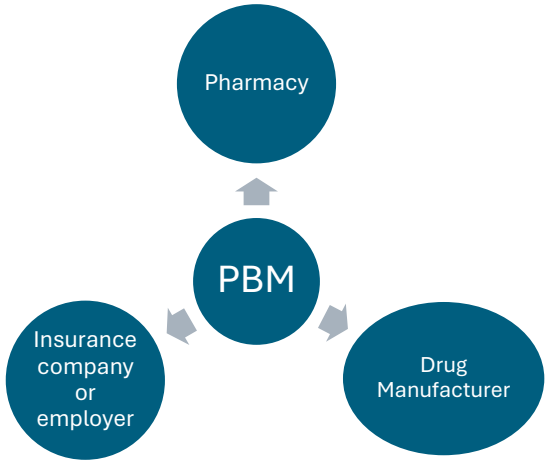


Figure 1. PBMs Act as an Intermediary[4]
Abbreviations: PBM: Pharmacy Benefit Manager

Typical Flow of Payments in the Prescription Drug Market

The supply chain for prescription medications in the US is complex and involves payment flowing between multiple parties. In simple terms, drug manufacturers sell the drugs they have developed to wholesalers (distributors). Distributors store these drugs, that are then sold to pharmacies. The pharmacy may be a member of a group-purchasing organization (GPO) which helps negotiate drug prices on behalf of its pharmacies (this is often the case with independent pharmacies). Pharmacies then process the prescriptions and dispense them to patients.[11] (Figure 3)

Where Did Things Start to Go Downhill with PBMs?

As previously stated, PBMs act as a "middle-man" or intermediary between drug manufacturers and insurance companies. There are a number of ways that PBMs make money,[13] including spread pricing, manufacturer rebates, administrative fees, and

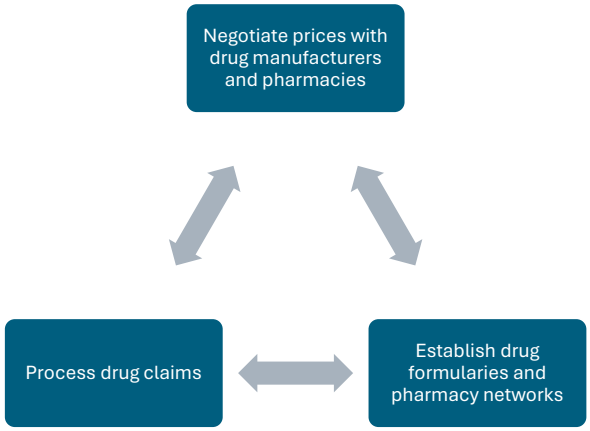


Figure 2. Functions of a PBM[9,10]

health plans) hire PBMs to negotiate drug prices for their members. These negotiated prices often include a rebate from the manufacturer. The manufacturer is incentivized to negotiate because the PBM's leverage formulary placement of medications. The placement of a drug on a plan's "preferred" formulary is financially beneficial, especially if there are multiple competitors (drugs in the same class) vying for market share. For example, when there were two branded COX-2 inhibitors on the market in the early 2000s, (Pfizer's Celebrex and Merck's Vioxx), both wanted preferred formulary status on as many insurance platforms as possible. If their COX-2 inhibitor obtained preferred status on a PBM plan's formulary, this would mean that those insured members (i.e., patients) would pay a lower co-pay (Tier 1) and have no insurance issues getting this prescription filled. Conversely, if a manufacturer has a "non-preferred" drug on a PBM formulary, this results in higher costs for the patients and fewer prescriptions sold.

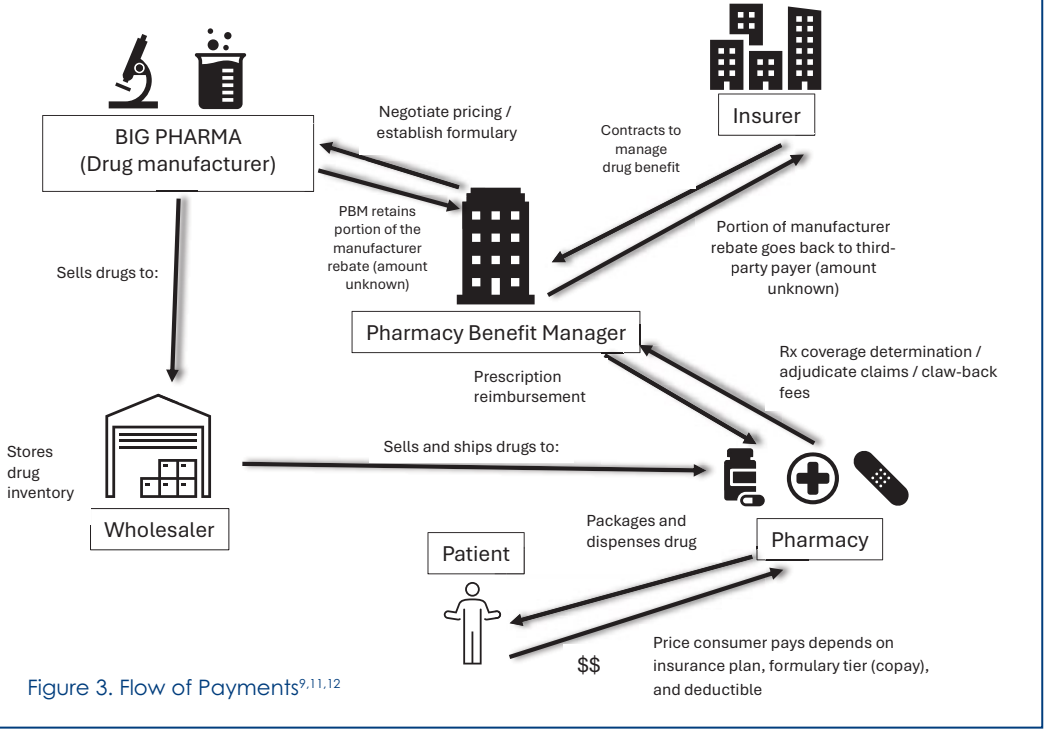


Figure 3. Flow of Payments[9,11,12]

requiring patients to fill medications at the PBM-owned mail order pharmacy. With spread pricing, the PBM reimburses the pharmacy a certain amount for a prescription drug (e.g., $30) while charging the plan sponsor a higher amount (e.g., $45); the difference (i.e., $15) the PBM keeps.[14] The lack of transparency, through proprietary contracting, enables the PBMs to perpetuate this practice.

Another means by which PBMs make money is via manufacturer rebates. Third-party payers (i.e., the

The consolidation of the PBM market has enabled a rapid expansion of manufacturer rebates paid in exchange for preferred formulary status.[15] Estimates from 2022 indicate that rebates, as well as discounts and price concessions, accounted for $223 billion for brand-name medications—with rebates factoring as the largest and most significant portion.[3] PBMs are not forced to publicly disclose how much of the manufacturer rebate they retain. Likewise, the percent of the manufacturer rebate that is passed through to the insurer is not disclosed. The

Table 2. Examples of Vertical Integration.[25,26,27,28]

Umbrella Company	CVS Health®	The Cigna Group©	Unitedhealth Group©
Insurance company	Aetna®	Cigna©	United Healthcare®
PBM	CVS/Caremark®	Express Scripts©	Optum Rx®
Specialty pharmacy	CVS Specialty®	Accredo©	Optum Specialty Pharmacy©
Provider Service Examples	CVS minute clinic® Oak St Health (CVS Healthspire) ™	Evernorth Health Services(SM) MD Live®	Optum Care©

insurers can use these pass-through rebates to reduce the premiums for all plan participants.. While the lack of rebate transparency obfuscates this situation, it is believed that a significant percent of these drug rebates are kept by the PBMs.[16] The same is true for 340B rebates as well.

PBMs also benefit financially through 340B contracting and rebates.[17] The federal 340B Drug Discount Program enables qualifying healthcare organizations (e.g., hospitals and clinics), or "covered entities," to receive discounted prices on qualifying outpatient medications.[18] The intent is that these savings would be used to provide services to uninsured and low-income patients per the Public Health Service Act.[19] According to the Health Resources and Services Administration (HRSA), enrolled covered entities can see savings of up to 50% in their drug spend.[18] Pharmacy benefit managers have penetrated the 340B program by increasing contract pharmacy agreements with covered entities as well as gaining 340B market share.[17] As PBMs own a vast number of these contracted 340B pharmacies throughout the country, a large percentage of these prescription profits are also going to PBMs.[20]

PBM reimbursements are significantly harming dispensing pharmacies.[21,22] PBMs pay pharmacies through a complex reimbursement model. What is being paid by the PBM (to the pharmacy) is often less than what the pharmacy paid the wholesaler for the drug. There is also a lack of transparency in these pricing structures which leads to financial challenges and payments to pharmacies being delayed. This practice is unique to pharmacy. For example, this would NOT be the case in fast food. Think of going to McDonalds and ordering a double cheeseburger. The owner of the local McDonald's pays its distributor for the components of the double cheeseburger (bun, cheese, burger, pickle, onion, ketchup, mustard); however, the owner is forced to sell the cheeseburger to the consumer for a price lower than what the restaurant paid the distributor. In this example, McDonalds makes zero profit; it actually loses money. This is essentially what PBMs are doing to independent pharmacies. Not only are these drugs being sold below the acquisition cost to the pharmacy, but many business expenses—including staff salaries, utilities, and property taxes—are not being reimbursed when prescriptions are filled. This

is not sustainable and has led to many independent pharmacy closures.[21, 22] In some areas of the country, this has led to pharmacy deserts.

A pharmacy desert is a neighborhood with an average distance to the closest pharmacy of 10 or more miles.[23] A rural pharmacy desert is a community with lower density of both chain and independent pharmacies, fewer 24-hour pharmacies, and fewer pharmacies offering delivery service.[24]

What is Meant by Vertical Integration?

The term "vertical integration" reflects the business relationships among the largest US healthcare companies: insurers, PBMs, specialty pharmacies, and even provider services. The aim of these vertically integrated companies is to keep patient's healthcare needs "in house" or to themselves. For example, the umbrella company financially incentivizes the patient to stay within the closed network (of vertically integrated companies) to obtain medical care and medications (Table 2).

Vertical integration has come to be the norm over the past decade as multiple parties involved in the drug distribution and reimbursement arena have merged or been acquired.[28] There have also been the creation of GPOs or group purchasing organizations; some of which are also owned by PBMs. GPOs serve the healthcare system by working to collectively purchase for its members things like medical and surgical supplies, pharmaceuticals, equipment, IT supplies, and even food. Hospitals, nursing homes, long-term care pharmacies, assisted living centers, infusion pharmacies, and home healthcare providers are examples of GPO clients. By using a GPO, the cost of supplies should go down.

How Do PBMs Affect Providers in the State of Missouri?

Pharmacy benefit managers have inserted themselves between providers, patients, pharmacists, and even their health insurer. They create and control drug formularies for insurance companies while patients (and employers) continue to pay high premiums, deductibles, copays, and coinsurance. PBMs ultimately determine which drugs patients are able to acquire and afford by setting the prices via the tiered co-payment structure. PBMs likewise determine which medications are non-formulary and which drugs require prior authorization. By preferentially selecting higher cost medications and keeping a portion of the discounts (e.g., manufacturer rebates)[29] for themselves, PBMs increase their profits.

Pharmacy benefit managers own or contract with PBM-affiliated pharmacies (Table 2). They direct as much business to their pharmacies as possible to increase market share and profits. This is accomplished by requiring patients to use these PBM-owned or affiliated pharmacies. Some patients feel "forced" into using these pharmacies, as they are charged more (i.e., a higher co-pay) or given a reduced day supply at a non-affiliated pharmacy. This practice not only disadvantages many independent pharmacies, but also leaves patients feeling like they have limited choices. For example, a patient may wish to have a prescription for insulin filled at the local Medicine Shoppe that is not affiliated with a PBM (affiliated pharmacies are designated "in-network"). This patient prefers a 90-day supply for convenience. The PBM may force this patient to use a mail order pharmacy, as the Medicine Shoppe is out-of-network. The PBM may charge a higher co-pay to have it filled at the Medicine Shoppe. Additionally, the PBM may not allow more than a 30-day supply unless the prescription is filled through a PBM-affiliated mail order pharmacy. The patient, by no longer visiting their local pharmacy (where they have a relationship with their established and trusted pharmacist), may be deprived of the level of personalized service and attention that is required.[30] Patients are often confused by these in-network and out-of-network pharmacy requirements which may impact adherence, affordability, as well as patient outcomes.

How Is the Price of Medications Affecting Your Patients?

Measuring drug spending is a challenge due to limited public data on how much the various third-party payers and supply chain intermediators pay for prescription drugs.[31] Only 4% of prescription drugs were covered by third-party sponsors in the 1960s, but this increased to 32% by 1980.[32] Private health insurance, Medicare, and Medicaid accounted for approximately 90% of prescriptions covered in 2022.[33,34] The Centers for Medicare and Medicaid Services (CMS) estimates that the US experienced a 26.8% rise in total retail prescription drug spending between 2012-2016. The annual spending in today's

America vastly exceeds that of even a decade ago. The US medication market grew by 5% in 2022 and was valued at approximately $430 billion.[35] The growth of new and expensive specialty drugs, such as those used to treat Hepatitis C and various cancers, has significantly impacted the overall cost of medications in the US[31]

Interestingly, many patients that have prescription drug coverage are electing to simply not use it. Patients elect to pay cash (or out-of-pocket) for medications instead of having them run through their prescription insurance plan.[36] In one survey, respondents listed the following reasons for paying cash for medications: using discount cards is less expensive, the preferred pharmacy is out-of-network, the medication is not covered, or the deductible has not yet been met.[36]

What Can Be Done?

Lawmakers have taken notice and drug prices are in the political spotlight. Several modifications were made to the drug reimbursement system through the 2022 Inflation Reduction Act.[9] In an effort to shed light on these confidential discounts, legislators want to increase transparency surrounding these transactions. The state of Ohio is leading the charge in stopping PBM abuse. Their attorney general (AG) is waging war on the PBMs; he has filed four different lawsuits against the PBMs related to the cost of prescription drugs and violations of antitrust laws.[37] In one case, the Ohio AG is suing Express Scripts claiming that the company overcharged the state's Highway Patrol Retirement System, a public pension fund. In another, he is suing Optum for drug overcharges.[38]

In 2015, Arkansas passed a law making it illegal for PBMs to reimburse pharmacies at a lower rate than what it cost to dispense the medication.[39] This same law allows pharmacies to refuse to sell a medication if the reimbursement is too low.[39] This case made it all the way to the Supreme Court, which sided with the Arkansas lawmakers, paving the way for other states to follow suit.

The Department of Justice has formed a Task Force on Health Care Monopolies and Collusion. As part of their Antitrust Division, this task force is considering competition concerns brought forth by the public and providers. The task force will also be reviewing issues with payer-provider consolidation and is empowered to investigate and enforce both strategy and policy in this area. [40]

On a local level, in the state of Missouri, several bills have been proposed for both the House and Senate in the past couple of years. These reform bills center around increasing PBM transparency with regard to rebates, incentives, pricing, and oversight.[41]

Pharmacies that serve vulnerable patient populations should be protected by maintaining in-network status with insurance plans. Pharmacies must also be reimbursed adequately for offering pharmacy services to this patient population. Accordingly, these patients will continue to have a steady, reliable, and trustworthy pharmacy to fill their prescriptions.[42]

Conclusion

Pharmacy Benefit Managers do hold a valuable place in the delivery of healthcare to patients. However, without reform, their practices are harming the healthcare arena and the patients they serve. Future regulation of PBMs is needed. Changes in unreasonable drug pricing and improved transparency will benefit everyone. Health plans, drug manufacturers, and pharmacies will be better informed to negotiate contracts and regulators will be able to hold PBMs accountable to fair business practices.[43]

Addendum

The Federal Trade Commission recently brought administrative action against the top PBMs — CVS Health's Caremark Rx, Cigna's Express Scripts, and United Health Group's OptumRx — saying the companies created a "perverse drug rebate system" that artificially inflates the cost of insulin. This action demonstrates the government also feels that PBMs raise the cost of drugs as explained in this manuscript.

References

1. Mattingly II TJ, Hyman DA, Bai G. Pharmacy Benefit Managers History, Business Practices, Economics, and Policy. JAMA Health Forum 2023; 4(11):e233804. doi:10.1001/jamahealthforum.2023.3804. Accessed May 13, 2024.
2. Anderson M. How Three Companies Came to Dominate the PBM Market. February 15, 2023. Healthbrew.com Accessed May 3, 2024.
3. Fein AJ. The Top Pharmacy Benefit Managers of 2023: Market Share and Trends for the Biggest Companies—And What's Ahead. Available at: https://www.drugchannels.net/2024/04/the-top-pharmacy-benefit-managers-of.html#:~:text=Three%20is%20still%20the%20magic,Rx%20business%20of%20UnitedHealth%20Group Accessed May 21, 2024.
4. PBM 101. Available at: Truthrx.org/PBMbasics. Accessed April 23, 2024.
5. National Association of Insurance Commissioners. Pharmacy Benefit Managers. June 1, 2023. Available at: https://content.naic.org/cipr-topics/pharmacy-benefit-managers#:~:text=Background%3A%20When%20insurance%20companies%20began,formularies%20and%20administered%20drug%20claims Accessed March 13, 2024.

6. Santangelo M. Historical Perspective on Adding Drugs to Medicare. Health Care Financ Rev. 2005 Winter; 27(2): 25–33.
7. Wirtz R. Cash, Check, or Third-Party? Prescription Benefit Plans are Squeezing Retail Pharmacies. Jan 1, 2006. Federal Reserve Bank of Minneapolis. Available at: https://www.minneapolisfed.org/article/2006/cash-check-or-third-party Accessed Feb 1, 2024.
8. Blogpost: Improving your pharmacy claims processing workflow: A biller's guide. Inovalon. Available at: https://www.inovalon.com/blog/improving-your-pharmacy-claims-processing-workflow-a-billers-guide/#:~:text=The%20pharmacy%20claims%20adjudication%20process,requires%20additional%20documentation%20to%20resubmit Accessed Feb 21, 2024.
9. Hernandez I, Hung A. A primer on brand-name prescription drug reimbursement in the United States. J Man Care and Spec Pharm 2024; 30(1):https://doi.org/10.18553/jmcp.2024.30.1.99
10. Fiedler M, Adler L, Frank RG. A Brief Look at Current Debates about Pharmacy Benefit Mangers. Brookings Sept 7, 2023. Available at: https://www.brookings.edu/articles/a-brief-look-at-current-debates-about-pharmacy-benefit-managers/ Accessed May 3, 2024.
11. Prescription Drugs: Spending, Use, and Prices. Congressional Budget Office. January 2022. Available at: https://www.cbo.gov/publication/57772 Accessed March 13, 2024.
12. U.S. Distribution and Reimbursement System: Patient-Administered, Outpatient Drugs Available at: https://drugchannelsinstitute.com/files/Drug-Channels-2019.pdf Accessed May 21, 2024.
13. The PBM Story. 2022 Available at: https://www.ncpa.co/pdf/PBM-Storybook-12pg.pdf Accessed May 21, 2024
14. Eban K. Painful Prescription. Oct 10, 2023. Available at: https://fortune.com/2013/10/10/painful-prescription. Accessed May 21, 2024.
15. Fein AJ. Four Trends That Will Pop the $250 Billion Gross-to-Net Bubble—and Transform PBMs, Market Access, and Benefit Design. Drug Channels. April 4, 2023. Available at: https://www.drugchannels.net/2023/04/four-trends-that-will-pop-250-billion.html Accessed May 21, 2024.
16. Schladen, M. Congressional watchdog: Rebates increase drug costs for seniors. Ohio Capital Journal. Sept 11, 2023. Available at: https://ohiocapitaljournal.com/2023/09/11/congressional-watchdog-rebates-increase-drug-costs-for-seniors/ Accessed May 24, 2024.
17. For 2023, Five For-Profit Retailers and PBMs Dominate an Evolving 340B Contract Pharmacy Market. July 11, 2023. Drug Channels. Available at: https://www.drugchannels.net/2023/07/exclusive-for-2023-five-for-profit.html Accessed May 21, 2024.
18. Martin R, Karne H. The 340B Drug Discount Program Grew to $124B in 2023. IVQIA Available at: https://www.iqvia.com/-/media/iqvia/pdfs/us/white-paper/2024/iqvia-update-on-size-of-340b-program-report-2024.pdf Accessed May 21, 2024.
19. American Hospital Association. Fact Sheet: The 340B Drug Pricing Program. March 2023. Available at: https://www.aha.org/fact-sheets/fact-sheet-340b-drug-pricing-program Accessed May 13, 2024.
20. Longo N. PBMs using 340B program to drive profits at patients' expense. Phrma.org Available at: https://phrma.org/Blog/PBMs-using-340B-program-to-drive-profits-at-patients-expense#:~:text=PBM%20profits%20are%20propped%20up%20by%20the%20340B%20program.&text=The%20average%20profit%20margin%20earned,medicines%20dispensed%20through%20independent%20pharmacies Accessed May 13, 2024.
21. Independents Closing Fast; PBMs Grabbing Cash. IVQIA Available at: https://ncpa.org/sites/default/files/2024-04/IndependentsClosing_2024FlyerEdit_0.pdf Accessed May 21, 2024.
22. Local Pharmacies on the Brink. New Survey Reveals. National Community Pharmacists Association. Available at: https://ncpa.org/newsroom/news-releases/2024/02/27/local-pharmacies-brink-new-survey-reveals Accessed May 17, 2024.
23. Gebhart F. What is a Pharmacy Desert? Drug Topics. Sept 24, 2019. Available at: https://www.drugtopics.com/view/what-pharmacy-desert Accessed May 13, 2024.
24. Anderson M. How Pharmacy Deserts are Formed. Healthcare Brew. March 20, 2023. Available at: https://sites.usc.edu/pmph/2023/03/20/how-pharmacy-deserts-are-formed/#:~:text=A%20pharmacy%20desert%20in%20the,miles%20from%20the%20nearest%20 pharmacy. Accessed May 21, 2024
25. CVSHealth.com Accessed May 13, 2024
26. TheCignaGroup.com Accessed May 13, 2024.
27. UnitedHealthgroup.com Accessed May 13, 2024.
28. Fein AJ. Mapping the Vertical Integration of Insurers, PBMs, Specialty Pharmacies, and Providers: A May 2023 Update Available at: https://www.drugchannels.net/2023/05/mapping-vertical-integration-of.html Accessed May 21, 2024.
29. HealthPartners. How High Prescription Drug Rebates can Derail Pharmacy Benefit Plans. Available at: https://www.healthpartners.com/plan/blog/prescription-drug-rebates-and-pbms/Accessed May 3, 2024.
30. How PBMs Negatively Impact Patients. Keycentrix. Available at: https://keycentrix.com/2023/01/23/pbms-hurt-pharmacies-and-patients/#:~:text=Because%20of%20their%20position%20in,and%20lower%20reimbursements%20for%20pharmacies Accessed April 23, 2024.
31. The Pew Trust. The Prescription Drug Landscape; Explored. A Look at Retail Pharmaceutical Spending from 2012 to 2016. March 8, 2019. Available at: https://www.pewtrusts.org/en/research-and-analysis/reports/2019/03/08/the-prescription-drug- landscape-explored Accessed May 3, 2024.
32. Smith C. Retail prescription drug spending in the National Health Accounts. Health Aff (Millwood). 2004;23(1):160-167. doi:10.1377/hlthaff.23.1.160
33. Cubanski J, Rae M, Young K, Damico A. How Does Prescription Drug Spending and Use Compare Across Large Employer Plans, Medicare Part D, and Medicaid. Henry K Faiser Family Foundation. May 20, 2019. Available at: kff.org Accessed April 23, 2024.
34. NCPA Digest Financials. 2024. Available at: https://ncpa.org/newsroom/news-releases/2023/10/15/ncpa-releases-2023-digest-report Accessed May 21, 2024.
35. IVQIA. The Use of Medicines in the U.S 2023. Usage and Spending Trends and Outlook to 2027. May 2, 2023. Available at: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2023 Accessed March 13, 2024.
36. Rewriting the Script. Independent Pharmacy Trends 2022 Research Report. Available at: https://prescryptive.com/2022-pharmacy-study/ Accessed March 14, 2024.
37. Lepard C. What are pharmacy benefit managers, and why are the state of Ohio and the city of Cleveland suing them? A closer look at the rising costs of medications. News5cleveland. Available at: https://www.news5cleveland.com/news/local-news/what-are-pharmacy-benefit-managers-and-why-are-the-state-of-ohio-and-the-city-of-cleveland-suing-them Accessed April 24, 2024.
38. Minemeyer P. Ohio AG sues Express Scripts to reclaim drug overcharges. July 15, 2020. Available at: www.fiercehealthcare.com/payer/ohio-ag-sues-express-scripts-to-reclaim-drug-overcharges. Accessed May 24, 2024.
39. Minemeyer P. Supreme Court upholds Arkansas law regulating pharmacy benefit m anagers. Dec 10, 2020. Available at: www.fiercehealthcare.com/payer/supreme-court-upholds-arkansas-law-regulating-pharmacy-benefit-managers. Accessed May 24, 2024.
40. NCPA applauds DOJ task force on vertical integration and consolidation. NCPA.org Available at: https://ncpa.org/newsroom/qam/2024/05/14/ncpa-applauds-doj-task-force-vertical-integration-and-consolidation Accessed May 21, 2024.
41.Missouri Pharmacy Association. Legislative Day brochure. PBM Reform: Pharmacists Unite for Truth and Transparency. April 3, 2024
42. Pisikien K. How Pharmacy Deserts Impact Communitities. Goodrx.com March 30, 2022. Accessed May 13, 2024.
43. Payerchin R. Congress needs to crack down on PBMs, state attorneys general say. Medical Economics. Feb 28, 2024. Available at: www.medicaleconomics.com/view/congress-needs-to-crack-down-on-pbms-state-attorneys-general-say Accessed May 24, 2024.

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