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The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine September/October 2025

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Missouri Medicine

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Mission—Submissions—Peer Review—Polices

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You Have Sudden Onset Chest Pain? The Doctor Can See You in 5 Months. The Travesty of Physician Unavailability

by John C. Hagan, III, MD

How do we as a profession and as a nation address a shortage of physicians estimated to be over 90,000 within the next decade? Patients are dying to know.

United States (US) healthcare, once a citadel of innovation and quality, has sadly devolved into a complex, frustrating, and frequently inaccessible system. It so disorganized and inefficient it might not even meet the definition of a "system." US Healthcare fails to meet the needs and expectations of patients on many, perhaps most, occasions. For most of my career, I have considered US healthcare the best in the world. Now I think not. This distressing—and for me painful—editorial articulates the challenges and failures of a system that is increasingly unacceptable to patients and their physicians. What the US healthcare system is superb at is generating massive profits for hospitals, pharmaceutical companies, trial lawyers, and Medicare fraudsters.

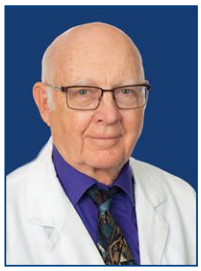
If you are looking for answers to these enormous challenges and shortcomings of US healthcare read no further; I have no answers only questions. What purpose, you may ask, will this editorial then serve?

Glad you asked. It will help delineate and define the problems. The perspective will be mine; an 81-year-old physician retired from clinical practice. I am now a consumer of medical care rather than a provider.

I am also a constant care-giver for my beloved 80-year-old wife of 58 years. Becky has severe Vascular Parkinsonism and Cognitive Impairment. She is confined to a wheelchair and lives in an assisted living facility. Daily, I serve as her advocate in a deteriorating, often indifferent, healthcare system. Months long waits for her to see specialists, five-hour ER visits, personal physicians that do not see urgent and emergent cases expeditiously…been there, done that!

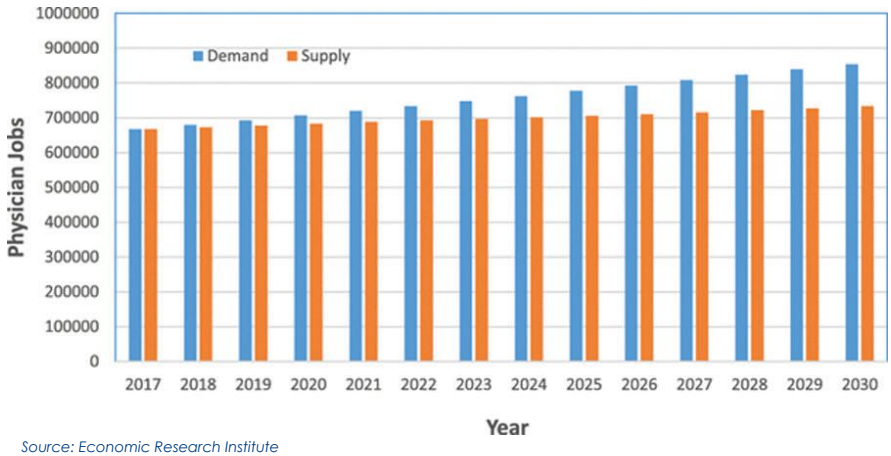
Physician Unavailability Will Default Primary Care to Non-Physicians.

Case in point: my wife has been hospitalized several times for leg cellulitis. Recently she developed another episode. I quickly called her physician's office. He is a hospital-employed internist. I told the office gatekeeper my wife needed to be seen today, tomorrow at the latest, by her physician for an urgent condition. "The doctor can see her in a week," she said coldly and unmoved. I told her this was unacceptable, that my wife had been hospitalized for cellulitis before and in a week the infection would be out of control.



John C. Hagan, III, MD, is Past President of the Kansas City Medical Society, the Missouri Society of Eye Physicians & Surgeons and the Clay-Platte County Medical Society. He is Editor of *Missouri Medicine* and a Contributing Editor to *Kansas City Medicine*. Dr. Hagan is an ophthalmologist, author, and researcher in Kansas City, Missouri USA. Learn more at www.msma.org/MoMed-Editor.

Figure 1. The Physician Shortage Becomes More Critical Each Year



Source: Economic Research Institute

"Sorry, as I said, the soonest the doctor can see her is a week from now. But the nurse practitioner (NP) can see her this afternoon or tomorrow morning." I immediately took that appointment in spite of my concerns about non-physician medical care. Any port in a storm.

The NP was terrific and the anthesis of most of our physician encounters. Becky was seen on time! The NP was professional, pleasant, listened intently, asked nuanced questions, and didn't interrupt. She projected competence, care, and concern. At the bellwether 15-minute mark of the exam, the NP did not jump up and brusquely leave the room in the manner of many physicians. We did not feel rushed or unheard. She prescribed an appropriate antibiotic and said if we saw no improvement or worsening over the next 48-72 hours to call her and she would expeditiously get my wife in to see the internist. Becky got much better over the next couple of days. I shudder to think what would have happened if we had waited a week. Physicians should have an RN, NP, or physician assistant triage all calls that request urgent/emergent/expedited office visits. Slots in the schedule should be created daily to accommodate these patients.

I note with pride that the then-physician owned ophthalmology group where I practiced would see same day patients reporting ominous symptoms, moderate to severe pain, hyper-concern, and of course always same day for physician requests.

Given the existing scenario it is inevitable that the scope of practice for non-physicians will greatly expand. Frustrated patients will seek out the much more available non-physicians. Ersatz 'doctors' will be NPs, physician assistants, podiatrists, optometrists, midwives, chiropractors, pharmacists, and occupational and physical therapists. They will practice, for the most part, autonomously without physician supervision. With prompt physician access denied inevitably most primary care will default to non-physicians. An ever-increasing number of patients now consider Doctor Nurse their physician.

How do we as a profession and as a nation address a shortage of physicians estimated to be over 90,000 within the next decade (Figure 1)? Don't ask me, I told you I don't have any answers.

Medicine As a Very Profitable Industry

For-profit hospitals are straightforward in letting the public know they are trying to wring as much money as possible out of healthcare. Paradoxly, so called "non-profit" hospitals also often operate like for-profit corporations. They are equally rapacious. Healthcare dollars flow in a green tsunami to highly compensated administrators and staff. Your pain is their gain. The US spends much more money on administration than other wealthy countries (Figure 2). Hospitals, like colleges and universities, have excessive, unnecessary, and expensive administrative staffs. There are now 10 administrators for every one physician in the US (www.nphp.org). That bloat just won't float.

Just when you think it can't get worse enter stage left the Private Equity (PE) firms scarfing up physicians' practices at breakneck speed. This includes right here in River City. Most of the major Kansas City ophthalmology groups have already sold out to PE. I have witnessed the adverse changes made in practices acquired by PEs. These include, but are not limited to, staff reductions, patient encounter time limits (usually 15 minutes), mandatory referrals within the group, raised fees, higher billing expectations, more surgery, and promoting high profit procedures when less expensive options are adequate. Minimal



Figure 2. Annual Hospital Administrator Salary in Missouri

Source: Economic Research Institute

monthly billings are assigned for each physician by the PE money mongers. Those physicians that frequently miss their quotas are pilloried, threatened, and sometimes actually fired for low production.

So called "routine' or primary care is often shunted off to non-physicians so physicians and surgeons can do the more profitable secondary and tertiary care. In my specialty this means primary vision care is diverted to optometrists. This implementation of extreme profit generating measures does not seem to be in the interests of patients. Every independent study I have reviewed documents lower quality and higher patient cost when PEs come to town. To whit: https://hms.harvard.edu/news/what-happens-when-private-equity-takes-over-hospital.

The price of most drugs is often unaffordable and beyond ridiculous. How does pharma get away with this? New drug development costs are intentionally kept arcane and obfuscated allowing pharma to kite the numbers to increase profit to obscene levels. Also, they have lots of friends in Congress. In the period 2023 to 2024, pharma donated $26.4 million dollars to Democrats and $16.1 million to Republicans (www.opensecrets.org). Money can't buy you love but it sure buys Congressional votes.

I have personal experience with the cupidity of pharma. The innovative Migliazzo-Hagan-Kosa treatment of acute migraine with liquid timolol 0.5% is effective, safe, inexpensive, and available. What is not to like about that? I have been pitching its development to pharma for over a decade. I've lost count of the number of pharmaceutical companies that have passed. They have acknowledged the treatment is innovative and effective but posit it will not generate enough profits. Note it would generate a profit but not a large enough profit to suit pharma even though hundreds of millions of migraine patients might be benefited.

How To Address the Profound Unavailability of Physician Care and Where is All This Going?

Suggestions from assorted pundits include: more medical schools, larger medical school classes, shortening medical school from four years to three years, import more international medical graduates, expand the number of residencies and truncate their duration. Every legislative session in Jefferson City we see the default solution which is expand the scope of practice of non-physicians and have them do the great majority of primary care.

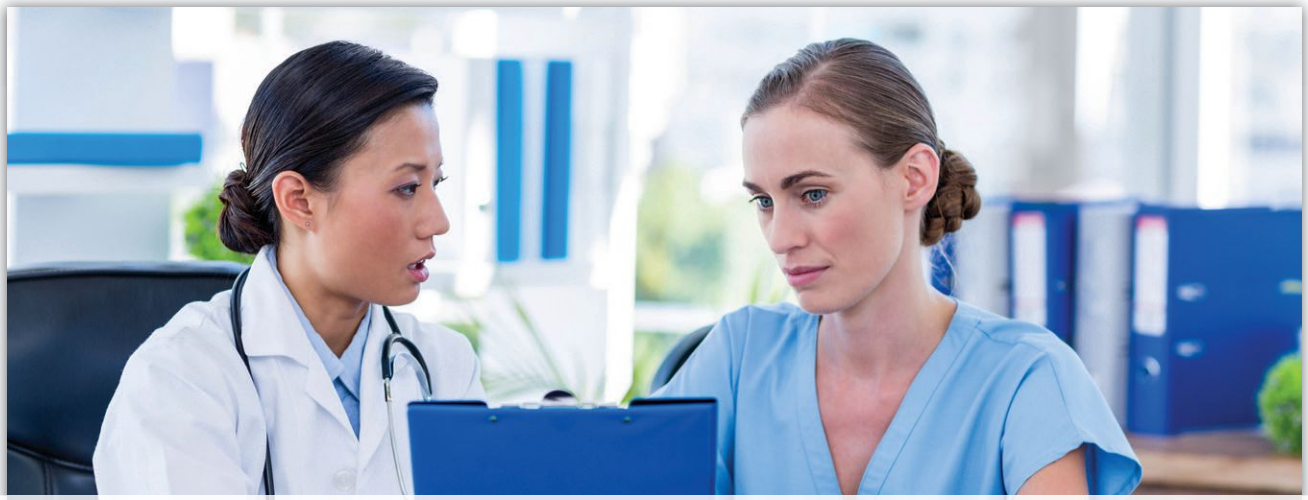
"Minute Clinics" usually staffed by nurses in shopping centers and commercial areas offer excellent accessibility but variable quality. Other evolving solutions include "Be your own doctor" kits now being hawked on TV. Costing about $300, TV ads shill physician unavailability and emphasize they contain a variety of prescription medicines, mostly antibiotics for common diseases. What if things (inevitably) go bad? I guess the patient can sue themselves for malpractice.

Medical tourism is where people leave the US for treatment or procedures on foreign shores. It is used presently for cosmetic and extremely expensive procedures. It will be a non-starter for most people. Telemedicine, expanded greatly during COVID, may help. But most visits requiring physical exams or procedures and are outside the purview of telemedicine.

Then there is Artificial Intelligence (AI) which is paradoxically touted as the solution to all the world's problems and the biggest threat to world peace. There is real promise in AI diagnosis in a medical specialty like pathology, radiology, and dermatology. AI does not provide sympathetic care or concern and AI cannot hold the patients' hand or pat their back. Maybe future AI will do these also. However, I think compassion cannot be digitalized.

By regular methods (Call and Plead for an appointment) I rarely can get my wife a physician appointment in reasonable time. I confess to playing the "I'm a doctor" card. If that doesn't work then I can call a physician colleague to help me help my wife with an appointment in reasonable time. Obviously that option is not open to most patients.

As a nation and as a profession we must do much better. Lives depend on it. **MM**



Nonphysician Unsupervised Practice of Medicine: Examining the Evidence

by Rebekah Bernard, MD

Between 2002 and 2024, the National Practitioner Database shows a downward trend in adverse action and malpractice reports for physicians and an increased trend for NPs and PAs.

Abstract

Medical school graduates must complete extensive supervised residency training before practicing independently. In contrast, many states allow nurse practitioners (NPs) and physician assistants (PAs) to engage in the unsupervised practice of medicine (UPM) with significantly less clinical experience. Despite decades of such legislation, data on safety, quality, and outcomes remain limited. This article reviews current evidence evaluating nonphysician UPM, finding that most studies used to support UPM legislation involve physician oversight, low-risk patients, or measure minor outcomes. Recent data suggest higher costs, increased resource use, and potential safety concerns when NPs and PAs practice independently. Malpractice trends further underscore the need for caution. Robust, high-quality research is urgently needed to assess the safety and effectiveness of nonphysician UPM.



Rebekah Bernard, MD, practices at Gulf Coast Direct Primary Care in Fort Myers, Florida, USA.

Introduction

Medical licensure laws are determined by state legislatures, including whether a clinician may practice medicine independently, also known as 'unsupervised practice of medicine' (UPM). No state allows UPM rights to medical school graduates with a Medical Doctor (MD) or Doctor of Osteopathic Medicine (DO) degree without an additional period of formal residency training, ranging from one to three years (Table 1).

Table 1. Minimum Training and State Requirements for Unsupervised Practice of Medicine (UPM)

Clinician	Minimum Clinical Hours	States Allowing UPM Immediately Upon Graduation	States Requiring Postgraduate Experience
Physician (US)	4 yrs undergrad + 4 yrs med school **6,000 hrs**	**None**	**1 yr residency:** AL, AZ, AR, CO, DE, FL, GA, HI, ID, IN, IA, KS, LA, MD, MA, MN, MS, MO, NE, NY, NC, ND, OH, OK, OR, SC, TN, TX, VT, VA, WV, WI, WY **2 yrs:** AK, CT, DC, IL, KY, ME, MI, MT, NH, NM, PA, RI, UT, WA **3 yrs:** CA, NV, NJ, SD
Physician (IMG)	6–8 yrs med school **6,000 hrs**	**None**	**1 yr residency:** OR, WI **2 yrs:** FL, HI, ID, IL, IN, IA, KY, MD, MA, MI, MN, NH, NM, OH, OK, TX, UT, WA, WY **3 yrs:** AL, AK, AZ, AR, CA, CO, DE, DC, GA, KS, LA, ME, MS, MO, MT, NE, NV, NJ, NY, NC, ND, PA, RI, SC, SD, TN, TX, VT, VA, WV
Nurse Practitioner	4 yr undergrad + 1–2 yrs grad school **500 hrs**	**AK, AZ, DC, HI, ID ID, IA, MT, NH, NM, ND, OR, RI, UT, WA, WY, DC**	**< 1 yr experience:** CO*, SD* **1–2 yrs:** MD*, MN*, NV, DE, IL, ME*, NE*, VT* **3 yrs:** AK, CT, FL – primary care only, WV (*May be supervised by another NP)
Physician Assistant	4 yrs undergrad + 2 yrs PA program **2,000 hrs**	**WV**	**2 yrs:** ND, WY **3 yrs:** SD **4 yrs:** AZ, IA, MT, NH **6 yrs:** UT

The goal of residency training is "to provide an educational venue with graduated responsibility and increasing levels of independence as preparation for entering the unsupervised practice of medicine."[1]

While at least 9,000-12,000 minimal hours of supervised experience are required for physicians before UPM, many states have enacted UPM for nonphysicians with shorter educational paths, ranging from 500 clinical hours for nurse practitioners (NP) to 2,000 clinical hours for physician assistants (PA). As of May 2025, 28 states have authorized UPM to NPs, including 14 states and the District of Columbia (DC) that allow NPs to practice without physician supervision immediately upon graduation. Nine states have authorized UPM by PAs (Table 1).

Extensive data show that team-based care involving NPs and PAs working under physician supervision or following physician-created protocols can provide excellent care. However, there is a paucity of data on nonphysicians practicing without physician involvement, despite decades of UPM across many states. For example, Idaho granted UPM rights to NPs in 1971, Oregon in 1979, Alaska in 1984, and Iowa, Montana, and New Mexico in the 1990s. Advocates in favor of scope expansion for nonphysicians argue that states that have allowed UPM have not experienced negative impacts on patient health.[2] This paper examines legislative trends and data evaluating care provided by nonphysicians practicing without physician oversight or involvement.

A Brief Overview of the Physician Shortage

With the aging of the US population, increases in chronic disease, improvements in diagnostic capabilities, and expansion of effective medical treatments in recent decades, there has been an increased demand for healthcare services, outstripping the supply of physicians. While acknowledgement of a 'physician shortage' is accepted as fact today, just 40 years ago, experts were predicting the exact opposite problem: a physician surplus. A 1980 report produced by the Graduate Medical Education National Advisory Committee warned that the US was training too many physicians, estimating a major surplus by the year 2000. To solve the problem, the committee recommended drastically decreasing class sizes and halting the creation of new programs. In response, medical school admission rates were reduced, foreign medical graduate entry was restricted, and residency training funds were capped and frozen, with the government funding pilot projects paying hospitals not to train physicians.[3]

By 2006, analysts began to realize that the physician surplus prediction was incorrect, having failed to consider increased economic expansion and increased population growth.[4] Experts began to warn of a physician shortage across all medical

Table 2. Total Number of Clinicians and Projected 10-Year Growth Rate (2022)

Type of Clinician	Total Number (2022)	Projected 10-Year Growth Rate
Physician	1,074,000	3%
Nurse Practitioner	355,000	40%
Physician Assistant	158,000	28%

specialties, and especially in primary care.[5] While medical schools responded by gradually increasing enrollment by 30%, residency slots increased by just 1% due to a lack of funding,[6] and in 2018, the US had one of the lowest ratios of physicians per population among Western countries, with just 2.6 physicians per 10,000 compared to the average of 3.6 in similar nations.[7] Instead of training more physicians, government policy has pivoted toward training nonphysicians, with the growth rate of nurse practitioners and physician assistants rapidly rising and far surpassing that of physicians (Table 2).

Policy Trends for Nonphysician UPM

Physicians created both the nurse practitioner and physician assistant professions in 1965, and the roles were designed to provide complementary care, with physicians treating the most complex patients and providing careful supervision and mentoring. But within a decade, nurse practitioner leaders began efforts to separate from physicians, organizing and forming political advocacy coalitions to lobby Congress for 'provider' status—a designation allowing them to be directly reimbursed for services.[8] The Balanced Budget Act of 1997 granted this provider status as well as direct Medicare reimbursement to NPs,[9] clearing the way for UPM.

Government policy has long incentivized nonphysician practice. The Rural Health Clinic Act of 1977 required that federally-funded rural health clinics must be staffed at least 50% of the time by NPs or PAs and in 1989, the Omnibus Budget Reconciliation Act added reimbursement for rural NPs working outside of these settings.[10] Rural pass through legislation laws initiated in the 1980s provided additional funding for nonphysician anesthesia services but not for anesthesiologist care.[11] The Affordable Care Act of 2010 funded new community-based nurse-managed health centers and authorized millions of dollars to increase training program enrollment.[12] The result of these policies has been a rapid rise in the number of nonphysicians, and in 2017, over one in four Medicare beneficiaries received some outpatient care from a NP.[13]

In the last decade, physician assistant leaders began similar efforts to separate from physicians, changing their name to 'physician associate' and lobbying for independent practice. North Dakota became the first state to grant PAs UPM rights in 2019, with other states quickly following.

Evidence Regarding UPM

A comprehensive evaluation of the literature on UPM, as outlined in the books *Patients at Risk*[14] and *Imposter Doctors*[15] found very little research evaluating nonphysicians practicing without physician oversight. One study that has been cited over 1,400 times in the medical literature to endorse UPM policy for NPs was published by Mundinger, 2000 and evaluated the care of 1,300 mostly Hispanic female patients in their mid-40s with stable hypertension, diabetes, or asthma. Patients were randomized to care by a physician or a nurse practitioner. Patient satisfaction, health status (based on a short self-assessment survey of general health), blood pressure, hemoglobin A1C, and peak flow results were compared at six months and two years. With little difference between these minor outcomes, the authors concluded that "patient outcomes for nurse practitioner and physician delivery of primary care do not differ." In addition to a high degree of bias as noted by a Cochrane review,[16] Mundinger omitted important details about the advanced training and supervision of NPs in the study, including close collaborative physician relationships.[17,18]

A 2022 review of Accountable Care Organization Hattiesburg Clinic found that NPs and PAs with independent patient panels (but access to physicians for help when needed) had poorer outcomes and higher cost of care than physicians. Nonphysician

practitioners had higher emergency room and specialist referrals, costing the clinic an estimated $28.5 million annually. The results of this study led the clinic to transition away from UPM by nonphysicians and back to team-based, physician-led care.[19]

A 2022 paper analyzing care provided by independent nurse practitioners at the Veterans' Administration (VA) determined that NPs working in emergency departments use more resources and have poorer patient outcomes than physicians. Calculation models showed that using nurse practitioners increased overall healthcare costs, even when lower wages were considered.[20]

Data After 2023

Since the publication of *Imposter Doctors*, several additional studies involving NPs practicing without physician supervision have become available for review. The Impact of Nurse Practitioner-Led Primary Care on Quality and Cost for Medicaid-Enrolled Patients in States with Pay Parity, 2023 evaluated the care of children with asthma and adults with diabetes by primary care NPs. While both groups had similar performance in ordering Hemoglobin A1c and LDL cholesterol tests, children with asthma primarily cared for by NPs were less likely to be on the appropriate medication and more likely to require emergency treatment.[21]

Schuttner, 2023 evaluated 'over-treatment' of diabetes, comparing VA patients with renal disease, dementia, or cognitive impairment who were randomized to an NP or a physician. Patients had an initial average A1c of 7.16, and after two years, NP-assigned patients had a non-statistically significant decrease in the number of patients with an A1c under 7, which the authors argued to be beneficial due to a potential reduction in the risk of hypoglycemia.[22]

James, 2023 studied care provided to patients with chronic kidney disease (CKD), concluding that: "Nurse practitioner care for patients with CKD was associated with better guideline-concordant care than primary care alone or nephrologist care, with clinical outcomes that were better than or equivalent to primary care alone and similar to those with care by nephrologists." However, the specially trained NPs in the study were not practicing independently—they were following physician-created care protocols with nephrologist consultation as needed.[23]

Several new meta-analyses have also become available in the last few years. A Systematic Review of Outcomes Related to Nurse Practitioner-Delivered Primary Care for Multiple Chronic Conditions, 2023 examined 15 studies between 2003 and 2021.[24] Eight of the 15 studies were performed in states and settings requiring physician oversight, therefore not assessing UPM. Of the remaining seven studies, four also involved team-based care, with just three comparing seemingly independent NPs to physicians—Hummel, 2017, Fraze, 2020, and Morgan, 2019.

Hummel, 2017 examined end-of-life care for VA patients, showing an increase in hospice referrals by NPs compared to physicians.[25] Fraze, 2020 found that 8% of Medicare patients receive most of their care from NPs. This subset of patients tended to be more medically complex, more likely to be disabled adults, over 85, with higher rates of poverty, living in rural areas, and more likely to die during the year. The study reported that patients receiving most of their care from NPs had similar hospital/emergency room utilization but more outpatient visits and long-term care/skilled nursing expenses than physicians.[26] Morgan, 2019 evaluated VA patients and found that medically complex patients cared for by NPs had fewer hospitalizations and lower expenditures but more outpatient visits than physicians. Differences in other outcomes, including mortality rates, were not evaluated.[27]

Psychiatric Mental Health Nurse Practitioner Job and Patient Outcomes: A Scoping Review, 2024 reviewed 24 studies,[28] but only one was a head-to-head comparison between NPs and physicians: Jacobs, 2005 compared psychiatrists to psychiatric mental health nurse practitioners (PMHNP) and found similar medication adherence rates among 122 patients.[29] Indeed, there is little data regarding care outcomes in the field of psychiatry. A 2022 commentary on PMHNP workforce data and access to care[30] cited just two studies analyzing clinical outcomes: a 2018 study showing the NPs were more likely than physicians to prescribe psychotropic

medication to children on Medicaid[31] and a 2022 study showing that NPs and PAs prescribed more benzodiazepines and pain medications including opioids than physicians to nursing home residents with dementia.[32]

A Global Perspective of Advanced Practice Nursing Research: A Review of Systematic Reviews, 2024 evaluated 117 articles, concluding that NP care "was equal or superior to [physicians] for 29 indicator categories... Mixed findings were noted for quality of life, consultations, costs, emergency room visits, and health care service delivery where some studies favored [physicians]."[33] All of the studies included in this meta-analysis involved physician-led care teams or NPs following physician-created algorithms and treating patients with low risk health conditions.

The Effectiveness of Nurse Practitioner Care for Patients with Mental Health Conditions in Primary Care Settings: A Systematic Review, 2024 evaluated 17 studies, most of which involved physician oversight. For example, Jiao, 2018 reported similar outcomes between nonphysicians and physicians (except for poorer quality prescribing for children with asthma and less appropriate use of antibiotics for ear infections among nonphysicians) but clarified that the study involved NPs and PAs working within physician office practices. The authors noted: "the quality of care provided by these nonphysicians may be different from that of their counterparts practicing in other independent settings," and cautioned that "these data are not informative on the expansion in the scope of practice for NPs and PAs over time and its effect on quality of care provided."[34] Wang, 2020 also examined NP practice in a setting of physician supervision, finding similar NP outcomes to physicians regarding smoking cessation, depression, and hyperlipidemia.[35] Just one study in the meta-analysis analyzed unsupervised NPs. Nurse Practitioner Independent Practice Authority and Mental Health Service Delivery in US Community Health Centers, 2017, found that patients living in states that legislated UPM were twice as likely to receive mental health care from a NP rather than a physician, and three times more likely to be prescribed psychotropic medications from an NP than patients living in supervised practice states.[36] Ultimately, the review concluded: "More high-quality evidence is needed to determine the effectiveness of NP care for patients with mental health conditions in primary care settings."

Impact of UPM on Adverse Events

While there is very little research data on the safety of nonphysician UPM, malpractice claims against NPs are increasing, with a 2022 report showing a 10.5% increase. The highest claims occurred among NPs in self-owned practice.[37] A review of National Practitioner Database reports between 2005-2014 found that NPs and PAs were more likely to have malpractice allegations based on diagnosis related events than physicians.[38] In fact, the National Practitioner Database shows a downward trend in adverse action and malpractice reports for physicians and an increased trend for NPs and PAs between 2002 and 2024.[39]

Conclusion

Research evaluating true UPM by nonphysicians is limited. Most studies used to endorse UPM have involved physician oversight, excluded high risk conditions, and evaluated minor outcomes. Further research regarding care provided by nonphysicians without physician oversight is essential to determine safety and efficacy of care.

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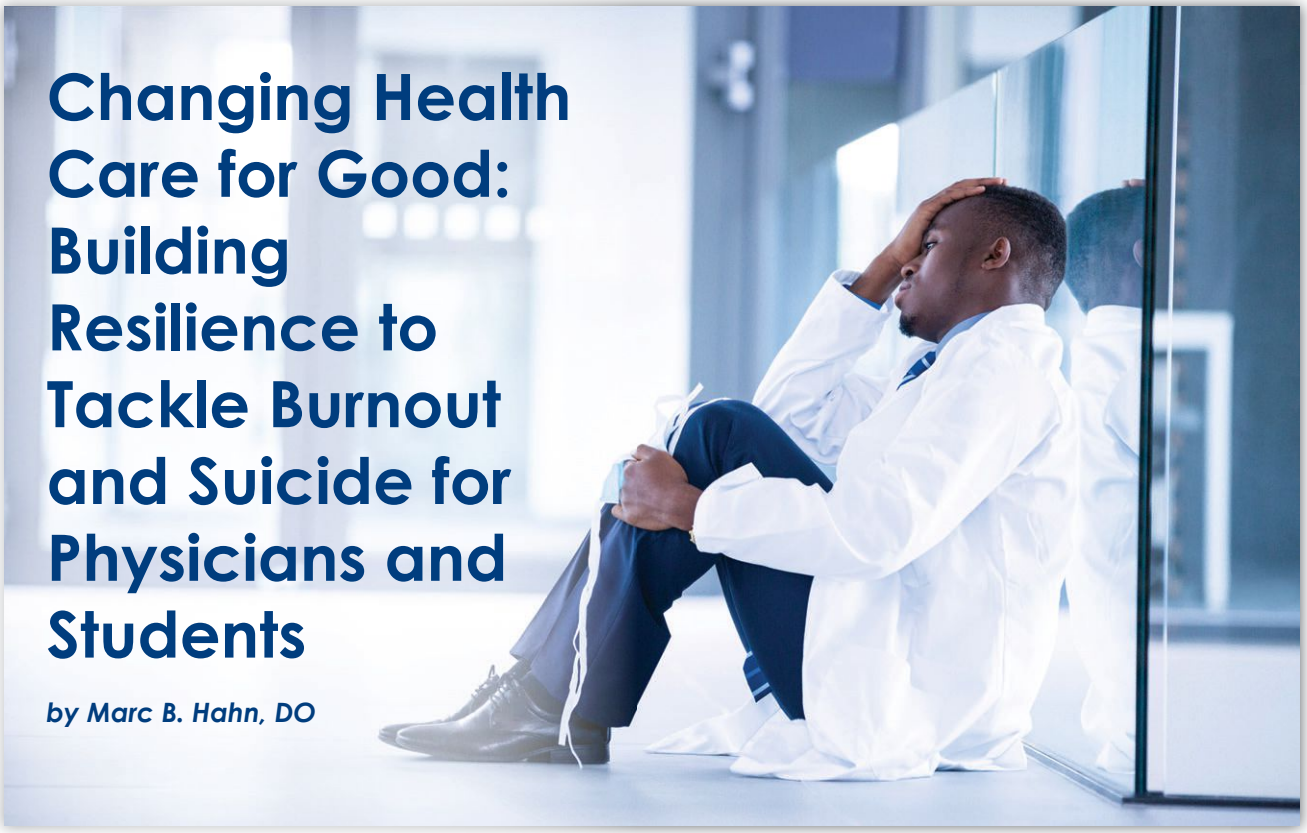
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Changing Health Care for Good: Building Resilience to Tackle Burnout and Suicide for Physicians and Students

by Marc B. Hahn, DO



The holistic philosophy and interconnectedness of mind, body, and spirit drives our approach to health and wellness for all of our communities, including the future health professionals we educate and prepare.

September 17 marked National Physician Suicide Awareness Day. Sadly, physicians have one of the highest suicide rates of any profession, with an estimated 300 to 400 physician deaths annually.

During my career in health care—formerly as an anesthesiologist and pain management specialist and now in university administration—I've witnessed and, at times, personally experienced the overwhelming stresses and challenges of the profession. Practicing medicine has always come with significant mental, emotional and physical demands. And it was generally understood that the work of the dedicated, compassionate physician often required long hours, challenging one's work-life balance, and inviting an emotional toll.



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However, the demands placed on clinicians today rises to a higher level than in times past. Our doctors suffer from unprecedented demands that have increased notably over the last couple of decades. These are largely a result of systemic flaws in our health care that compromise physician well-being and hinder safe, high-quality patient care.

A recent Mayo Clinic Proceedings study found that 45.2 percent of US physicians surveyed reported at least one symptom of burnout in 2023; physicians are 82 percent more likely to experience burnout than those in other professions.

Undue administrative and regulatory burdens, increased technology, a loss of autonomy and fewer opportunities for more direct, personal patient care are

to blame for crisis levels of physician stress, burnout, declining mental health and, in the worst cases, suicide. This tragic situation belies the very advice we give our patients about their own health and well-being and most certainly flies in the face of the oath we take to do no harm.

Most of the physicians I know are passionate about what they do. Yet, understandably, some are deciding to decrease the hours they work or even leave the profession altogether. Left unchecked, this has the unintended consequence of exacerbating the growing physician shortage in our country, a deficit now projected to be as much as 86,000 by 2036. Continued efforts must more broadly include organizational and systemic strategies and policy change, as well as individual strategies.

So, what can those of us who work within the system do? How do we as health sciences universities, in particular, help reverse these disturbing trends?

I was gratified earlier this year to have been appointed the American Association of Colleges of Osteopathic Medicine representative for the National Academy of Medicine Collaborative on Clinician Well-Being and Resilience. Carlton Abner, DNP, KCU associate provost of Campus Health and Wellness, serves as the University's member representative.

The Collaborative, which was launched in 2017, is a great example of the kind of joint effort needed to improve clinician well-being and ensure the best patient care. Leaders from health professional organizations and health systems across the country work to raise awareness of burnout and suicide, improve understanding of the contributing factors and advance multidisciplinary, evidence-based solutions.

Dr. Abner is also the architect of THRIVE, a key KCU initiative that provides our students with a better toolbox for navigating the challenges of today's world. The goal is to strengthen resilience, reduce burnout, facilitate social belonging and help students feel empowered to achieve their goal of becoming the health care providers of the future.

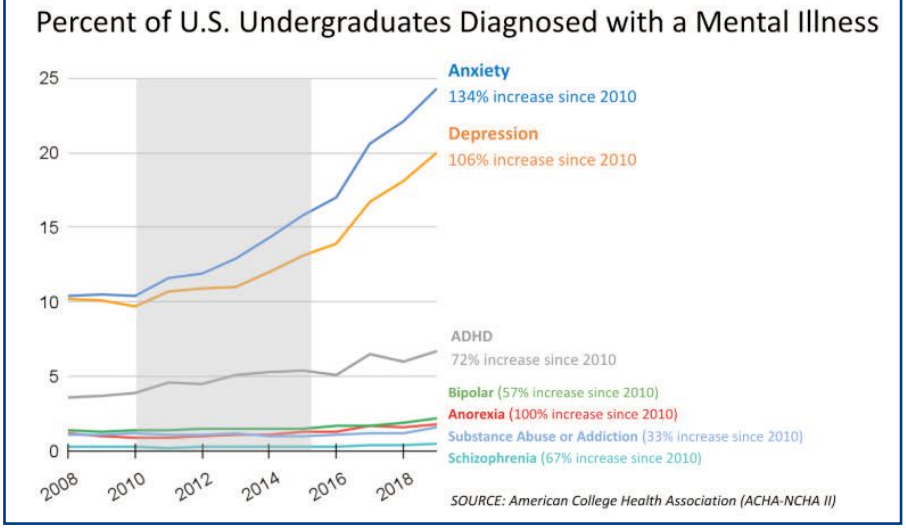
THRIVE brings together interdisciplinary KCU faculty, staff, and students to maximize resources, expertise, and competencies in the areas of psychology, curriculum, mentorship, technology, and data analysis. The initiative's two core components, curriculum and connections, is built into the student experience across our College of Osteopathic Medicine, College of Biosciences, clinical psychology program, and College of Dental Medicine.

At KCU, we also continue to push for policy changes that will reduce the bureaucratic and administrative burdens that are major contributors to stress, burnout and depression. Currently, reauthorization of the Dr. Lorna Breen Health Care Provider Protection Act offers the greatest potential for impact. Originally passed in 2022, the legislation provided grant funding for peer-support programs, mental and behavioral health treatments, and educational resources aimed at reducing burnout and suicide. Funding under the reauthorization would prioritize those experiencing burnout from administrative burdens, as well as those in rural areas and communities with provider shortages.

With our osteopathic medical school as the foundation, Kansas City University is deeply rooted in the interconnectedness of mind, body, and spirit. This holistic philosophy drives our approach to health and wellness for all of our communities, including the future health professionals we educate and prepare. Providing them with the skills, resources and tools needed to counter the stresses and challenges of our health care environment—both in school and once serving in practice—is essential for ensuring their personal well-being and that of their patients.

I'm proud of that KCU demonstrates a commitment to address these issues in continued pursuit of our vision to "Change Health Care for Good." **MM**

1 PICTURE = 1,000 WORDS





Cyber Attacks and the Dark Web: Primer for Physicians

by James R. Rekowski, BS, Joseph T. Kannarkat, MD, Eric A. Packel, JD & Genevieve P. Kanter, PhD

The transition of medical record-keeping from paper charts to electronic health records (EHRs) has transformed clinical workflows, boosting physician productivity and enhancing patient care. However, dependence on EHRs and their integrated technologies—clinical reference guides, decision support, artificial intelligence (AI) prediction tools, and e-prescribing—have opened up new vulnerabilities. From covert theft of medical record data to paralyzing treatment and billing systems, cyberattacks can cripple health care institutions and threaten patient care.



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In this article, we offer a primer for physicians on cybersecurity, providing an overview of hacking and ransomware threats in health care, guidance for post-attack recovery, and practical advice for minimizing the risk of falling victim to cyberattacks.

Background

Ransomware Basics

Operating in an evolving technological landscape, hospitals, physician practices, and other health care delivery organizations (HDOs) face a growing threat of cyberattacks and other deliberate attempts to gain unauthorized access to computer systems and protected data. Ransomware is a particularly disruptive and costly type of cyberattack, in which attackers encrypt data, making the data inaccessible by the HDO without a special, digital key. Attackers will leave a "ransom note" with instructions on how to contact them and how to pay.

Encryption gives attackers leverage in demanding payment for decryption of the data. Many attacks involve a double form of extortion, in which a ransom payment, often in the form of cryptocurrency, is sought both to decrypt the data and to prevent protected health information (PHI) stolen during the attack from being publicly published by the threat actor. The payment through cryptocurrency is generally facilitated using a third-party intermediary and allows for the attacker to protect their own identity during the transfer of funds.[1]

Between 2010 and 2024, the annual number of patient records associated with large health care data breaches increased from six million to 170 million. In 2024, ransomware was shown to have been involved in incidents of 69% of affected patients.[2] Ransomware attacks have been posing serious cybersecurity threats to a range of industries—from energy and transportation to banking. However, the health care sector is unique in that health care data often includes sensitive health information as well personal financial information. Unlike credit cards or bank account information, personal health care information doesn't expire or change.

During a ransomware attack, with PHI encrypted by threat actors—and health information security teams forced to temporarily bring down systems to limit the spread of the ransomware—EHR systems, critical medication schedules, treatment status, or allergy information can become completely inaccessible, leading to life-or-death decisions. The urgent need to resolve these attacks places HDOs in a more vulnerable position than businesses in other sectors.

Threats to Health Care Organizations

As health care organizations face increasingly sophisticated threats, understanding the common cause of data breaches and ransomware incidents becomes crucial. In 2023, 80% of reported health care data breaches were from hacking or IT incidents.[3] These data breaches occurred at HDOs (hospitals, physicians), health plans (insurance companies, health maintenance organizations), business associates (companies that perform services for the organization including billing, cloud storage providers), and health care clearinghouses (organizations that process health information into standard formats).

Additionally, despite advances in security, phishing attacks remain prevalent and effective. Phishing attacks attempt to deceive employees into revealing sensitive information or downloading malicious software. Often, health care employees under typical work pressures are vulnerable to well-created deception sent by individuals who do not have authorized access.[4] A phishing email may appear to come from a hospital administrator requesting verification of login credentials. However, when that document or webpage is opened, ransomware is downloaded onto the device.

With the introduction of AI tools, sophisticated phishing campaigns are now targeting health care organizations. These modern AI systems can create personalized, convincing communications that may appear to come from someone within the organization. Traditional phishing attempts were easily exposed because of their frequent grammatical errors or stilted language. These new AI-crafted messages use appropriate language, organization-specific terminology, and can even mimic writing styles. This emerging technology allows attackers to create persuasive text, significantly increasing the likelihood that recipients will interact with the content. Also alarming is the development of "deep voice" technology, which can clone individuals' voices using small audio samples.[5] With this technology, attackers can use voice phishing, also known as vishing, to simulate calls from health care leadership, with the intent to deceive financial staff into transferring funds in response to urgent directives.

Threat Actors

Actors involved in these attacks fall into primarily state-sponsored groups, organized crime syndicates,

and, to a lesser extent, "lone wolf" hackers. State-sponsored actors are typically characterized by substantial resource backing and are driven by a variety of nation-state interests. Motives can include espionage and property theft, although financial gain is an important factor for countries known to be under international sanctions like Russia, China, North Korea, or Iran.[6] According to the 2025 Data Breach Investigations Report from Verizon, financial motivations were associated with 90% of all healthcare data breaches in 2024.[7]



In 2023, 80% of reported health care data breaches were from hacking or IT incidents.

Organized crime syndicates are another significant threat to the healthcare sector. These groups often benefit from either tacit approval of or lack of aggressive law enforcement against their activities in their country of origin. ALPHV/Blackcat, the group behind the massive cyberattack against Change Healthcare in 2024, is often characterized as an organized crime syndicate.

The traditional image of a "lone wolf" hacker, or an individual operating without affiliation to any group or country, is becoming less of a threat facing the healthcare sector. Though these actors undoubtedly still exist, most attackers are part of the larger organized groups described above. "Lone wolf" attackers may be motivated by notoriety, ideological reasons, or even simply the thrill of the intellectual challenge.

Fundamentals of the Dark Web

When health care data is stolen—through ransomware or other attack vectors—that data can often journey to hidden layers of the Internet that are invisible to the public. To fully appreciate this process, it is helpful to know the underlying structure of the Internet.

The Internet is divided into three distinct layers: the surface web, deep web, and dark web. Common daily Internet interactions such as shopping, reading news sites, posting on social media, and Google searches take place in the surface web, yet this represents only 4% of the entire Internet. The remaining 96% lies within the deep web and the dark web, layers that are not accessible through the standard search engines.[8] The deep web often requires passwords to access and is frequently used for secure commercial transactions. Some common websites are found within the deep web, including streaming services or banking sites.

The dark web describes a smaller, more notorious layer designed for anonymity, which hosts illicit marketplaces for stolen health care data, as well as terrorist activity and child pornography. The dark web is different from the surface web because it cannot be accessed by standard web browsers. The most common browser used to access the dark web is TOR (an acronym for "The Onion Router"). This system, formerly used by the United States Naval Research Laboratory for government communication, was made available to the public in 2002.[9] Data transmission on the dark web, through TOR, encapsulates data in multiple layers of encryption that creates a nearly untraceable communication system to protect user identity and location. Health care data stolen from ransomware attacks frequently appears for sale on dark web marketplaces precisely because these sites facilitate anonymous transactions.

Economics of Ransom Payments

When health care organizations fall victim to attacks, they face complex, difficult decisions that pose economic and ethical dilemmas. A central question facing these organizations is: pay the ransom or refuse?

To make this decision, organizations must first determine if the payment is even legally permissible. The Office of Foreign Assets Control (OFAC) prohibits transactions of any kind with entities on the Designated Nationals and Blocked Persons List (SDN LIST), or individuals that are covered by country or region embargoes. These organizations include terrorist organizations and their members, narcotics traffickers, and known arms dealers. Certain countries and regions identified to be involved in corruption are also included.[10] Organizations may face significant civil penalties from the US Treasury Department for making payments to these sanctioned actors, despite feeling under pressure to recover patient information.

Once that legal bar has been cleared, the decision may come down to whether the organization needs the data that was encrypted (for example, the attackers may have accessed only an old legacy system), or if the encrypted data can be restored. If organizations have a backup system in place that allows for data to be successfully restored, then the incentive to pay diminishes significantly. However, many modern ransomware actors today use a double extortion tactic. This means they not only encrypt critical data, but also exfiltrate ("steal") sensitive data, and threaten to publicly release the data if their ransom demands are not met.

This situation presents a dilemma in which, even with perfect backups, organizations may consider paying the threat actor to prevent patient information from appearing on dark web marketplaces. Regardless, paying the ransom does not guarantee that the data will not be leaked or sold in time. After all, if these ransomware actors are engaging in criminal activity and unwilling to abide by laws, there is no particular reason to think they would abide by any other agreement.

Moreover, once PHI has been accessed or acquired by an unauthorized third-party, a breach has occurred, per Health Insurance Portability and Accountability Act (HIPAA) regulations and state laws. Thus, payments made to prevent publication of PHI do not resolve the legal/compliance issues related to the breach. Organizations may still have legal obligations to notify patients and can still be investigated and penalized by regulators for the incident even if all data is restored and even if the data is not published on the dark web. Accordingly, a decision on whether to pay the ransom is typically driven primarily by business needs, such as whether decrypting the data is necessary to remain fully operational or to have access to critical data.

But why pay a criminal anyway—can they be trusted? Surprisingly, contrary to what may be expected from a criminal enterprise, ransomware actors do generally fulfill promises when payment is made. Groups operate as a business, protecting their "reputation" in these criminal circles and to healthcare organizations. If organizations did not receive the decryption key or tool after payment, then the ransomware business model would collapse as word would spread amongst organizations that paying yields no benefit. Only on rare occasions do actors not fulfill their promise—often demanding additional funds for full access to compromised records.[11]

Beyond the direct cost of the ransom itself, healthcare organizations frequently face indirect expenses that are just as significant, even if some of the costs are covered by cyber insurance. These include:

- Legal expenses regulated to incident response, potential class-action lawsuits, and regulatory fines and penalties.
- Forensic investigation costs to contain the incident, determine the root cause and scope of the attack.
- Recovery costs related to restoring and/or replacing systems subject to the attack.
- Long-term reputational damage affecting patient trust which may reduce future revenue for the organization.

The financial impact associated with the attack extends beyond this immediate crisis. Healthcare organizations experience elevated direct and indirect expenses, underscoring the necessity for prevention and preparedness for these attacks.

Assessment

Case Studies of Notable Attacks

In February 2024, Change Healthcare, a data processing firm owned by UnitedHealth Group was the victim of an attack by the ransomware group ALPHV/Blackcat.[12] This resulted in encryption and theft of the PHI of approximately 190 million individuals, the largest health care data breach ever reported. This attack resulted in significant disruptions in the processing of claims across the country, impacting both patients

and physicians. Lawsuits have been filed against UnitedHealth by both individuals who had their data compromised in the attack as well as providers who were affected by disruption to their revenue cycles.[13]

Other regional attacks have demonstrated similar patterns of disruption to health care operations and compromising of patient information. In Missouri, two hospitals have experienced large security breaches in recent years. In December 2023, a hospital in Liberty detected a disruption due to a cybersecurity attack, prompting it to take its computer network entirely offline and necessitating the transfer of high-need patients to other hospitals.[14]

In Kansas City, a second hospital experienced a significant breach through a phishing campaign. Links in an email directed employees to a website where they disclosed their credentials. With these exposed credentials, attackers were able to download the mailbox of these compromised email accounts, resulting in the unauthorized access of the PHI of more than 63,000 patients.[15] These incidents underscore how organizations with strong security infrastructure can still be vulnerable to breaches of patient data and the need for continuing employee cybersecurity and technology training.

Enforcement and Litigation

The US is actively pursuing perpetrators of health care cyberattacks. These international actors can be difficult to track down, but there have been some reported arrests and criminal charges. For example, in October 2024, two Sudanese nationals were indicted in a federal grand jury for a variety of cyberattacks against the US including against a hospital.[16]

On the other side, claims by patients in the wake of a breach of PHI are filed as class action lawsuits. These matters usually settle prior to formal adjudication. Settlements are frequently made to avoid the costs of litigation and discovery and are not necessarily indicative of valid claims. Plaintiffs face significant hurdles in data breach claims, including certification of the class and proof of actual damages or losses sustained as a result of the breach. In Federal court, Plaintiffs must have "standing" to proceed with a claim, demonstrating that the alleged facts show concrete harm, and not simply that their data has been accessed by an unauthorized party.

Guidance for Recovery Processes

Recovering from a ransomware attack or data leak requires a multifaceted approach that can extend over a long period of time. The initial response should focus on containment of the incident with temporary manual stop-gap measures (physically shutting down systems, disabling an account, or switching to paper records) to prevent further spread of attack in the system. Cyber insurance providers should be alerted, and legal and technical assistance should be engaged. The response typically involves isolation of affected systems, deployment of endpoint detection and response (EDR) tools, restoration of critical systems using secure backups, forensic investigation to determine details on the scope of the attack and file systems affected, and gradual reintegration of systems following security validation using EDR.

Clinicians and non-clinical staff should be made aware that system capabilities will likely not all be restored at once. The recovery process could take weeks or months, not days. As electronic capabilities return, there will be additional resource demands, as charts need to be reconciled, transferring information manually collected during the downtime to electronic format. Organizations must consider this extra burden on employees who also still need to perform their daily duties. Other available staff may need to assist with the high volume of data entry or determine that some manually recorded data will not being reconciled with the EHR for the time being.[17]

Upcoming Regulatory Change

With the technological landscape constantly evolving, the health care cybersecurity regulatory landscape is also constantly adapting. In early 2025, the Department of Health and Human Services (HHS) proposed updates to the HIPAA Security Rule to address the modern cybersecurity challenges faced by healthcare organizations. The Security Rule was first published in 2003, but had its last major modifications in 2013 as part of the "Omnibus HIPAA Final Rule."[18] The latest proposed modifications provide more clarity about many of the security requirements. For example, covered entities (i.e., HDOs, health plans) are required to encrypt ePHI, with limited exceptions, whereas previously, entities were able to assess whether the encryption was reasonable in their environment. This proposal would eliminate the need for entities to perform any analysis on whether encryption is reasonable and appropriate.

This proposed change to the Security Rule would provide 180 days for compliance after the effective date of the rule. HHS notes that many of

these processes should already be in effect given the current cybersecurity landscape, but security practices and procedures may need to be made more explicit internally.

There may, however, be different priorities or modifications to the originally proposed updates with the new administration and new leadership at HHS. See for example the recently announced Request for Information (RFI) from HHS, where "[HHS] is planning the largest deregulatory effort in the history of the Department."[19]

Recommendations for Providers

These recommendations apply to, not only clinicians, but also health administrators and other support staff working in HDOs and other health care organizations.

User education remains an extremely effective preventive measure. Regular training on identifying and reporting phishing emails should be provided to all staff members who work with PHI. The phishing scheme affecting a hospital in Kansas City, discussed in the Case Studies, is a good example of the importance of this type of education. One errant click on a link can compromise entire networks and affect thousands or millions of patients. Phishing simulation software tools are now available and should be used to train and test employees' response to phishing emails.

Several excellent off-the-shelf online training resources exist for organizations to support employee training. HHS is currently producing a series of "Knowledge on Demand" cybersecurity training videos that align with the top five cybersecurity threats mentioned in previous its Health Industry Cybersecurity Practice materials.[20] Certification courses such as those created by Coursera allow students to flexibly learn leadership and management strategies in cyberattacks and the importance of a positive cybersecurity culture.[21]

Health care providers should implement Multi-Factor Authentication (MFA) for access to systems and use an authorized organization-supported Virtual Private Network (VPN). MFA requires users to go through a second verification process beyond a password to access systems. This additional authentication uses a cellphone or other secondary device. With the increased use of remote work, VPNs are now regularly deployed to create secure connections to the organization's network from an outside location. The security ensured by VPNs can reduce unauthorized access.

Widespread utilization of AI tools for transcription and clinical support means organizations need to pay special attention to these systems and their processes for storing information. AI vendors, like other healthcare business associates, should be vetted for HIPAA compliance. Clear business associate agreements should define the proper use of patient information. These agreements, established between a covered entity (such as a provider, health plan, or clearinghouse) and a business associate (any person that performs functions with PHI) must legally bind the business associate on how they can use PHI, prohibit disclosures of data, and require data breach notifications. The health care organization needs to understand data retention defaults and evaluation or audit capabilities before using any AI tools that use patient data.

Healthcare organizations should implement advanced security software such as Endpoint Detection and Response, or EDR, tools. EDR systems monitor all network devices and can often detect suspicious behavior before the breach takes place in the first place. These tools can be a significant investment but provide necessary protection against cyber threats that are targeting health care data in increasingly sophisticated ways. EDR collects data from "endpoints" or system data, which is then analyzed in real time using advanced analytics and machine learning to identify potential threats. EDR is then capable of isolating the "endpoints" that may be infected by ransomware, preventing the spread to additional data.[22]

Every healthcare organization should have policies and procedures in place to comply with the HIPAA privacy and security rules. These include having an appropriate incident response plan. This plan should define roles, communication protocols, and standard operating procedures for recovery processes. Having a template ready for patient notifications and regulatory system reporting can save time if an actual breach were to occur. Providers should familiarize themselves with their designated roles, follow communication protocols, and understand recovery processes. They should be prepared to document accordingly and coordinate with IT security teams. Regular training sessions with incident response experts may help prepare providers to respond effectively when an actual breach occurs.

Health care professional associations and societies often offer resources around security practices that can be helpful for guiding clinicians in specific specialties. The American Medical Association published updated physician cybersecurity information in November 2024

which included information on recent cybersecurity incidents as well as guides for both large health systems and office practices for strong cybersecurity hygiene.[23] Other societies such as the American Academy of Family Physicians (AAFP) have proposed innovative ways of boosting cybersecurity efforts. In a 2023 report to Congress, the AAFP included several novel recommendations such as student loan forgiveness opportunities for cybersecurity professionals willing to work for healthcare organizations in under-resourced areas, whether rural or urban.[24]

Conclusion

The health care sector faces a critical moment in cybersecurity, with increasing sophistication of cyberattacks that threaten patient care and public organizational trust. Addressing these vulnerabilities requires technical safeguards as well as education and awareness to minimize the human role in data breaches. Potential upcoming changes to the HIPAA Security Rule reflect responsiveness to this growing risk and a recognition of cybersecurity as central to patient privacy protection. By implementing the recommendations outlined above, HDOs and other health care organizations can both prevent incidents from occurring in the first place and also be prepared and rise to these challenges if they do occur.

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Navigating the Legal Landscape: Responsibilities in Prescribing Opioids to Patients with Opioid Use Disorder

by Cara Arnold, JD, Brooke Griffin, JD & Katey Hinz, JD

Opioid medications are categorized as Schedule II controlled substances under the Controlled Substances Act (CSA) due to their potential for abuse and physical/psychological dependency.[1] The prescribing of these medications is subject to a complex web of federal and state laws, designed to balance the needs of patients with the necessity to prevent misuse, diversion, and addiction. In this article, we examine the legal requirements and professional responsibilities that govern opioid prescribing on a federal level and in Missouri, with a particular focus on the obligations of healthcare providers when a patient is identified as having, or being at risk for, opioid use disorder.

The Legal Landscape

The requirements for prescribing narcotics and opioids are found in both federal and state law, as well as guidance. On the federal level, one of the primary controlling laws is the CSA, which is enforced by the Drug Enforcement Administration (DEA). On a state level, each state has its own statutes, regulations, and professional board guidelines, so the specific requirements for prescribing controlled substances can vary significantly from one state to another.

DEA Registration

Unless an exception applies, providers must obtain a valid registration from the DEA to dispense, prescribe, or handle controlled substances.[2] A separate registration is necessary for each principal place of business or professional practice where controlled substances are dispensed, unless the location is exempt under specific conditions (e.g. prescribing without dispensing or storing controlling substances at that location).[3]

State Authorization

Typically, providers must also be authorized by the state in which they are licensed to prescribe controlled substances. This state authorization is a prerequisite for obtaining and maintaining DEA registration.[4] Specific requirements for state authorization vary by jurisdiction, so providers should be certain to check their state's requirements in addition to federal mandates.[5]

In Missouri in order to prescribe controlled substances, a provider, called an "individual practitioner," must first obtain a registration issued by the Department of Health and Senior Services (DHSS), Bureau of Narcotics and Dangerous Drugs (BNDD).[6] As part of the BNDD registration application, "individual practitioners" are required to disclose their anticipated drug activities; practices that fall outside of these disclosed activities may be considered irresponsible prescribing and could result in revocation of the practitioner's BNDD registration. DHSS has also promulgated a regulation, Determining Lawful Prescribing, Dispensing and Administering of Controlled Substances, which provides that determinations by DHSS of whether controlled substances are being lawfully prescribed, dispensed, and administered are made by reviewing Chapter 195, RSMo, 19 CSR 30, 21 U.S.C. 801-966, and 21 CFR 1300-1399, as well as other state statutes and rules, and protocols established by the respective licensing boards.[7]





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Legitimate Medical Purpose and Professional Practice

Prescriptions for controlled substances must be issued for a legitimate medical purpose and in the usual course of professional practice. This standard is codified in 21 C.F.R. § 1306.04(a) and is a critical requirement for lawful prescribing of opioids.[8]

In Missouri, the Board of Registration for the Healing Arts (BHA) provides guidance for prescribing practices. Section 334.107, RSMo, authorizes the BHA to deny, revoke, or suspend the license of any physician who:

1. Prescribes, administers, or dispenses a controlled substance that is nontherapeutic in nature or manner, or fails to keep complete and accurate ongoing records of the diagnosis and treatment plan;

2. Fails to keep complete and accurate records of controlled substances received, prescribed, dispensed, administered, and disposed of, including the date of receipt, sale or disposal, name and address of the recipient, and the reason for disposal or dispensing;

3. Writes false or fictitious prescriptions for controlled substances; or

4. Prescribes, administers, or dispenses in a manner inconsistent with Missouri or federal drug control acts.[9]

Additionally, Missouri's Comprehensive Drug Control Act states that a physician may prescribe controlled substances in good faith and only in the course of professional practice.[10]

Patient Information and Medical Need

Under the CSA, a prescribing practitioner must document the patient's name, address, and medical need for the opioid prescription.[11] This documentation must be completed by a licensed and registered medical practitioner and must be available for inspection by the Attorney General.[12] The medical record should include a detailed medical history and physical examination, documenting the nature and intensity of the pain, current and past treatments, underlying or coexisting conditions, the effect of the pain on physical and psychological function, and any history of substance abuse.[13]

In Missouri, BNDD guidelines further require that the prescriber be properly registered, the patient must desire treatment for a legitimate illness or condition, a legitimate need must be established through assessment and diagnostic modalities, there must be a patient-provider relationship, and there must be reasonable correlation between the drugs prescribed and the patient's legitimate needs.[14]

Treatment Plan and Monitoring

Providers should create a treatment plan, and the rationale for continuing or modifying therapy with opioid prescriptions must be documented. Monitoring of the patient's use of controlled substances, including random urine screens, ensures compliance and allows for assessing the effectiveness of the treatment.[15]

In Missouri, initial prescriptions for acute pain are restricted to a seven-day supply unless exemptions apply (such as cancer, hospice, or end-of-life care).[16] There are also specific prescribing limitations for certain providers, including dvance practice nurse practitioners (APRNs) and dentists, for some scheduled medications.[17] Physicians with collaborative practice agreements with an APRN should be particularly aware of those limitations.[18]

Prescription and Training Requirements

Prescriptions must include specific information, including the date of issuance, the patient's full name and address, the drug name, strength, dosage form, quantity prescribed, directions for use, and the provider's name, address, and DEA registration number.[19] Providers may need to complete specific training, such as courses on treating and managing patients with substance use disorders, depending on the nature of their practice and the substances they prescribe.[20]

Record Keeping Requirements

Providers must maintain accurate records of controlled substances prescribed and comply with any DEA inspections pursuant to federal law.[1] Consequences for non-compliance with DEA inspections can range from loss of licensure to criminal prosecution, depending on the circumstances and the severity of any violations.[2]

Missouri law and BNDD regulations also require complete and accurate records of all controlled substances received, prescribed, dispensed, administered, and disposed of. Failure to maintain these records can result in disciplinary action by BNDD.

A Health Care Provider's Responsibility to Report Opioid Addiction Under Federal and State Law and Guidelines

If a provider identifies or suspects that a patient is suffering from substance abuse disorder (SUD) or opioid use disorder (OUD), they should follow a structured, evidence-based, and ethical approach. Current guidelines and recommendations illustrate that the responsibility of the practitioner is to treat patients with SUD or OUD with special care and determine a path forward

out of addiction. The exact steps may vary based on the specific jurisdiction, clinical setting, and severity of the addiction, but will generally include the following:[3]

Assess and Confirm Diagnosis

Providers should conduct a thorough assessment of each individual patient using validated screening tools (e.g., DSM-5 criteria for OUD[4]). Providers should also assess the severity of the addiction, risk of overdose, and co-occurring mental or physical health conditions. Further, utilizing a state's Prescription Drug Monitoring Program[5] (PDMP) that can assist a provider in determining whether a patient is visiting multiple providers and obtaining opioid prescriptions from more than one source, a pattern often referred to as provider hopping or doctor shopping.[6]

Ensure Patient Safety

If a provider determines that a patient is at risk of an overdose or withdrawal, they should provide or arrange for urgent care to address the patient's immediate risks. Providers may also consider prescribing naloxone, a medication designed to rapidly reverse opioid overdose, and educating the patient and their family on its use. The Centers for Disease Control and Prevention (CDC) recommends offering naloxone to all patients who are prescribed opioids, particularly those at an increased risk for opioid overdose.[7]

Develop a Treatment Plan

Providers may discuss options with a patient such as Medication-Assisted Treatment (MAT), including prescriptions for buprenorphine, methadone, or naltrexone, as well as cognitive-behavioral therapy, contingency management, and the like.[8] Moreover, providers should consider pairing an opioid prescription with a non-opioid alternative, and avoid prescribing opioids for chronic or undifferentiated pain.[9]

Coordinate Care and Provide Ongoing Support

Providers should consider referring a patient identified as having SUD or OUD to appropriate specialists and/or treatment programs. A multidisciplinary approach involving mental health professionals, Licensed clinical social workers, and other care team members may also be appropriate. Monitoring progress through regular follow-ups and addressing social determinants (e.g., access to housing, employment, and other support services) is also critical.[10]

Documentation and Legal Obligations

Providers confronted with a patient who is addicted to opioid medications should carefully record their assessments, discussions, and treatment plans. They must also follow all applicable local laws regarding reporting if the patient poses a risk to themselves or others.[11] When reporting a patient for suspected SUD or OUD, the provider should take care to maintain patient confidentiality, balancing their privacy obligations with their duty to the public in helping mitigate the ongoing opioid crisis.[12]

Missouri Law Definition of Addict

Missouri defines addict as a person who habitually uses one or more controlled substances to such an extent as to create a tolerance for such drugs, and who does not have a medical need for such drugs, or who is so far addicted to the use of such drugs as to have lost the power of self-control with reference to his or her addiction.[1]

As mentioned above, in Missouri, regulations provide that a physician cannot prescribe controlled substances to a patient that the physician knows is using the medication in a non-therapeutic manner, unless the physician is approved and registered as a narcotic treatment program or a federally approved office-based opioid treatment provider.[2]

There is no shortage of cases that detail the legal consequences for health care practitioners that prescribe opioids or other narcotics with flagrant disregard for their patients' status as addicts or risk that they may become dependent on those prescribed substances.[3] What is clear is that a practitioner prescribing opioids or other narcotics to treat patient pain should always look closely for the indicators of SUD or OUD, as well as know their legal obligations as to privacy and reporting in their specific jurisdiction.

Best Practices for Prescribing Opioids

The CDC offers clinical practice guidelines for opioid prescribing, that emphasize a cautious and evidence-based approach to managing pain with opioids.[4] These guidelines recommend that practitioners carefully evaluate the risks and benefits of opioid use, particularly for chronic pain, and prioritize non-opioid therapies when possible. For chronic pain, the CDC advises that opioid dosages should not exceed 90 morphine milligram equivalents (MME) per day, with extra precautions recommended for dosages above 50 MME/day. These guidelines also stress the importance of

regular patient re-evaluation, monitoring signs of misuse, and using the lowest effective dose for the shortest duration necessary.[5]

The legal significance of these guidelines is evident in their influence on federal and state laws, as well as their use in legal proceedings. For instance, the guidelines have been cited in cases involving allegations of overprescription or inappropriate opioid prescribing practices. Courts have referenced the CDC's recommendations to establish benchmarks for safe prescribing and to evaluate whether a practitioner's actions deviated from accepted medical standards. In *United States v. Moon*[6], the court noted that the defendant's prescribing practices exceeded the CDC's recommended dosages, contributing to findings of inappropriate prescribing. Similarly, in *United States v. Bauer*[7], the court highlighted the risks associated with exceeding CDC-recommended dosages and prescribing opioids in combination with other controlled substances, which increased the risk of addiction and overdose.

Additionally, the guidelines have shaped federal initiatives and statutes aimed at addressing the opioid crisis. For example, the Federal Public Health and Welfare Code mandates the dissemination of evidence-based opioid prescribing guidelines, including the CDC's, to healthcare providers to promote safer prescribing practices.[8] This statute also supports education and awareness programs to mitigate the risks of opioid misuse and abuse. Furthermore, the guidelines have informed state-level legislation, such as West Virginia's Opioid Reduction Act, which incorporates CDC recommendations to limit opioid prescriptions and promote alternative pain management strategies.[9]

Conclusion

The CDC's opioid prescribing guidelines serve as a critical framework for promoting safe and effective pain management while minimizing the risks of opioid misuse and addiction. Their legal significance lies in their role as a standard for evaluating prescribing practices in both regulatory and judicial contexts, as well as their influence on public health policies and legislation. Therefore, in addition to following the above discussed federal legal requirements and guidelines, it is best practice for practitioners to stay current on research and reports published by the CDC and other similar organizations. While these recommendations do not necessarily carry the force of "law," they do have considerable influence on the court decisions in this area and serve as a guidepost for determining whether a provider's prescribing policies and practices are of the kind that should be prosecuted.

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6. *See* 19 CSR 30-1.011(1)(F). An individual practitioner is defined as "a physician….or other individual licensed, registered or otherwise permitted by the United States or Missouri to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, a pharmacy or an institutional practitioner[.]
7. 19 CSR 30-1.060.
8. 21 C.F.R. § 1306.04; *United States v. Hofschulz*, 105 F.4th 923, 926 (7th Cir. 2024); *United States v. Pham*, 120 F.4th 1368, 1371 (9th Cir. 2024).
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11. 21 USCA § 827(i)(5).
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14. *See* Controlled Substance Guidelines for Missouri Practitioners, Bureau of Narcotics and Dangerous Drugs, available here: https://health.mo.gov/safety/bndd/doc/practitionersguidelines.doc.
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38. *Moon*, 33 F.4th at 1288.
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40. 42 USCA § 290bb-2, *et seq.*
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MM

Sleep Medicine: My Dream Career

by Pradeep Sahota, MD

I struck the birth lottery when I was born to educated parents in India (Figure 1)—my beloved father (Sh. Gurbaksh Singh Sahota), an engineer and my angel mother (Mrs. Subhadra Sahota) who had a degree from Delhi University (Bachelor with Honors). My father was always posted to where a new dam was being constructed. Thus, we lived in rather modern housing as new towns were built near dam construction sites.



Figure 1. Dr. Sahota's father and mother. His sister is on his father's lap and Dr. Sahota is in the middle.

Although a family of modest means, we lived comfortably and with the highest ethics and honesty. My parents believed children, not property, were the best investment and made certain me and my sister (also a physician) got everything we desired—books, journals, sports equipment, you name it, so long as we excelled in our education. My parents loved me beyond measure (more than I deserved) and championed every one of my accomplishments. My father taught me the value of selfless hard work and respect for all—no matter their status (financial, position, or otherwise). Once, he stayed at work for about 60 hours straight when some in his team were involved in an accident until the last worker was accounted for. Real respect could only be commanded not demanded. I was a very ill child—respiratory infections, enteric fever (relapsed twice) and more—to the point of questionable survival. But my mother was the rock; she took care of me and the family. She led the toughest life imaginable without complaining or looking for recognition (tough to copy her). I miss them. My sister Archna was, and remains, my eternal support. She and my brother-in-law Om helped my parents so much.

I did well at school—scoring in the top 20 in high school graduates in the entire large state of Punjab. This was a first for our small-town school and a source of great community pride. My name was in the newspapers in the State Board Merit list. I was beyond thrilled. I immodestly showed the newspaper article to anyone and everyone that I met for at least a week. My schoolteachers played an immense role in shaping the trajectory of my life and career. I owe them a great deal and am forever grateful. Initially I chose math but found theoretical math uninteresting. Encouraged by my teachers: Ranjit Singhji, Amar Nathji, Onkar Nathji, Ramesh Chanderji, Avtar Singhji, and others I switched to biology. My father had saved his engineering books and hoped I would follow his path. The great father that he was, he supported me to follow my heart.

My early college education was at Dayanand Anglo-Vedic (DAV) College Jalandhar, one of the oldest and finest. I made it to the College Merit List, Punjab University Merit List, and was awarded "Outstanding Scholastic Achievement" (my award was a book I still have). Medical school was at Christian Medical College (Figure 2), which laid foundations for my journey in medicine. I will always be grateful to Professors



Figure 2. The young Dr. Sahota in Medical School.



Pradeep Sahota, MD, is a Professor Emeritus of Neurology and Director of MU Sleep Disorders Center and Sleep Medicine Fellowship Program at University of Missouri-Columbia School of Medicine, Columbia, Missouri, USA. He is the *Missouri Medicine* Editorial Board Member for Neurology.

Singh, Satija, Saha, Cowan (British), Howie (New Zealander), Fairburn (Scottish); special thanks to Dean Rao, you were the best! My interest in neurology developed during my internship rotation with neurosurgeon Dr. Shadangi (excellent teacher). Like more than a billion people world-wide, I developed migraines. What a pain! My friend Anit helped me immensely during these excruciating headaches.



Figure 3. Dr. Sahota with his wife Shaku and children, Shawn and Sheena.



Figure 4. Dr. Sahota and his family; wife Shaku; daughter Sheena and her husband, Junal, with their children; and son Shawn and his wife, Amanda, with their children.

Looking around the world, the greatest opportunity for professional advancement and practicing the most advanced medicine in the world was in the United States. It was during a brief stint as a medical officer/resident when I decided to emigrate to the USA. My first job was in New York City—doing physical examinations on new employees. My wife and family supported me. My friends, Perminder and Neena Grewal did so much for us. I did well in the qualifying exams and got a neurology residency at the University of Missouri in Columbia, Missouri.

Finding a residency was challenging then for international medical graduates; gratefully it is much better now. Thanks to James Dexter, MD, who interviewed me at Laguardia Airport and offered me the position and Drs. Byer, Davenport, and Pickens who taught and supported me during the transition and shaped my career. I was extremely apprehensive about integrating into a unfamiliar system in a culture and country unfamiliar to me. Interns—Bill Blanchet, Denny Weber, and Joseph Alcorn helped me tremendously. Medical students were a joy to work with. Special thanks to Daniel Keniston, MD— Dan was senior Neurology Resident who unofficially adopted me. I arrived in Columbia on a football weekend—no hotel room available (quickly learned that college football is as important as breathing to many). Dan offered me his place to stay, gave me his books (with the pretense he didn't need them anymore). Dan was my guardian angel. He was so modest he tried to stay below the radar in the many ways he aided me.

Once I began to see patients, I felt rather at home. Coming from an agricultural state in India, I felt folks working with mother earth (farmers) or living in Midwest agricultural states have similar mindsets no matter the geography. They are honest, polite but direct, don't complain about minor issues, and appreciate you. Even the country music across oceans sounds similar. During my residency, my wonderful wife Shaku and I became parents to our beautiful daughter Sheena (now a Hematologist/Oncologist). I was the happiest Dad ever and still am! My salary of $18,000 per year barely bought essentials but for the birth of Sheena's celebration (Figure 3), I sprung for French Champagne with friends!

Enamored by Neurophysiology during residency, I chose a fellowship in Clinical Neurophysiology. My achievements during residency and exceptional recommendation letters by mentors helped secure a fellowship at Duke University. Once, while awaiting path results on the phone, I began singing a local jingle. The rest of the team entered without my realization; aside from performance details, that little gesture made it to one recommendation letter saying how easily I had adapted to the Midwest. Duke had recently added sleep medicine to the fellowship—an unexpected bonus. That serendipitous new inclusion was to shape my professional life and interests in ways I could not then imagine. Duke staff and faculty (Radtke, Shin, Erwin, Lewis, Rozear, Crane, McNamara) provided a world-class training. Anything I didn't learn was my deficiency. While at Duke, we were blessed with our second child, my wonderful son Shawn, who is now an Orthopedic surgeon. Sheena and Shawn are my and Shaku's pride and joy—the best gifts God has given us! Our children are happily married (Son-in-law Kunal, Daughter-in-law Amanda; two wonderful additions to the family) and have given us five beautiful angelique granddaughters (Figure 4). Ladies rule! I so love my time with them!

I was trained in Neurology, Clinical Neurophysiology, and Sleep Medicine and, having spent a great deal of time in each discipline, I decided to take all three boards. Incredibly, all three exams occurred in the same week in different locations. Our family climbed into the family wagon and off we went. With my wife doing most of the driving, and me doing some last-minute cramming, we made each testing venue on time. I passed all three! With multiple academic opportunities available, some facilitated by my mentors, I decided in 1987 to go back to the University of Missouri School of Medicine. I was proud of MU and grateful for extending me, an international medical graduate, a resident position. This initiated a long, productive, and gratifying academic career.



Figure 5. Dr. Sahota with Dr. Thakkar.

Dr. Dexter asked me to lead Clinical Neurophysiology, and Dr. Crowley wholeheartedly supported me. Sleep Medicine, a relatively new discipline, had thoroughly claimed my interest. We developed an accredited sleep disorder center. Many thanks to Anne, Fred, Jodi, Tammy, Troy, Donna. We also developed a Clinical Neurophysiology fellowship which morphed into a Sleep Medicine fellowship and got certified when ACGME began accreditation. Working with Dr. Dexter, an authority in treating headache, I had my first scientific paper accepted and published. With additional publications, I was asked to be a peer-reviewer by several journals. My first funded grant was in 1991-1992, multiple funded studies have followed. Much of the credit goes to our distinguished faculty and research staff, especially Anne Bonnett. As my curriculum vitae grew, so did opportunities for research.



Figure 6. Opening ceremony of MU's Neurosciences Inpatient Center.

In 2002, with the departure of distinguished Steve Horowitz, MD, I felt ready to assume a leadership position as Neurology Chair. Dean Crist gave me the opportunity and support to develop a comprehensive neurology department with a full spectrum of clinical services and excellence in medical education and research. A chance meeting with Mahesh Thakkar, PhD, at a 2006 Denver conference, where he was chairing a session on the role of GABA in sleep, led to his departure from Harvard to join our faculty. He is the lynchpin of basic neuroscience research with extensive funding—including National Institutes of Health and Veterans Administration Merit Awards. (Figure 5). Later Asgar Zaheer, PhD, with his team joined us.

Our faculty grew from four (Drs, Burger, Dhand, White, and me) to 24. Teaming with Neurosurgery Chief Scott Litofsky, MD, we established a Neurosciences Inpatient Center (Figure 6) and Neurocritical Care unit. We established programs in Stroke, Neuromuscular, Behavioral Neurology, Movement Disorders, Epilepsy, and Sleep Medicine.

I was fortunate to have fantastic faculty join—Dr. Shenker, recognized as best Program Director (PD) by American Academy of Neurology (AAN), is now Associate Dean for Curriculum Development. Drs. Lardizabal and Govindrajan were recognized as Best Clerkship Directors by AAN. Kudos to them and all my colleagues, staff and residents who led our ascent to an excellent neurology department. I saw myself as a servant leader and treated all like family. I tried my best to get to know the faculty and match them to the task they had a passion for—sometimes they knew and sometimes we figured out together. Dr. Shenker (now Associate Dean), Drs. Rolan (served as PD), Asher, and Lardizabal (now Neurology Chair), came from private practice to excel in academics. Our programs expanded to provide comprehensive neurological services to

Mid-Missouri and beyond. Residency program expansion followed along with post-residency fellowships in Stroke, Endovascular Intervention, Neurocritical Care, Clinical Neurophysiology, and Sleep Medicine. My father had sleep apnea and had a stroke at age 51. Sleep apnea had not made it to medical awareness then. I will never forget the sight when my father was brought to the emergency room (I was an intern) and have since tried to practice and teach the trainees to "Treat all our patients like we want our family treated."

My educational efforts were recognized by our students and residents with Best Teacher award and MUlation award (recognizing teachers that students may emulate). I have had opportunities to serve my department, my institution, my state, on a national level (committees for AAN, American Epilepsy Society, United Council for Neurologic Subspecialties), international level (as member and then chair of Sleep Research Group of the World Federation of Neurology), and as member/contributor for the Committee for International Classification of Sleep Disorders (ICSD). It was an honor to get Lifetime Achievement Awards by American Brain Foundation's AINA Lifetime Achievement Award committee (Washington DC, 2015) and AAPIOS (American Association of Physicians of Indian origin—Sleep) in Boston (2017).

As in all lives and careers, I have had my share of challenges in clinical and academic medicine. I do my best to understand the issues clearly, address it in the best way and learn from experience. Some things, however, are timeless: hard work, honesty, perseverance, getting the best education possible, and thoughtful planning.

I believe it important to have interests, indeed passions, outside medicine—a healthy mind in a healthy body. I enjoy sports—especially badminton. I invited some residents and faculty to join me in batting the birdie. Dr. Gomez was a quick learner! Badminton is a welcome respite from work—concentrating on hitting the shuttle. Not religiously inclined, I like Swami Vivekananda's saying: "You can be closer to God through football (he meant soccer) than through Holy Gita"—point being concentration on one thing and nothing else is a type of worship. Hence badminton! Also it improves quality of sleep.

After serving as Chair for over 20 years, I retired in 2022. Drs. Shenker, Zweig, Whitt, and Barohn spoke at my retirement event—their words touched me. Thanks to Brandi French, MD, (superb resident, served as Director Stroke program, Neurosciences Inpatient Center and now Chair), and Dean Richard Barohn for honoring me with title of Professor Emeritus—giving me opportunity to continue to serve —especially Sleep Medicine Education and Fellowship. In 2023, I was surprised during the University of Missouri - Columbia School of Medicine graduation ceremony where a new annual award was announced—"Pradeep Sahota MD Aspirational Leadership award for Best Student Leader in Neurology." Thanks Drs. Ashraf, French, our faculty, and institution for this great honor!

Along my life's highway so many people have inspired and assisted me, there is no room to thank them all. Please know I am grateful to all of you. My parents and my sister bore an immense burden during my childhood. My parents used their retirement savings to put me through medical school, my exceptional school and college teachers who encouraged me— "Your performance is excellent but you can do better," my classmates and friends who made my life's journey joyful, my wonderful wife who has supported me even as I put in long hours, my children who are my heartbeat, MU for accepting me as resident and teaching me, my Duke mentors for their guidance, Dean Bryant and William Crowley who first trusted me with the reins of leadership, and Dean Crist who gave me the opportunity. I am grateful to my colleagues, our residents, fellows, our staff, and School of Medicine and MU HealthCare administration—as I said too many to mention who played significant roles. I thank my patients who trusted me with their care. They sometimes couldn't pronounce my name correctly, but their acknowledgement of my competence and caring for them was the best reward. Even with the price of gasoline soaring, they often traveled more than 150 miles to see me and declined my offer to find physicians nearby. This touches my heart.

As I enter the late innings of life, my mind sees the student I was and remain, questioning, trying my best, staying grounded, remembering my roots in India but adopting the great country of the United States, treating all with courtesy, patients and family with compassion, care and competence and nourish and support my neurology family (modeled after my parents). A parting suggestion for younger colleagues "Get to know yourself well before you choose—profession, specialty, or other. Find the best mentors who can provide honest input. Once you do, follow your dream with drive and perseverance." Luck plays a role, but genuine and sustained efforts usually have a way of bringing luck! My request to all is to stay engaged with medicine—in Missouri and at the national level. My parting conjecture: continue to provide the best care, education, and meaningful research.

I thank Kristy Huffman for assistance with this manuscript. Thanks also to *Missouri Medicine* and its distinguished, long-time editor John C. Hagan, III, MD for this opportunity to reflect on and share my personal and professional life.

MM

MSMA Launches Patient Advocacy and Education Campaign: "Your Care is at Our Core"

Your Missouri State Medical Association (MSMA) announces Your Care is at Our Core campaign launch, a statewide patient advocacy and education program to restore and protect the physician-patient relationship, which is the foundation of health care in Missouri. The campaign is in partnership with the American Medical Association (AMA) and more than half the states in the nation.

"Missouri physicians believe the heart of medicine is the relationship between physician and patient," said MSMA President Brian Biggers, MD, a breast surgical oncologist and general surgeon with CoxHealth in Springfield. "Care begins not with paperwork, but with trust, compassion, and time spent face-to-face."

Missouri's physicians, in all medical specialties and in all 114 counties, are facing administrative overload, prior authorization delays, and third-party interference. They are increasingly constrained by decisions made by insurance companies, pharmacy benefit managers, and other bureaucratic interventions. This limits not only the time physicians can spend with patients, but also the treatments they can offer. These systemic barriers threaten the integrity of care, and the trust patients place in their doctors.



"Healthy aging means avoiding illness as much as possible and dealing with illness when it occurs. We need to pay attention to this because how we age matters."

- Keith Ratcliff, MD, New Haven, Missouri - MSMA Member

The focus is being pulled away from what matters most—compassionate, evidence-based care delivered by trusted physicians. Recent data from the AMA underscores the urgency of reform: 89% of patients agree that the doctor-patient relationship is central to health care and 79% say bureaucracy makes it harder for physicians to provide the best care.

"Missouri physicians are leading the charge against the bureaucracy that stands between us and our patients. These barriers are eroding the very foundation of care," said Dr. Biggers. "Your Care is at Our Core isn't just a slogan—it's a call to action. We are standing with physicians nationwide and the AMA to restore the time, autonomy, and respect that every patient and physician deserves."



Brian D. Biggers, MD, FACS, is a breast surgical oncologist and general surgeon with CoxHealth in Springfield, Missouri, USA, and the 2025-2026 MSMA President.





Students across Missouri have returned to campus for another year of medical school and are readying themselves for the important role of the patient-physician relationship. Students are preparing to be caring, trusted healers, and advocates for their patients, their communities, and their profession.

The Your Care is At Our Core campaign aims to amplify physician voices across Missouri, engage patients in advocacy, and call on lawmakers to prioritize reforms that protect physician-led, patient-centered care.

Contact Rachel Bauer at rbauer@msma.org for more information.



85% of patients agree the bond physicians form with their patients is central to health care. Physicians choose medicine because they want to treat patients, to understand their health care needs and how to best help them, and to provide the care they need to get better. That's why physicians prioritize time spent with patients, building trusted relationships that lead to effective care and treatment.



"At the heart of physician training is care of the individual in front of us and finding the root cause of their concern. The core of my joy as a physician is doing just that - listening to a patient's concern, diagnosing the underlying issue, creating a treatment plan that aligns with his or her values, and helping every patient get to his or her health goals."

- Joanne Loethen, MD, Kansas City

In Memoriam



H. Jerry Murrell, MD

October 20,1937– September 6, 2025

H. Jerry Murrell, MD, a radiation oncologist and MSMA's 136th President, passed away September 6, 2025, at the age of 87.

Born and raised in Texas, he received his MD from the University of Texas in 1962. On active duty with the US Navy until 1965, his medical training included a family practice residency in California and a radiology residency begun at the University of Kansas Medical Center and completed at the Mallinckrodt Institute of Radiology at Barnes Hospital, Washington University, in St. Louis, Missouri.

After private practice for over a decade in Albuquerque, Dr. Murrell moved to Columbia, Missouri, to become head of radiation oncology at the University of Missouri School of Medicine and the Veterans Hospital in 1985. He also directed radiation oncology at Boone Hospital in Columbia. In 1988, Dr. Murrell became director of Jefferson City's Mid-Missouri Cancer Foundation. That practice eventually formed Missouri Cancer Associates, which now has eight locations for radiation oncology in seven cities.





Long active in organized medicine, Dr. Murrell chaired the MSMA Legislative Committee and served as a Delegate to the American Medical Association. Awards include a Fellowship in the ABR, Doctor of the Year of the Boone County Medical Association, Distinguished Eagle Scout by the Great Rivers Council of BSA, Outstanding Missourian by the Missouri House of Representatives, and President's Award from MSMA.

He served on the boards of Boone Hospital Trustees, Museum of Art and Archeology, We Always Swing Jazz Series, Columbia Civic Orchestra, Primaris, the Great Rivers Council of Boy Scouts, the Community Foundation of Central Missouri, and the Columbia Rotary Club.

He was married to Beverly Robertson, MD. She preceded him in death in 2014. They had three children and five grandchildren.



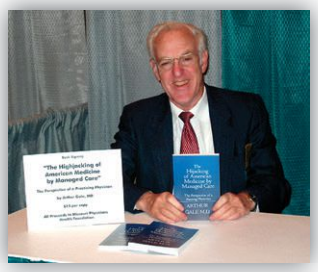
Arthur H. Gale, MD

September 11, 1930 – September 17, 2025

Arthur H. Gale, MD, an internal medicine physician and a Contributing Editor to *Missouri Medicine* since 1991, passed away September 17, just after his 95th birthday.

Born in St. Louis, Dr. Gale graduated from University City High School where he was class president. He studied at the University of Chicago and completed his undergraduate studies at Washington University in St. Louis. Dr. Gale graduated from the University of Missouri School of Medicine and went on to practice internal medicine for over 60 years.

Dr. Gale was *Missouri Medicine*'s longest serving Editorial Board member (34 years) and was deeply involved in education and taught generations of students as a Clinical Associate Professor at Washington University. His competence and compassion were exemplary.



Dr. Gale had superb writing skills and contributed more articles to MSMA's journal than any other physician. He also wrote many articles for the St. Louis Metropolitan Medical Society (SLMMS) magazine. He authored four books and established three lecture series, including the Arthur Gale Medical Arts Series at the St. Louis County Library, the Jewish Lives Series at the St. Louis Jewish Book Festival, and the Arthur Gale Family Lecture series at the St. Louis Holocaust Museum. Dr. Gale also founded the Arthur H. Gale Writing Award presented to the best commentary article published in *Missouri Medicine*.



He was very active in advocacy for medicine in SLMMS and MSMA and a Delegate to the American Medical Association. He was awarded Doctor of the Year by the SLMMS Alliance in 2019,

Dr. Gale was preceded in death by Marilyn, his wife of 58 years. They had three children, two grandchildren, and one great-grandchild.

His biography was featured in our May/June 2024 issue (pages 210-212). It is a record of a life well-lived.



NEW MSMA MEMBERS!

** = Resident/Fellow

* = Medical Student

Saqib Abbasi, MD – Oncology – Misson
Syed Ijlat Ahmed, MD – Neurology**
Sam Alexander, MD – Emergency Medicine – Fair Play
Lawrence Andrade, MD – Family Practice – Carthage
Estylan Arellano, DO – Emergency Medicine – Honolulu
Cody Barnes, MD – General Surgery – Nixa
Daniel Barnes, MD – Emergency Medicine – Nevada
Samer Bou Karroum, MD – Pediatrics**
John Braun, DO – Diagnostic Radiology – St. Joseph
Rakesh Chandra, MD – Psychiatry – Carbondale
Samuel Coster, DO – Cardiology**
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Thao Duong, MD – Cardiology – Independence
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UMKC School of Medicine

Who's Your Doctor? The Primary Care Crisis Through the Lens of a Family Physician

by Beth Rosemergey, DO & David A. Voran, MD

When patients lose access to regular primary care physicians, it is detrimental to their health, while strong patient-physician relationships improve outcomes.

The National Academy of Medicine defined Primary Care as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community."[1]

Though this is our stated ideal, the current reality is that fewer and fewer patients are able to establish and maintain a lasting relationship with a personal physician. Why?

Primary Care is Facing Increasing Threats from Many Sources

Here are threats to family care:

1. Administrative cuts to healthcare agencies that undermine the research and services physicians rely on.
2. Proposed cuts to Medicaid that will further erode the ability of states like Missouri to attract and support primary care physicians (who see more Medicaid beneficiaries than other physicians).
3. Education cuts that threaten the pipeline for physicians.
4. Expanding scope of practices of non-physician healthcare providers and growth of retail and convenient urgent care centers.[2]
5. Demographically, the supply of primary care physicians is expected to increase only 3% by 2037, while demand is projected to increase 12%.[3,4] This mismatch is even more pronounced for physicians providing geriatric care.
6. Geographic disparities, especially in rural and inner-city areas, exacerbate the issues for broad swaths of Missouri residents.[5]



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Primary care was a central focus of the Institute of Medicine's Study of Primary Care, initiated in 1994 and published in 1996. Despite the 2010 Affordable Care Act's expansion of Federally Qualified Health Centers, Medicaid, and healthcare information technology, most recommendations for primary care have not been actualized. The US healthcare system remains highly fragmented, overspecialized, and functions within a profit-driven environment. This is not a structure that lends itself well to producing improvements in the overall health of the nation nor to responding adequately to national health emergencies.



Shortages of primary care physicians and hospital closures have broader economic impacts on jobs, local economies, and community well-being.

Profit-driven healthcare mergers and acquisitions, while promising efficiencies of scale, are causing instability as physician groups adjust. Retail companies like Amazon, CVS, and Walmart are expanding their footprint in primary care, offering virtual and preventative services but are struggling to gain traction. Theoretically, this should increase availability of primary care but is not because they are profit driven. Nevertheless, this movement is leading self-employed physicians to move to contract and retail-based primary care.

In addition, the current healthcare financing and regulatory system is dysfunctional and disruptive. Primary care physicians are struggling to compete for resources. Inadequate reimbursement for primary care is a key driver of burnout and workforce challenges.[6] Perceptions and reality are often at odds regarding the realities of primary care in our US system. Patients indicate that primary care is very important to US health and perceive that significant funds are being spent on primary care. A recent study published in the *Annals of Family Medicine* found that US adults estimate that 51.8% of US healthcare funding is spent on primary care compared to actual spend of 4.7%.[7]

Access to high quality primary care disproportionally affects rural communities. Lack of rural primary care physicians across the country impacts the immediate health of each individual living there as well as the overall health of that rural community. Additionally, critical access hospitals are closing at an alarming rate. These hospitals/healthcare systems are a significant employer in rural areas.[8] Shortages of primary care physicians and hospital closures have broader economic impacts on jobs, local economies, and community well-being. Rural and low-income communities are hit hardest, exacerbating existing health disparities in these underserved areas.

When patients lose access to regular primary care physicians, it is detrimental to their health, while strong patient-physician relationships improve outcomes. Without adequate access to primary care, medical conditions may go undiagnosed or untreated until they become more severe. Fragmented care can also lead to missed diagnoses, redundant tests, and medication errors, compromising overall healthcare quality and driving up costs.

New technology often promises to be the solution to increase patient care delivery, and efficiency, improving health outcomes while addressing physician burnout. Lack of regulation can make it difficult for all physicians to adopt new technology, and the jury is still out whether these technologies will address administrative burden once implemented. The most relevant example of this is Artificial Intelligence (AI). A Rock Health survey commissioned by the AAFP showed 87% of Family Physicians use AI daily.[9] Like other new developments, these tools offer to reduce workload, automate documentation, enhance diagnostics, streamline administrative tasks, and provide personalized treatment plans. Yet

regulations mandating documentation of a physician's involvement in the work is preventing physicians from fully exploiting this tool in the same way most other businesses have been able to do. It is also important to consider these tools are quite costly and often beyond the reach of many rural practices with prices near $100-$600 per user per month and have varied levels of EHR integration.

Without necessary regulatory changes, AIs potential may still be over the horizon for most primary care physicians. There is no doubt AI will be fully integrated into physicians' practices but, like other technologies, will not solve fundamental problems facing primary care today.

As our healthcare system continues to evolve, the importance of primary care cannot be overstated. The need for comprehensive, accessible, and effective primary care services in Missouri has reached critical levels. Physician-led primary care should be the gold standard. Among the various disciplines within primary care, Family Medicine is well positioned and ready to address the diverse needs of our communities and enhance the future of healthcare delivery.

Family Medicine physicians are uniquely trained to provide holistic care to patients of all ages and backgrounds. Their rigorous education encompasses a wide range of medical fields, including but not limited to acute and chronic ambulatory primary care. This allows them to diagnose and treat a variety of conditions locally while fostering meaningful relationships with patients. This broad training not only improves individual health outcomes it impacts the system while lowering healthcare costs. Family Physicians strengthen community ties, as they serve not only the first point of contact in the healthcare system but also for chronic care across the continuum of care.

Family Medicine physicians are adept at addressing social determinants of health, which play a crucial role in patient well-being. By understanding the complex interplay of factors such as socioeconomic status, geography, and cultural context, these physicians can tailor their care to meet the specific needs of their patients and advocate for resources that promote health equity.

One key driver in the workforce development that is needed to address the lack of family physicians and primary care, rests with how our medical education is funded and administered. This includes the fact that across the US the location of many of our medical schools and residency programs are in urban centers. Students who may initially want to practice in the rural communities in which they grew up move to urban areas for their education and wind-up practicing where they trained. Missouri has made significant progress in developing/supporting rural regional medical schools as well as offering programs to support primary care residency training in rural areas. Any long-term solutions must address these workforce problems.

In Missouri, the future of primary care depends on recognizing the vital role that Family Medicine and all primary care physicians play in our healthcare landscape. With a commitment to preventative care, chronic disease management, and patient education, these physicians are well-positioned to lead initiatives that improve overall health outcomes and lower healthcare costs.

Investing in Family Medicine training programs, increasing support for loan repayment for rural and underserved service, and advocating for policies that empower these physicians will be essential. Addressing payment reform and compensation, reducing administrative burden and making technology accessible are also critical steps in growing this workforce. By doing so, we can ensure that primary care in Missouri is not only sustainable but also truly reflective of the diverse needs of our population.

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Moving Towards Health: Exploring the Multifaceted Benefits of Lifestyle Medicine

by Margaret E. Gibson, MD, Angela Barnett, MD & Rachel Sachs, DO

Implementation of any of the ideals of lifestyle medicine can make a significant impact on your patient's overall health and well-being.



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Abstract

Lifestyle medicine focuses on evidence-based practices to help individuals adopt healthy behaviors. It is supported by six foundational pillars: a plant-predominant diet, regular exercise, restorative sleep, effective stress management, avoidance of risky substances, and positive social connections. These pillars offer both therapeutic and preventive benefits against chronic diseases. This article will focus on the how a plant-predominant diet, physical activity and sleep impact cardiovascular health, type 2 diabetes mellitus, weight management, and cancer. Lifestyle changes can significantly impact each patient's individual health and make a large financial impact on healthcare spending.

Introduction

Lifestyle medicine is an evidence-based approach that emphasizes the use of therapeutic lifestyle interventions to prevent, manage, and reverse chronic diseases (Table 1). Though often regarded as a new and emerging field, its origins can be traced back over 2,500 years to Hippocrates. The Greek physician employed lifestyle modifications to address health issues. Hippocrates stated, "Illnesses do not come upon us out of the blue. They are developed from small daily sins against Nature. When enough sins have accumulated, illnesses will suddenly appear."

There has been a notable shift in mortality causes, from infectious diseases in the 20th century to noncommunicable, chronic diseases at the turn of the 21st century.[1] This epidemiological transition prompted investigators to explore the underlying causes of these conditions.[2] Unhealthy lifestyles contribute to the pathophysiologic inflammatory response observed across a wide range of diseases. [3,4]

Current research estimates that up to 80% of chronic diseases are linked to poor lifestyle choices, making these modifiable behavioral risk factors the leading causes of mortality in the United States (US).[5] Furthermore, unhealthy behaviors significantly impact healthcare costs, with an estimated 90% of the nation's $4.5 trillion in annual healthcare expenditures being attributed to chronic disease and mental health conditions. Presently, 60% of American adults are living with at least one chronic disease, and over 40% have been diagnosed with two or more.[6]

Table 1. Chronic Diseases Impacted by Lifestyle Choices

1. Cardiovascular Disease
2. Hypertension
3. Hypercholesteromia
4. Obstructive Sleep Apnea
5. Respiratory Diseases (Asthma, Chronic Obstructive Pulmonary Disease)
6. Type 2 Diabetes Mellitus
7. Metabolic Syndrome
8. Obesity
9. Stroke
10. Dementia
11. Migraines
12. Mental Health Disorders
13. Gastrointestinal Disorders (Gastroesophageal Reflux, Cholelithiasis, Metabolic Dysfunction-Associated Steatotic Liver Disease, Irritable Bowel Syndrome)
14. Chronic Kidney Disease
15. Cancers (Breast, Colon, Kidney, Endometrial, and others)

The increasing prevalence of chronic diseases and the substantial economic burden highlight the need for a lifestyle medicine approach. The aim is to identify and address the root causes of preventable disease through lifestyle interventions. Lifestyle medicine has the potential to improve outcomes beyond conventional approaches that rely on pharmaceutical management. Addressing the underlying cause will reduce medication side effects and healthcare costs.

The American College of Lifestyle Medicine was founded in 2004. A national panel of primary care physicians defined lifestyle medicine and identified 15 core competencies.[7] Lifestyle medicine focuses on evidence-based practices to help individuals adopt healthy behaviors. It is supported by six foundational pillars: a plant-predominant diet, regular exercise, restorative sleep, effective stress management, avoidance of risky substances, and positive social connections. These pillars offer therapeutic and preventive benefits against chronic diseases.

Pillar One: "Food as Medicine"

Decades of research underscore the pivotal role of dietary patterns in the development, prevention, and management of chronic diseases. Changes in more modern lifestyles and dietary choices impact cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), obesity, and certain cancers. The China Study, a seminal work, demonstrated that countries characterized by high consumption of meat, dairy, fat, refined grains, and sugar, along with low intake of plant foods, exhibit significantly elevated disease rates.[8] Supporting this, further studies showed that diets with minimal animal products were associated with lower risks of T2DM, cancer, and overall mortality.[9] A study of 6,000 adult Americans revealed that high animal protein intake increased overall mortality by 75% and cancer death risk fourfold.[10] The risk was comparable to smoking. These associations were mitigated with plant-based proteins. Diets low in plant-based foods are associated with systemic inflammation, oxidative stress, tissue damage, and immune system overactivation.

The concept of "food as medicine" has gained traction, particularly regarding whole food plant-based diets. These diets are rich in fruits, vegetables, legumes, nuts, and seeds while minimizing animal products. Numerous health benefits have been described, and the next section will focus on those benefits regarding four chronic diseases that affect many Americans.

Cardiovascular Health

Plant-based diets improve cardiovascular health by lowering blood pressure and cholesterol. Dr. Dean Ornish's research demonstrated that a low-fat, plant-based diet could reverse coronary artery disease.[11] This was further supported by a 2019 meta-analysis which showed significant reductions in low density lipoprotein cholesterol and systolic blood pressure with plant-based diets.[12]

Diets rich in plant-based foods also lower myocardial infarction risk.[13] Mediterranean-style, plant-based diets specifically showed a 72% reduction in secondary prevention of cardiovascular events.[14] Recent studies, continue to confirm the cardiovascular benefits of plant-based diets, demonstrating lower blood pressure, reduced cholesterol, and decreased CVD risk.[15] These studies collectively highlight the robust cardiovascular advantages of adopting a plant-based eating pattern.

Type 2 Diabetes Mellitus

Research indicates that plant-based diets can improve glycemic control and reduce the risk of developing T2DM. A meta-analysis revealed that plant-based diets significantly improved hemoglobin A1c levels and insulin sensitivity.[16] Additionally, plant-based

diets reduce fasting blood glucose and improve beta-cell function in patients.[17] The high fiber content and low glycemic index of plant-based foods are believed to play a crucial role in these beneficial effects.

Weight Management

Plant-based diets are linked to more effective weight management, including lower body mass index (BMI). A meta-analysis found that individuals on plant-based diets had lower overall body weight and reduced fat mass compared to those on non-plant-based diets.[18] These effects are attributed to the lower energy density and high fiber content of plant foods, which promote satiety, enhance the gut microbiome, and decrease overall caloric intake.

Cancer Prevention

Studies show that diets rich in fruits, vegetables, legumes, and whole grains are linked to a lower risk of various cancers. For instance, a large cohort study revealed that higher consumption of plant-based foods was inversely associated with colorectal cancer risk.[19] This protective effect is attributed to the high levels of antioxidants, vitamins, and phytochemicals in plant foods, which may help reduce oxidative stress and inflammation, both of which are involved in cancer development.

Patient Implementation

One of the most effective methods for physicians to assess a patient's diet is by inquiring about their typical meals, snacks, and beverages. People tend to consume the same foods repeatedly, so this approach offers a quick and relatively accurate understanding of a patient's overall dietary pattern. The health care provider can then make informed recommendations. Additionally, it is important to ask about food allergies, restrictions, and preferences to enhance the success of dietary changes.

In advising patients on healthy eating, a targeted approach focusing on the most impactful dietary changes can yield significant benefits. Key recommendations to improve metabolic health include reducing the intake of processed foods, which are high in sugars, unhealthy fats, and artificial additives. Encouraging the consumption of colorful fruits and vegetables not only boosts nutrient intake but also supports a diverse microbiome and provides an abundant source of antioxidants. Incorporating healthy fats from avocados, nuts, and olive oil helps reduce inflammation.

Pillar Two: "Physical Activity as Medicine"

The United States Center for Disease Control and most international guidelines recommend that adults participate in 150 minutes of moderate aerobic physical activity per week and engage in muscle strengthening exercises as least two days per week. Unfortunately, only 17% of adults are meeting these recommendations.[20] The number of older adults, obese adults and those of lower social economic status meeting these recommendations is even lower. Clear benefits of increasing physical activity and decreasing sedentary behavior have been shown in decreasing morbidity of 25 chronic diseases and all-cause mortality.[21]

Cardiovascular Health

Physical activity has benefits in the prevention and improvement of CVD across all stages of life. Adults, aged 18-44, who participated in aerobic exercise and resistance training lowered systolic blood pressure (-4mm Hg), lowered diastolic blood pressure (-3mm Hg), lowered levels of triglycerides and increased high-density lipoprotein levels.[22] During middle ages, 45-64 years, levels of cardiometabolic diseases increase in prevalence. Data from the Framingham Heart Study and subsequent studies using wearable monitors have associated greater physical activity and lower 10-year risk for atherosclerotic cardiovascular disease.[23,24] Adults >65 have been shown to benefit from walking, which leads to lower levels of coronary artery disease and stroke.[25]

Type 2 Diabetes Mellitus

Prevention of T2DM and improved disease control have been shown in patients who are regularly physically active. Irrespective of age, sex, body mass index, or sedentary time greater amounts of physical activity of any type were associated with lower risk of T2DM.[26] Physical activity improves blood glucose control in patients with T2DM by decreasing insulin resistance, increasing production of glucose transporter type 4, lowering visceral adipose tissue, and increasing pancreatic function.[27]

Weight Management

Almost 75% of the adult population in the US are obese. The number of obese children and young adults continues to grow and will follow most individuals into adulthood. Physical activity leads to a higher metabolic rate and higher energy expenditure which leads to less weight gain over time. Physical activity is a way for patients to actively manage obesity.[28] In addition, increased physical activity in obese individuals independent of weight loss has shown to have physiological benefits.[29]

Cancer Prevention

Physical activity lowers the risk of cancer by reducing long-term inflammation in the gut, improving hormone balance and the immune system so the individual is better able to fight cancer. A meta-analysis including 35 breast cancer studies and 19 colon cancer studies showed higher levels of physical activity were associated with lower risk of all outcomes.[30] When examining cancer mortality, a minimum of 2.5 hours per week of moderate intensity exercise led to a 13% reduction in cancer mortality.[31]

Patient Implementation

Review of this literature provides undisputable evidence of the benefits of physical activity. There is also evidence of synergistic benefits of physical activity in the setting of dietary changes that were reviewed as the first pillar.[32] Change is difficult and it is important to focus on tangible ways to add these aspects of lifestyle medicine to your practice and your patients daily lives.

Encouraging your patients to engage in physical activity can seem daunting. Using the physical activity vital signs is an efficient way to screen a patient's level of physical activity.[33] If a patient is not meeting the guidelines this can trigger a discussion about goals around physical activity and health benefits for that patient. Recognizing and addressing barriers to physical activity is important. Consider self-monitoring with wearable technology, support from family, friends, co-workers and connecting with local community resources to help support patients.[34]

New studies have shown that exercise and decreasing sedentary behavior can be accomplished in multiple ways. The greatest benefit is seen in individuals moving from no level of physical activity to some amount of physical activity.[35] Brief intermittent bouts of exercise are an emerging option to increase physical activity and these "exercise snacks" have been shown to reduce all cause, cardiovascular, and cancer mortality.[36] There is no difference in health benefits based on the timing of physical activity, so any time is a good time to be more active.[37] Encouraging patients just to sit less has health benefits. Sitting less than five hours per day compared to 12 hours per day was associated with a decreased risk for all-cause and cardiovascular mortality in a study of over 150,000 adults with no major chronic diseases.[38]

Exercise prescriptions from physicians increase levels of physical activity. A prescription should be written out and include Frequency, Intensity, Time, Type, Volume, and Progression (FITT-VP).[39] When considering whether to recommend an exercise program, realize that while exercise does pose some risk to the patient, most patients are able to engage in some level of physical activity. Extra consideration can be given to those previously inactive patients at risk for heart, metabolic, and renal diseases. In addition, patients with symptomatic heart, diabetes, or renal disease should contact a health care provider before starting an exercise regimen. The American College of Sports Medicine, Exercise is Medicine program, and the Center for Disease Control physical activity guidelines provide great resources for physicians on their websites.

Pillar Three: "Sleep as Medicine"

It comes as no surprise with our ever-changing busy lives that 50-70 million US adults are found to have insufficient sleep (<7 hours of sleep/night).[40] More than 40% of adults complain of disrupted sleep at least one night a week with 23% of adults having trouble sleeping more than five nights a week.[59] As was presented with the previous two pillars, sleep has a significant effect on chronic disease burden. When discussing lifestyle modifications, it is important to understand that it is not only active choices patients make during the day, but that adequate sleep is necessary for optimal health.

Cardiovascular Health

Studies have shown that multiple unhealthy lifestyle factors can explain a large amount of cardiovascular and chronic disease causes.[41] One study showed a J-shaped relationship between CVD risk and mortality with the lowest risk at seven to eight hours

of sleep per night.[42] In another study, participants with "ideal" sleep (six to eight hours) had 52% lower CVD risk and 46% lower stroke risk than those who had poor sleep quality.[43]

Evidence has shown that sleep behaviors are also related to hypertensive events.[44–46] Improved sleep score from all variables was associated with 12% lower risk of hypertension.[47] The lifestyle factors that were associated with increased risk of hypertension included short or long sleep duration, snoring, excessive daytime sleepiness in addition to poor diet and physical inactivity. Compared to controls, people with poor sleep and poor lifestyle factors had over two times the risk of developing hypertension. Many guidelines and consensus statements focus on diet, exercise, and avoidance of alcohol. However, these studies show that the right amount of sleep can be just as important and should be included in future guidelines to reduce CVD burden.

Type 2 Diabetes Mellitus

Many studies have shown a correlation between poor sleep quality and metabolic syndrome.[48] One meta-analysis showed there was an association between T2DM and all varieties of poor sleep quality (short sleep, long sleep, insomnia, obstructive sleep apnea (OSA). On average patients with poor sleep quality have a 30% increased risk of developing diabetes or a relative risk of 1.28 compared to those with good sleep quality.[43] The risk was further increased for those greater than 65 years of age. When compared with counterparts without a diagnosis of OSA, those with OSA had three times the risk of developing T2DM.[49] In pregnant women, the risk of gestational diabetes is almost two times greater in women with poor sleep habits.[50]

Weight Management

Poor sleep is also associated with obesity. One meta-analysis noted for every additional hour of sleep; BMI was reduced by 0.35 points.[51] Participants of an additional study, who slept between six to eight hours of sleep a day had the lowest BMI.[42] There are many thoughts for why this occurs. Factory workers with sleep disturbances had more irregular eating habits including snacking between meals, less consumption of vegetables, and less variety of foods.[43] In addition, the National Sleep Foundation found that increase in sedentary time was strongly associated with poorer sleep quality and length of sleep.[43] Compared to people who slept eight to ten hours, participants in one study who had less than four hours of sleep were found to ingest 180-560 extra kcal per day.[52]

Cancer Prevention

There are numerous reasons that cancer patients and survivors do not have adequate sleep patterns including nightmares, medication side effects, insomnia, and sleep disruption during hospital stays. Studies looking at cancer survivors have noted almost 25% increased risk for those patients who suffer from insomnia.[53] A study looking at 10,000 cancer survivors noted that participants who had the worst quality of sleep were female, current smokers, and less likely to be physically active.[54] At 10-year follow-up these participants with poor quality of sleep were found to have 33% increased incidental cancer findings. Similarly, the Women's Health Initiative surveyed 140,000 postmenopausal women and noted significantly higher risk of thyroid cancer in women with poor sleep scores, especially in non-obese women.[55] In men, short sleep duration (less than seven hours) was associated with increased risk of prostate cancer.[52] A few studies have postulated about the pathophysiology of why poor sleep can increase cancer risk. One study noted patients with poor sleep quality had decreased production of melatonin.[56] This is concerning as melatonin has been studied and there is a growing body of evidence that supports melatonin as an "anti-cancer" agent. More specific pathways have been found such as increased TSH level or chronically elevated estrogen levels causing thyroid and breast cancer respectively.[55,57]

Patient Implementation

When evaluating and counseling patients about lifestyle medicine, it is important to consider patient's sleep routines. Most adults with trouble sleeping fall into two diagnoses: insomnia or OSA. Evaluation of sleep dysfunction during a clinical visit can be accomplished with the Epworth Sleepiness Scale. In addition, patients with risk factors for OSA should be screened with polysomnography. The most effective non-pharmacological treatment for chronic insomnia is cognitive-behavioral therapy for insomnia (CBT-i). A 2015 meta-analysis of 20 randomized controlled studies of CBT-i for patients with chronic insomnia found average reductions of time to sleep between

eight to ten minutes and 10% improvement of sleep efficiency associated with doing CBT.[58] Furthermore, weight loss through behavioral or surgical interventions and instructing patients on good sleep hygiene are effective interventions.[59] Although there is not a consensus on pharmacologic treatment options for insomnia, melatonin has been found to be safe and found to be effective in 56% of patients in reducing sleep dysfunction.[43]

Conclusion

Implementation of any of the ideals described in the first three pillars of lifestyle medicine can make a significant impact on your patient's overall health and well-being. Additional benefits can be obtained when examining the three other pillars: effective stress management, avoidance of risky substances, and positive social connections. Unfortunately, it is beyond the scope of this article to review those pillars. It is often best to start with one pillar when working with a particular patient. Talk with your patient and determine which area they are the most motivated to start making a change. Once they have started to see success in one area then consider using the guidance from a second pillar to further improve their health. Remember that the changes can start small, and the progress will not always be linear, but over time the impact will be great.

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Pregnant for Nine Months, Postpartum for Life: Long-term Implications of Pregnancy Related Conditions

by Helen Suzanne Hill, DO & Kelly Jo Sandri, MD

Although pregnancy is a transient condition, it results in a permanent transformation as the patient is then postpartum for life, and complications experienced in the pregnancy likely impact their long-term health and well-being.



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Abstract

Maternal mortality in the state of Missouri remains among the highest in the nation. Recognizing that the burden of making corrective actions does not rest solely with obstetric providers, it is time to consider how pregnancy affects our patients before, during, and after childbirth. Reviewing pregnancy history and pregnancy intention can be a chance to address modifiable risk factors to improve patient outcomes when providing medical care.

Introduction

Several medical conditions previously considered confined to pregnancy such as gestational hypertension, diabetes, preterm delivery, or fetal growth restriction actually require short- and long --term follow-up. In the United States (US) it is now estimated that nearly one in five pregnancies are affected by one or more adverse pregnancy outcomes.[1,2] Furthermore, these conditions are not spread equally across all pregnancies. Racial and ethnic minority groups are disproportionately affected due to social determinants of health (SDOH).[3] Addressing these conditions are multifactorial and require a multidisciplinary approach (Figure 1). Understanding the long-term effects these conditions have on our patients can help bridge the gaps in care from a medical standpoint.

Surveys of multiple specialties revealed that despite increased awareness of the ramifications of pregnancy-related conditions, clinicians neither performed routine screening, nor did they know what to do with the information they collected.[4,5] A recent study found that among adolescent and young adults seen in a rheumatology clinic, they overwhelmingly wanted sexual and reproductive health counseling from their rheumatologist (84%) rather than primary care (66%) or OB/GYN or adolescent medicine (58%).[6]

Major societies in both the US and Europe are now recommending using information from pregnancy histories to guide future care of patients.[7,8] To this extent, a patient's pregnancy history and intention to become pregnant is a responsibility all physicians bear. Understanding a patient's history of pregnancy-related conditions can help guide future screenings and management

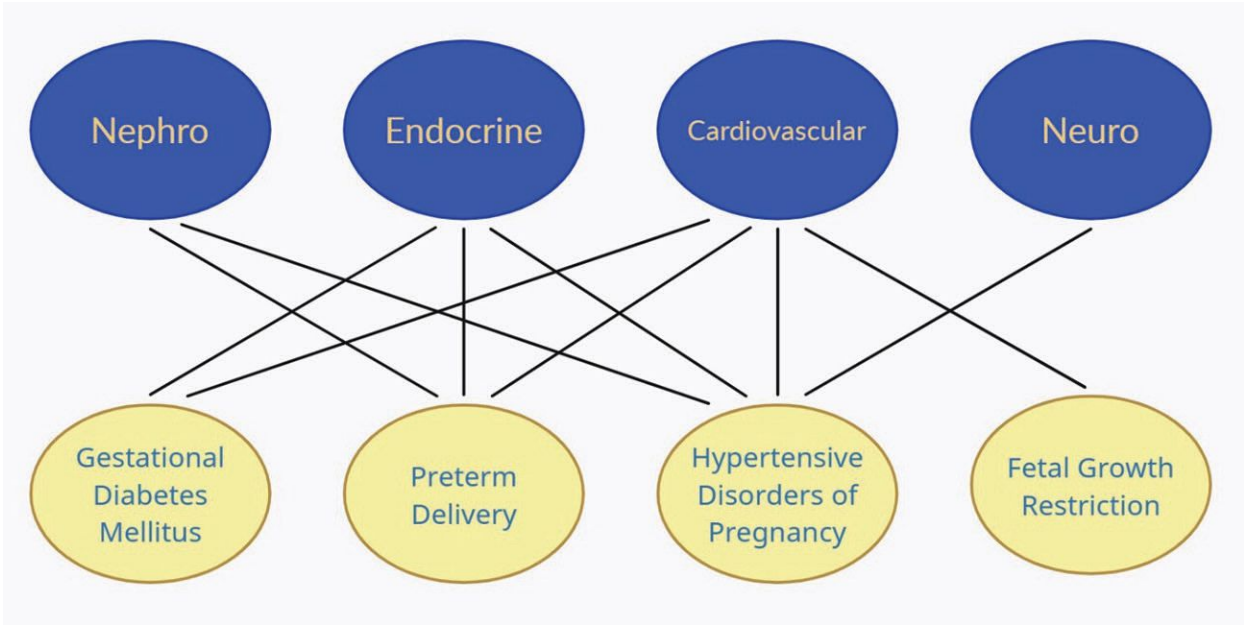


Figure 1. Visual representation of how pregnancy-related conditions can affect multiple systems long-term.

of chronic conditions. Equipping Missouri physicians with a better understanding of medical conditions during and after pregnancy from a systems-based perspective will help to address health disparities and improve health outcomes for the women of Missouri.

Cardiovascular

The diagnosis rate of hypertension (HTN) is on the rise due to the 2017 American College of Cardiology/American Heart Association guidelines redefining HTN starting at 130-139 mm Hg or 80-89 mm Hg.[9] With the age of onset of cardiovascular disease (CVD) gradually lowering over time, more patients will enter pregnancy carrying a diagnosis of chronic HTN. In addition, patients with hypertensive disorders of pregnancy may have a period of blood pressure normalization after pregnancy but still benefit from early interventions due to an underlying higher risk of significant cardiovascular complications.

Hypertensive disorders of pregnancy (HDP) which include gestational hypertension, preeclampsia (preE), eclampsia and chronic HTN, affect between 13-15% of all pregnancies in the US.[10] HDP and the complications resulting from it were the leading cause of mortality within the first year postpartum for Missouri women.[11] However, the risk for adverse events persists beyond the initial postpartum period and several studies have demonstrated the highest risk of cardiovascular complications are in the first 10 years with the average age being 38 years old.[12,13] Patients diagnosed with preE are at double the risk of stroke (both immediate and persisting), two to 12-fold times more likely to develop chronic HTN in the next 10 years, and have double the cardiovascular mortality risk.[12,14–16]

Aside from hypertensive disorders which have more obvious cardiovascular implications, there are several other conditions during pregnancy that are important to be mindful of from a cardiovascular standpoint. Gestational diabetes (gDM), fetal growth restriction (FGR), and preterm delivery (PTD) all reveal an increased risk for CVD.

A history of gDM increases the risk of CVD in the first ten years after pregnancy, a risk independent from patients who develop type 2 diabetes mellitus (T2DM). In that initial decade, there is a 2.3-fold increase in cardiovascular events with a higher 30-year risk of atherosclerotic CVD.[1,17] The risk continues beyond that timeframe with a history of gDM imparting a less favorable cardiovascular metabolic panel during menopause than counterparts without gDM and increases a patient's risk for CVD two-fold.[15,17] In a large, prospective cohort in the United Kingdom, patients who had "early menarche, early menopause,

[younger] age at first birth, and a history of miscarriage, stillbirth, or hysterectomy were each associated with a higher risk of CVD later in life." [18]

Patients who had pregnancies with FGR can have direct cardiac remodeling changes persisting after pregnancy leading to early development of CVD.[13] PTD incurred a two-fold risk for CVD, while recurrent pregnancy loss increased risk of ischemic heart disease.[8]

While not entirely understood, these conditions alter a patient's cardiovascular risk factors especially for patients less than 50 years old. Whether these pregnancy conditions cause long-term cardiovascular damage or unmask damage at an earlier age is not yet determined. But the risk persists despite controlling for other variables such as obesity, smoking, and family history. No clear guidelines exist but considering the evidence for increasing diagnosis at a younger age, screening and tracking for these conditions can help identify patients for whom aggressive modification of risk factors could be important.

Endocrine

Traditionally, patients are only under the care of their obstetric provider for a limited time postpartum which means metabolic conditions that are diagnosed or develop during pregnancy may be lost to follow up. An awareness of the recommended surveillance for endocrine conditions after pregnancy is important.

Diabetes is recognized in 7% of US pregnancies with 86% of those representing gestational diabetes (gDM).[19] Hyperglycemia is considered especially harmful during early fetal development and the American College of Obstetricians and Gynecologists (ACOG) has recognized that more patients are entering pregnancy with risk factors for T2DM. Screening patients for underlying T2DM or early gDM upon entry to prenatal care is now recommended.[19,20]

Of patients who are diagnosed with gDM, up to one-third will be diagnosed with impaired glucose tolerance during the postpartum period, with between 15-70% progressing to T2DM later in life.[19] After being released from obstetric care, the onus for knowing timing of screening often falls to the patient. In addition, they may lose access to healthcare coverage until their next pregnancy. For patients with a history of gDM, ACOG recommends screening for T2DM, insulin sensitivity, and insulin resistance between four and 12 weeks postpartum.[19,21] Recently ACOG released a practice update to consider screening in the immediate postpartum period prior to hospital discharge since less than half of patients undergo the recommended screening in the traditional four to 12 week timeframe.[21] Both ACOG and the American Diabetes Association recommend screening every one to three years for patients with history of gDM. Given the lifelong increased risk for the development of T2DM, knowing a patient's history allows for early screening and intervention.

Screening for a history of gDM is particularly important for patients who lack traditional or more obvious risk factors for T2DM like obesity or family history as these patients are much more likely to go without appropriate screening. Additionally, patients who would not typically be considered at increased risk for T2DM but do warrant increased surveillance based on pregnancy history include those with a history of PTD (both spontaneous or medically indicated). In one study, a history of PTD had a hazard ratio (HR) of T2DM 1.35 (95%, CI, 1.33-1.38) compared to delivery at term with even higher risk conferred at earlier gestational age at delivery.[22]

There is overwhelming evidence that knowledge of a patient's HDP would be important for our cardiovascular colleagues, but the process does not just have effects on the cardiovascular system. Patients with HDP had a hazard ratio (HR) of 1.72 for developing T2DM, even 30-46 years after delivery.[22]

Optimizing the treatment of thyroid disorders prior to conception is critical as uncontrolled thyroid levels can lead to miscarriage, placental abruption, hypertensive disorders, growth restriction, neonatal goiter/ hyperthyroidism, or congenital malformations.[23–25] For patients with hypothyroidism, levothyroxine supplementation will often require adjustments during each trimester beginning with an increased need at conception. Patients often return to prepregnancy doses shortly after delivery.[24] Counseling regarding pregnancy intention when treating hyperthyroidism is more often recognized given the association between treatment medications and birth defects. Graves' disease can relapse or manifest for the first time during the postpartum period. Postpartum thyroiditis can affect 6-7% of patients with almost half progressing to permanent hypothyroidism. In patients that recover, the risk remains elevated for developing hypothyroidism and they should have annual screening.[23,24]

Obesity is growing to be one of the most common risk factors affecting pregnancy. These patients carry elevated risks for developing adverse pregnancy outcomes most notably, HDP and gDM which then confer long term consequences.[26] Identifying a desire for pregnancy or contraceptive plan is an important component when counseling on weight loss.

Weight loss with the use of anti-obesity medications can lead to rapid return of fertility or alterations in contraception efficacy.[26,27] It remains unclear how much weight loss prior to pregnancy is beneficial and whether that benefit continues throughout pregnancy. With the pervasive prescribing of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), understanding the potential effects in pregnancy is an increasingly important area of research.[28] One review demonstrated increased weight gain during pregnancy similar to weight regain for patients who did not use medications and no increase of congenital anomalies or fetal death with use of GLP-1 RA in early pregnancy.[28] A large comorbidity-controlled study showed improvement in adverse obstetric outcomes when a GLP-1 RA was used within two years of conception, with the most benefit in the groups with longer duration of use.[27]

For our colleagues who are prescribing these medications, it is imperative to ask about pregnancy intention. The FDA recommends discontinuation of GLP-1 RAs or GLP-1 RA/Glucose-dependent insulinotropic peptide (GIP) receptor agonist based on half-life. For patients trying to conceive: liraglutide should be stopped 10-14 days, while semaglutide and tirzepatide should be stopped two months prior.[26,28–30] Especially important in tirzepatide counseling is an awareness of the decreased effectiveness of oral contraception.[26] When patients conceive while on anti-obesity medications, enrolling them in pregnancy exposure registries will help increase data in a population that is traditionally excluded from drug trials.

Renal

Renal conditions can either predate pregnancy or be discovered during routine laboratory work conducted during pregnancy. As more patients delay their first pregnancy, a larger proportion of patients have the potential to have underlying chronic conditions with renal complications that are either unrecognized or undermanaged. Renal conditions occurring during the reproductive years often have a delay in recognition, effective treatment, and referrals.[31] Patients with underlying chronic kidney disease (CKD) can have advancement of their stage during pregnancy and shorten the time to renal replacement.[31] Adequate counseling for patients with known CKD is essential for optimizing both pregnancy outcomes and long term care after pregnancy. However, a recent qualitative study demonstrated that many nephrologists felt unequipped to adequately counsel on contraception or risk of CKD during pregnancy. Patients were unaware of the potential interplay between CKD and pregnancy unless they had already experienced a pregnancy related complication. Patients were interested in discussing reproductive plans with their nephrologist but were unsure how to approach it. The authors identified that tools to accurately assess risk for patients are needed for nephrologists to have patient-centered discussions in addition to electronic medical record improvements to adequately screen for a patients' reproductive intentions.[32]

Clearly, hypertensive disorders both predating and during pregnancy have long term renal consequences. It is still unclear whether the renal injury is from the underlying pathology that leads to the HDP or the HTN itself that results in long term increased risk of renal disease.[33] The reduced glomerular filtration rate (GFR) that can be seen with preE can persist years after delivery or progress to end stage renal disease (ESRD). The proteinuria can persist even longer. If it persists beyond the first 12 weeks postpartum, patients should be seen by nephrology for further evaluation and all who have proteinuria during pregnancy should be screened annually for development of CKD or CVD.[34]

Pregnancies with low-birth-weight or PTD are also at increased risk for ESRD.[35] A recent meta-analysis determined that PTD increased risk of CKD by 82% and ESRD by 122%.[12] The interplay between PTD and CKD/ESRD is not fully understood. More studies need to evaluate the relationship while controlling for the potential variables such as obesity, T2DM, and HTN which may separately increase risk for CKD/ESRD.

Gastro-Intestinal

Several acute and chronic conditions can be determined by learning a patient's pregnancy history. Most conditions affecting the liver during pregnancy

Table 1. Summary of pregnancy-related conditions, their long-term impacts and care/screening suggestions by authors.

Pregnancy-related Condition	Long-Term Associated Risk	Management/Screening Consideration
Hypertensive Disorders of Pregnancy (preE, gestational hypertension, eclampsia)	• 2-12x risk of chronic HTN • 2x risk of stroke • 2x risk of CV mortality • Increased risk of T2DM • Increased risk of CKD	• Risk factor modifications • Annual screen for HTN • T2DM screen q1-3yrs • Annual screen for CKD/CVD if proteinuria present in pregnancy • If proteinuria persists postpartum, consult Nephrology
Gestational Diabetes	• 2x risk for cardiovascular disease/events • 15-70% risk of T2DM postpartum	• Risk factor modifications • T2DM screen q1-3yrs
Preterm Delivery	• 2x risk for CVD • Increased risk for T2DM • Increased risk of CKD/ESRD	• Risk factor modifications • T2DM screen q1-3yrs • Annual screen for HTN • Consider screening for CKD q1-3yrs, especially if other risk factors present
Fetal Growth Restriction	• Increased risk for CVD	• Annual screen for HTN • Risk factor modifications
Postpartum Thyroiditis	• >50% risk of permanent hypothyroidism	• Annual screen for hypothyroidism

are limited to the pregnancy but some may benefit from follow up.

Patients are screened for chronic Hepatitis B and Hepatitis C to reduce the maternal-child transmission rates. Patients can experience a hepatitis flair both during and after pregnancy and monitoring for several months can identify patients who need acute intervention.[36,37] While data does not currently support treatment during pregnancy, patients with Hepatitis C should be referred for treatment postpartum and followed through sustained viral resistance.

In preE, one of the defining target organ abnormalities can be within the liver with severe complications consisting of hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome or subcapsular hematomas. The liver damage is typically self-limiting and liver enzymes typically normalize following delivery but may take weeks to months.[38] Similarly, elevated liver enzymes with intrahepatic cholestasis of pregnancy typically are self-limiting to the pregnancy time period.[37]

Occasionally, elevated liver enzymes are discovered during pregnancy and not thought to be a result of preE but rather a component of metabolic dysfunction associated steatotic liver disease (MASLD). These patients need follow-up postpartum for disease management and discussion of future pregnancies. In a similar way that patients with mild CKD may not get adequate counseling about risk of progression during pregnancy, patients with known MASLD may not understand the increased risk for PTD (AOR 2.05), FGR (AOR 1.32), HDP (AOR 3.03), and overall maternal mortality (AOR 6.40) the disease has compared to matched controls.[39] This again highlights the importance of inquiring about reproductive intention by all clinicians.

Neurology

Pregnancy and the postpartum period are times of increased risk of stroke. While the physiology of pregnancy increases this risk of stroke, concurrent hypertensive disorders are the leading cause.[14] The overlapping cardiovascular and neurovascular effects of chronic HTN and preE are highlighted by the increased risk of stroke during and following a pregnancy. This risk increases when there is recurrence

of preE in a subsequent pregnancy or when preE is diagnosed early.[14,40] Patients who had a history of preE had 1.55 fold higher odds of stroke than matched patients with similar cardiovascular risk factors.[14] Patients with history of HDP should be counseled on the significantly increased lifetime risk of stroke.

Early treatment of HTN is also important for reducing the risk of seizures and lasting neurologic complications. For the rare number of patients who do experience eclampsia, establishing if there are any lasting sequelae is important. Seizures from eclampsia do not require long term antiepileptics or neurology follow up unless there is a delay in treatment and epilepsy, ischemic infarction, hemorrhage, cognitive disorder, visual abnormalities, or white brain matter lesions takes place.[41,42] In one study, 22.5% of hypertensive patients experiencing eclampsia had neuroimaging findings consistent with posterior reversible encephalopathy syndrome (PRES), a neurologic condition with headache, alterations in consciousness, visual disturbances and seizures.[42] When identified and treated quickly, MRI detectable subcortical edema can be decreased and the sequela prevented.

Conclusion

Having an increased awareness of how pregnancy can impact overall health is not a reason to fear or discourage pregnancy in our patients. Approaching all patients with the attitude that pregnancy is inherently and universally dangerous is a harmful mentality. ACOG recommends discussions regarding pregnancy and contraception planning be tailored to the individual's risk given the long history of inequity and inequality and the role SDOH have in contributing to pregnancy related morbidity in this country.[43,44] Pregnancy does not hold a universal risk or effect on long-term health for all patients (Table 1). Instead, looking at a patient's pregnancy history can be seen as looking through a window into conditions that would otherwise be hidden until potentially devastating complications occur.[2] While examining a patient's pregnancy history can highlight conditions that may occur earlier than anticipated, it remains important to also consider individual and systemic factors potentially contributing to underlying risks for developing chronic conditions.[3]

We recommend implementing universal screening for pregnancy intention as one method of opening the conversation. There are a multitude of tools available that clinics can adopt.[45] With the primary healthcare shortage, deferring counseling about pregnancy intention or contraception for patients with known comorbidities can be potentially dangerous.

Although pregnancy is a transient condition, it results in a permanent transformation as the patient is then postpartum for life, and complications experienced in the pregnancy likely impact their long-term health and well-being. No longer can the care that takes place during and around pregnancy be relegated to a subset of specialties in medicine. Reviewing pregnancy history and pregnancy potential are vital to all physicians. Informing patients that some conditions they thought were confined to pregnancy have long-term associations can help reinforce the importance of collaborative care, timely screening, and appropriate risk factor modification. Our goal with this article is to increase awareness across different disciplines of medicine of the role they may be able to play to positively impact long term health outcomes.

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Intravenous Fluids in Hospitalized Patients: A Review of Best Practices

by J. Lane Wilson, MD, Matthew Decker, MD, JD & Chelsie Cain, DO

The use of normal saline itself may be an unparalleled example of clinical practice inertia.



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Abstract

Judicious use of intravenous fluids in hospitalized patients can improve outcomes and prevent adverse events. For many clinical scenarios, balanced crystalloids have some advantages over normal saline, though the differences in outcomes are small. Excessive administration of normal saline can cause metabolic acidosis and kidney injury. For conditions with sodium and/or chloride deficits, normal saline is preferred. Hypertonic saline is used to rapidly correct severe acute hyponatremia, and hypotonic fluids are indicated for replacement of free water deficits. Intravenous albumin is indicated in only specific scenarios in the setting of cirrhosis and does not seem to have significant advantages for routine volume resuscitation over crystalloids. When intravenous fluids are administered, patient response should be closely monitored to guide subsequent therapy.

Introduction

Despite the nearly ubiquitous use of intravenous fluids in hospitalized patients – hundreds of millions of liters of normal saline (NS) alone are infused annually in the United States (US) – a relative paucity of evidence exists to guide physicians in their administration.

The choice and patterns of intravenous fluid use is largely driven by clinician preference, regional and institutional practice patterns, cost, and availability.[1] The use of NS may be an unparalleled example of clinical practice inertia. Experiments with saline solutions first began during the 1831 cholera epidemic, and Hartog Hamburger first described 0.9% sodium chloride as "physiologic" based upon an *in vitro* study in 1883, a claim not even consistent with his results. The usage of intravenous and rectal saline solutions was widespread by the early 20th century. However, in 1911 published dissenting opinions began to appear regarding the use of NS, which is neither "normal" nor "physiologic" as Hamberger described.[2] While not clear historically how NS caught on, it remains the most widely used intravenous fluid to this today.

Normal saline has been associated with a variety of adverse outcomes in specific clinical scenarios, largely due to its supraphysiologic chloride load. In other scenarios, it is the fluid of choice. Use of other intravenous fluids similarly have limitations and potential risks. Understanding basic physiologic principles of total

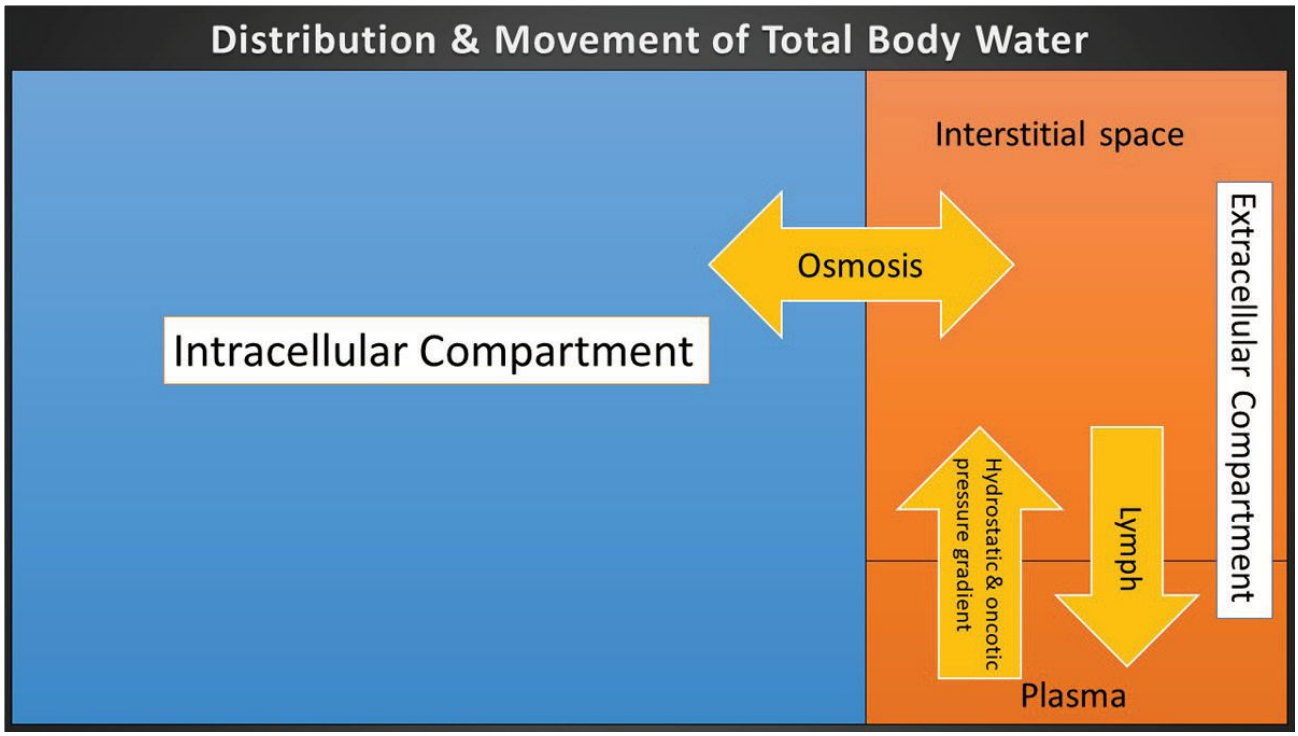


Figure 1. Distribution and movement of total body water. The compartments are represented by percentage of total body water: 67% in the intracellular compartment (blue) and 33% in the extracellular compartment (orange). The extracellular compartment is 75% interstitial fluid and 25% plasma. The arrows indicate the direction and mechanism of water movement from each space to the others.

body water distribution and movement, disease states, properties of different intravenous fluids, and recent evidence can guide physicians from clinical practice inertia to a more reasoned, thoughtful, and evidence-based application of intravenous fluid administration that can improve desired outcomes and limit adverse effects.

Physiologic Water Distribution

The percentage of total body water varies by age, sex, and body composition. Newborns are approximately 75-80% water by mass, a figure that decreases to about 65% by one year of age. Adult males and females are about 60% and 55% water by mass, respectively. Muscle mass has a much higher percentage of water compared to adipose tissue, and therefore younger and athletic individuals have a higher total body water percentage than older or obese individuals. In the elderly, total body water may be as little as 45-50% body mass. This declining percentage of total body water reflects muscle loss and an increase in adipose tissue that accompanies normal aging.[3]

Within the body, water occupies the intracellular and extracellular fluid compartments. About two-thirds of total body water is located in the intracellular compartment. Extracellular fluid is a heterogeneous group of fluids that can be thought of as being subdivided 75% into the interstitial space and 25% into plasma. Plasma, therefore, makes up about 8.25% of total body water (Figure 1).[4] Plasma is the only compartment in which the water is truly contained within one connected space and is the target of intravenous fluid therapy.

Physiologic Water Movement

Water may move out of plasma into the interstitial space via differences in hydrostatic and colloid osmotic pressure across the glycocalyx of the capillary endothelium. Conversely, most water moving from the interstitial space to the plasma does so via the lymphatic return of fluid to circulation. Osmotic forces dictate the movement of water between the

Table 1. Types of IV Fluids		Sodium (mmol/liter)	Chloride (mmol/liter)	Potassium (mmol/liter)	Calcium (mmol/liter)	Magnesium (mmol/liter)	Buffer (mmol/liter)	Gluconate (mmol/liter)	Glucose (grams)	Osmolarity (mOsm/liter)
	Human Plasma	135-145	94-111	4.5-5.0	2.2-2.6	0.8-1.0	Bicarbonate: 23-27 Lactate: 1-2			291
Crystalloids										
	Normal Saline (0.9% saline)	154	154							308
	Half-normal saline (0.45% saline)	77	77							154
	Lactated Ringer's	130	109	4	1.5		Lactate: 28			280
	PlasmaLyte	140	98	5		3	Acetate: 27	23		294
	3% Hypertonic Saline	513	513							1026
	Dextrose 5% in Water								50	252
Colloids										
	Albumin 5%	145								300
	Albumin 25%	145								1500

interstitial and intracellular spaces (Figure 1). During acute illnesses, capillary leak may contribute to increased intravascular volume redistribution.[5]

Fluid types

Crystalloids

Crystalloids are solutions containing electrolytes and/or dextrose which can move readily across capillary membranes. In contrast to colloids, they are inexpensive and easy to manufacture. Based upon the concentration of sodium plus potassium in the fluid, crystalloids may be classified by tonicity. Those that approach physiologic sodium levels, such as NS or lactated Ringer's solution (LR), are isotonic. Other concentrations of saline may create hypotonic or hypertonic fluids which have significantly different physiologic effects and thus indications. Dextrose may be added to crystalloid solutions without significantly affecting tonicity, as it is rapidly metabolized once entering circulation. "Balanced" crystalloids refer to LR and similar derivatives as a way to distinguish them from simple saline mixtures like NS, though none are truly physiologic.

Colloids

Colloids are solutions of protein or starches which remain intravascular for longer periods of time and are typically mixed with a saline solution. Albumin is the major colloid discussed in this review. Semisynthetic colloids are less common, have not demonstrated significant improvement in outcomes, have significant safety concerns, have greater cost, and are therefore not covered in detail.[6] Commonly used fluids and their contents and are detailed in Table 1.

Physiologic Distribution of Intravenous Fluids

Isotonic crystalloids remain within the extracellular compartment as no gradient exists with the intracellular compartment. While infusing, isotonic crystalloids may result in volume expansion of the plasma at rates of 50-60% of the infused volume. However, within 30 minutes of completion of the infusion, only 15-20% of the infused volume remains within the plasma with the remainder having entered the interstitial space.[7-8]

NS and LR are the most commonly used isotonic crystalloids. When given in large volumes, the high chloride content of NS can induce a non-anion gap metabolic acidosis (NAGMA) by shifting bicarbonate ions intracellularly and subsequently lead to renal vasoconstriction and acute kidney injury requiring renal-replacement therapy.[9,10] Balanced crystalloids, in contrast, contain a buffering anion (lactate or acetate) and can worsen a metabolic alkalosis if administered in the setting of chloride losses, such as with vomiting.[11]

Hypotonic fluids, including dextrose in water,

almost entirely redistribute quickly to the interstitial space and intracellular compartment. The more hypotonic the solution, the more it will redistribute into the intracellular compartment via osmosis. Hypertonic fluids, in contrast, create an osmotic gradient that shifts water from the intracellular compartment into the extracellular compartment, and therefore is used for indications such as cerebral edema.[7-8]

Colloids theoretically persist intravascularly much longer than crystalloids – some studies demonstrate several hours' worth – but they may have more volume redistribution in ill patients due to capillary leak. Trials have failed to demonstrate superiority over crystalloids for volume resuscitation.[6-8]

Maintenance Intravenous Fluids

Maintenance fluids serve to maintain extracellular fluid volume while maintaining a normal electrolyte balance. They are of limited to no utility in patients who are able to meet these needs through oral intake. Typically, isotonic and hypotonic crystalloids with or without the addition of potassium chloride and/or dextrose have been used as maintenance fluids in acutely ill adults and children.[1,12] Hypotonic maintenance fluids should be avoided because they are associated with hospital-acquired hyponatremia in both adult and pediatric populations.[13,14]

While concerns related to the adverse effects of large volumes of NS compared to balanced electrolyte solutions apply to maintenance fluids just as they do with resuscitation fluids, adverse effects are most pronounced at large volumes of administration. It is unclear if those concerns remain for patients placed on maintenance rates of NS for less than 72 hours. The addition of dextrose to maintenance fluids is neither helpful nor harmful outside of several specific clinical scenarios, such as hyperglycemia and hypokalemia.[13]

To date no formal society-sponsored guidelines exist in regard to maintenance fluids in the United States. For most adult patients, a maintenance rate of isotonic fluids of 100-120 mL/hour is appropriate. For children, the Holliday-Segar formula is used to calculate the rate: 100 mL/kg per 24 hours for the first 10 kg of body weight, plus 50 mL/kg per 24 hours for a weight of 10-20 kg, plus 20 mL/kg per 24 hours for weights above 20 kg. Doses should be adjusted down for oliguric conditions such as end-stage renal disease, acute glomerulonephritis, and acute tubular necrosis, or conditions prone to fluid overload such as heart failure or cirrhosis. Conversely, higher rates of administration may be required in disease states that result in an inability to appropriately concentrate urine such as diabetes insipidus, acute tubular necrosis, chronic kidney disease, hypokalemia, or hypercalcemia.[13]

Selection of Intravenous Fluids in Common Clinical Conditions

Sepsis

Sepsis-induced hypoperfusion in adults should be treated with at least 30 mL/kg of IV isotonic crystalloid within 3 hours of presentation with a small preference for balanced fluids.[15] In pediatric patients, the use of balanced crystalloids may reduce hyperchloremia and need for renal replacement therapy but increases length of hospitalization when compared to NS.[16] LR does not need to be avoided in the setting of lactic acidosis in sepsis, as the lactate in the fluid is sodium-lactate and will improve, rather than worsen, acidosis. A recent randomized-controlled trial comparing a restrictive versus liberal fluid management after an initial 1-3 liters in patients with sepsis-induced hypotension demonstrated no difference in 90-day mortality or adverse events. The restrictive group received about 2 fewer liters of fluid during hospitalization and was about twice as likely to receive vasopressor support.[17] Therefore, after initial resuscitation, ongoing fluid management can be dictated by patient response, including hemodynamic and laboratory markers, to maintain volume and avoid fluid overload.

The use of albumin has been proposed as a resuscitation fluid in sepsis based upon its oncotic properties, however, no benefit in morbidity or mortality has been demonstrated.[6,15] The use of albumin is also not recommended for volume replacement or to increase serum albumin levels in critically ill patients, including those with sepsis, thermal injuries, or acute respiratory distress syndrome (ARDS).[18] Capillary leak in these conditions limits the effects of the oncotic pressure colloids provide. The use of albumin with diuretics to

remove extravascular fluid is also not recommended.[18]

Renal Failure

Acute kidney injury is associated with increased risk of mortality, cardiovascular events, and progression to chronic kidney disease. Appropriate fluid management can prevent and sometimes treat this condition.[19] Crystalloids are the preferred resuscitative fluid in the setting of acute kidney injury due to intravascular hypovolemia.[20] Oliguria is not an indication alone for administration of intravenous fluid. Balanced crystalloids, despite their potassium content, are safe in the setting of chronic kidney disease and hyperkalemia and preferred over NS for the prevention of acute kidney injury.[19-21] In sepsis, aggressive fluid resuscitation of at least 30 mL/kg does not appear to worsen outcomes even in end-stage renal disease.[22]

Heart Failure

Fluid management should be restrictive and closely monitored in patients with heart failure. Renal function, electrolytes, daily weights, and intake and output should be monitored closely to inform volume status and fluid needs. A maintenance rate of 60 mL/hour with close monitoring is appropriate.[13,23] The addition of potassium chloride to maintenance fluid should be considered for patients on diuretics.

Intravenous fluids should not be given in the setting of acute heart failure, yet more than 10% of adults hospitalized with acute heart failure receive both diuretics and intravenous fluid. This is associated with increased risk of critical care admission, increased rates of intubation, increased need for renal replacement therapy, and increased risk of in-hospital death.[24]

Cirrhosis

Multiple scenarios in the care of a patient with cirrhosis recommend the use of IV albumin. First, following large-volume paracentesis (greater than 5 liters), 6-8 grams of albumin per liter of ascites removed should be administered to avoid post-paracentesis circulatory dysfunction. Second, IV albumin is the volume expander of choice in patients hospitalized with cirrhosis and ascites who present with acute kidney injury. It should be given at a dose of 1 g/kg daily for 2 consecutive days (with a maximum dose of 100 g/day). A lack of response to this form of volume expansion is part of the diagnostic criteria for hepatorenal syndrome-acute kidney injury. Third, patients diagnosed with spontaneous bacterial peritonitis should receive 1.5 g/kg on day 1 of treatment and 1 g/kg on day 3.[18] For other forms of volume resuscitation in cirrhosis patients, albumin has not been demonstrated to be superior to crystalloids for volume resuscitation.[24]

Hyperkalemia

Dextrose containing crystalloids are useful in the stabilization of hyperkalemia when given in conjunction with insulin. Multiple studies have demonstrated similar or lower rates of hyperkalemia with the use of LR despite its potassium content. Administration of LR in the setting of hyperkalemia will cause the potassium to trend toward its 4 mEq/L concentration rather than worsen.[25,26] Given the comparatively lower pH of NS and the potential for a non-anion gap metabolic acidosis when large volumes of NS are administered, the use of balanced electrolyte solutions for the management of hyperkalemia is safe and reasonable.

Hypokalemia

Dextrose-containing solutions should be avoided in patients with hypokalemia to avoid stimulating insulin release, which can lead to worsening of hypokalemia.[26]

Hypernatremia

Hypernatremia results from a free water deficit from poor intake or increased loss, and therefore hypotonic fluids are indicated to replace the deficit. First, the free water deficit should be calculated. Calculators are available online that take into account age range and sex.[7] The volume of the total deficit should then be administered over 24 hours via oral or enteral free water if possible. If oral or enteral free water cannot be given, 5% dextrose in water is the preferred intravenous fluid. Half-normal saline is also hypotonic and can normalize hypernatremia but contains a lower amount of free water per volume. Goal rate of correction should be a rate of 12 mEq/L

over 24 hours.[28] In infants, more rapid correction has been associated with seizures and poor neurologic outcomes.[29] Older children and adults do not seem to have these negative outcomes, even with more rapid correction.[28,30] In adults, exceeding 72 hours to normalize sodium levels is associated with higher 30-day mortality rates.[28,31]

Hyponatremia

Intravenous fluid management for hyponatremia is based upon its acuity and associated volume status. Acute symptomatic or acute severe hyponatremia (<125 mEq/L) should be emergently corrected with 3% hypertonic saline in boluses of 100-150 mL over 10-20 minutes up to 3 times while monitoring sodium levels between each bolus.[32] Alternatively, 3% hypertonic saline can be infused at 1-2 mL/kg/hour with hourly monitoring of sodium levels, though this method may be associated with higher rates or relowering treatment.[33]

Asymptomatic, non-severe, and chronic hyponatremia should be managed based upon volume status and underlying etiology. Hypovolemic hyponatremia should be corrected with NS with the total volume, rate of administration, and laboratory monitoring guided by the etiology and response.[32] Euvolemic hyponatremia should be managed with 500-1,000 mL per 24 hours fluid restriction and discontinuation of any sodium-wasting medications. Oral salt tablets can liberalize this fluid restriction but are not sufficient alone unless the etiology is a low-solute diet.[34] Hypervolemic hyponatremia is often due to heart failure, renal failure, or cirrhosis and is treated with fluid restriction and condition-specific therapies.

Vomiting and/or Diarrhea

In patients with prolonged vomiting leading to metabolic alkalosis, administration of NS for resuscitation is preferred over balanced crystalloids given the sodium and chloride deficit. Patients with high-volume diarrhea will have significant bicarbonate and potassium losses which are better replaced with LR. Some secretory diarrhea can cause proportionally more chloride loss in which case NS may be preferable.[11] For patients with both vomiting and diarrhea, laboratory markers can aid in the decision for fluid choice.

Alcoholic/Starvation Ketoacidosis

Treatment with dextrose containing solutions is recommended to increase insulin secretion and subsequently terminate ketone production.[35] For alcoholic ketoacidosis, administration of thiamine prior to dextrose theoretically reduces the risk of Wernicke's encephalopathy.[36]

Sickle Cell Crisis

A recent cohort study comparing the use of LR and NS for volume resuscitation in patients experiencing a sickle cell vaso-occlusive crisis resulted in more hospital-free days and a lower 30-day readmission rate in those who received LR.[37]

Conclusions

The administration of intravenous fluids is a fundamental yet nuanced aspect of patient care, influenced by historical precedent, physician preference, and evolving evidence. NS remains widely used, but its limitations and potential adverse effects underscore the need for a more nuanced approach to fluid selection. Understanding the physiologic distribution and movement of water, properties and content of available intravenous fluids, and pathophysiology of the condition being treated allows for more informed decision-making. Application of this knowledge and available and emerging evidence can optimize fluid management, improve patient outcomes, and minimize complications.

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Breaking the Stigma: Integrating Substance Use Disorder Treatment into Primary Care

by Kevin W. Gray, MD, Anna Maria Pletz, MD & Rebecca E. Aguayo, MD

We must recognize that respectful, person-centered addiction care is primary care and should be considered part of medical care provided by any clinician.



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Abstract

Substance Use Disorder (SUD) is a growing public health crisis, with rising rates of morbidity and mortality, particularly due to opioids and alcohol. Despite the increasing need for treatment, access remains inadequate, highlighting the critical role of primary care physicians (PCPs) in addressing this gap. By integrating evidence-based screening, pharmacologic and non-pharmacologic treatment approaches, and stigma-reducing language, PCPs can serve as a frontline defense against the devastating impacts of SUD. Special considerations for maternal health, adolescent risk, and co-occurring mental health conditions further underscore the need for comprehensive, patient-centered care.

Introduction

SUD remains a devastating public health challenge in Missouri and nationwide. According to the 2022 National Survey on Drug Use and Health (NSDUH), 17.3% of the surveyed population aged 12 or older met the criteria for SUD in the past year, however, only 14% of those received treatment for substance use disorder.[1,2] In Missouri rates of SUD are increasing, and remain higher than national average, along with rates of substance-related morbidity and mortality, particularly due to opioids and alcohol.[1,2] SUD is a leading cause of preventable death. Annually in the United States (US) there are more than 100,000 overdose fatalities and 170,000 alcohol-related deaths. The escalating mortality from opioids, alcohol, and other substances, driven by a paucity of efficacious treatment access and engagement, underscores the critical need for early intervention and evidence-based comprehensive treatment within primary care.

This need is only amplified when considering the impact of SUD and its inadequate treatment on mother-baby dyads and their families. According to the 2021 Missouri Department of Health and Senior Services Pregnancy-Associated Mortality Review, 43% of all pregnancies in Missouri involve a history of substance use, highlighting a critical population deserving appropriate related screening and care.[3]

Definition and Screening

SUD is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) as a problematic pattern of substance use leading to clinically significant impairment or distress.[4] Diagnosis is based on the presence of at least two of eleven criteria over a 12-month period (Table 1).[4]

Table 1. SUD Diagnostic Criteria[4]

Amount	Larger amounts or for longer than intended
Control	Persistent desire or unsuccessful efforts to cut down or quit
Time	Large amounts of time to obtain, use, or recover from effects
Cravings	Strong desire to use
Obligations	Inability to fulfill major obligations at work, school, or home
Social	Continued use despite persistent/recurrent social or interpersonal harm
Activities	Reducing/stopping important social, occupational, or recreational activities
Hazard	Use in physically hazardous situations
Harm	Knowledge of persistent or recurrent physical or psychological problems
Tolerance	Need for increased amounts to achieve desired effect or less effect with use of the same amount
Withdrawal	Presence of withdrawal symptoms or use to avoid symptoms
Severity	Mild (2-3 criteria), Moderate (4-5 criteria), or Severe (6+ criteria)

Appropriate identification of SUD is crucial to connecting individuals with this life-threatening disease to the care they need. This can be accomplished via SBIRT (Screening, Brief Intervention, and Referral to Treatment) with universal screening using standardized screening tools in an informative, non-judgmental manner that encourages honest response. Such tools can efficiently identify at-risk individuals and facilitate timely intervention. The NIDA (National Institute of Drug Abuse) Quick Screen is a single question regarding the frequency of heavy alcohol use, tobacco, prescription drugs for nonmedical purposes, and illegal drugs within the past year. The four Ps tool asks individuals about problem drug use in their Parents, Partners, Past, and Pregnancy. The CRAFFT (Car, Relax, Alone, Forget, Family/Friends, Trouble) tool is designed for screening ages less than 21.[5] Positive screening should not lead to punitive action but serve as an opportunity to offer life-saving care to persons who are at imminent risk of death. Urine drug screens are of limited utility, given their poor sensitivity and specificity for actual SUD and potential for undermining trust. These tests should be used with informed consent, with thorough patient history, physical exam, and clinical judgment, as an opportunity for brief intervention.[6]

Understanding of the pathophysiology and nature of SUD as disease has evolved over time, with significant care implications. While previously considered a personal flaw or failure, research characterizes SUD as a treatable chronic relapsing brain disease, akin to hypertension, diabetes, and heart failure.[7] Considering their expertise in chronic disease management via continuity of care, and the deadly mismatch between SUD treatment need and access, PCPs are uniquely positioned to identify and manage SUD using evidence-based approaches.

SUD Management – General Concepts

Treatment Engagement, Retention, and Non-Pharmacologic Considerations

Data clearly demonstrates that early engagement in and longer duration of substance use disorder treatment improves clinical outcomes.[8] Evidence-based recommendations to optimize this crucial treatment initiation, engagement, and retention can be viewed in Table 2 as part of American Society of Addiction Medicine (ASAM) Clinical Guidance Document.[9]

Clinician language and discussion of SUD as a chronic disease can aid in reducing stigma around addiction and its treatment and reducing barriers to life-saving care. Recognizing that each SUD-affected person has a story, which often involves significant trauma (40-90% among women who use drugs), and utilizing trauma-informed approaches can help mitigate caregiver stigma and barriers to care.[10]

Table 2. Improving SUD Treatment Initiation and Engagement[9]

Recommendations to Improve SUD Treatment Initiation and Engagement
1. Cultivate patient trust by creating a welcoming, nonjudgmental, and trauma-sensitive environment
2. Do not require abstinence as a condition of treatment initiation or retention
3. Optimize clinical interventions to promote patient engagement and retention
4. Only administratively discharge patients from treatment as a last resort
5. Seek to re-engage individuals who disengage from care
6. Build connections to people with SUD who are not currently seeking treatment
7. Cultivate staff acceptance and support
8. Prioritize retention of front-line staff
7. Align policies and procedures with the commitment to improve engagement and retention of all patients, including nonabstinent patients
8. Measure progress and strive for continuous improvement of engagement and retention

The impact of positive social connection on human health is well-demonstrated, and this certainly bears out in SUD cases and care.[11,12] Clinicians should encourage engagement in heathy relationships, behavioral health care, mind-body interventions, physical activity, and spiritual health considerations and practices as applicable.[13, 14, 15, 16, 17] PCPs are perfectly positioned for efficacious SUD treatment given the importance family-member engagement to lasting recovery, and the potential of family-centric SUD-care models.[18] Clinicians should also recognize important screening opportunities for family planning needs, intimate partner violence, sexually transmitted infections, and hepatitis C virus while caring for patients with SUD.[18]

Alcohol Use Disorder

Alcohol Use Disorder (AUD) is common and is associated with significant life-altering risks of medical comorbidity, injuries, and healthcare costs. Globally, 1.8 million deaths were attributable to high alcohol use in 2021, including 178,000 people in the US, with rates rising over 25% during the COVID-19 pandemic.[19] Alcohol's health impacts are most closely related to the total amount consumed, as well as the number of heavy-drinking days, with a dose-response increase in alcohol-related mortality for every heavy-drinking day (3+ standard drinks for women, 4+ for men).[20] Treatment of alcohol withdrawal alone is not effective treatment for AUD, but it should be considered an element of initiating and maintaining AUD treatment. A practice guideline for alcohol withdrawal management from the ASAM is available.[21]

Patients diagnosed with AUD should be offered pharmacotherapy and behavioral therapy. While there are multiple accessible medications shown to reduce heavy drinking days and maintain abstinence, less than 2% of those with AUD were prescribed medications to treat this disorder in 2019 .[22] Research implicates lack of knowledge about effective medications, including their efficacy and dosing, as well as treatment philosophy and stigma as barriers to prescribing.[23] *American Family Physician* has provided a recent review of several primary pharmacologic tools for treatment of AUD (SORT A and B).[24] Naltrexone (for those not using opioids), gabapentin, and topiramate can be offered despite non-abstinence to reduce heavy-drinking days and work toward abstinence, and acamprosate and disulfiram can help prevent those abstinent from returning to use.[25] Varenicline and baclofen can also help reduce heavy use (Table 3). Clinicians should also assess for and address any underlying or comorbid mental health disorders, stressors, and trauma that may be contributing to substance use.[25]

Opioid Use Disorder

Age-adjusted drug overdose deaths in the US significantly increased by nearly 300%, from 8.2 deaths/100,000 standard population in 2002 to 32.6 deaths/100,000, in 2022 – a loss of 3.1 million years of life.[1,2] Opioids, predominantly fentanyl, were the main drivers of drug overdose deaths.[1,2,3]

Medications for Opioid Use Disorder (MOUD) is likely the single most impactful life-saving interventions a physician can offer. The partial opioid agonist buprenorphine (the main component in

Table 3. Medications for Alcohol Use Disorder[25]

Medication	Dose	Number Needed to Treat
Naltrexone – oral	50 mg orally per day (25-100 mg as tolerated)	12 to decrease heavy-drinking days
Naltrexone – intramuscular	380 mg IM monthly	Too little data to calculate; likely similar to or better than oral naltrexone
Gabapentin**	300 mg on day 1; add 300 mg per day, titrate to maximum of 3,600 mg Typical dosage: 600 mg three times daily	5 to decrease heavy-drinking days
Acamprosate**	666 mg orally three times per day	12 to prevent return-to-drinking
Topiramate (immediate release)	25 mg daily; increase 25-50 mg every week to maximum dosage of 300 mg per day	5 for zero heavy-drinking days
Baclofen	Variable, 15-80 mg daily (trials from 30-300 mg daily)	Too few studies to calculate
Varenicline	0.5 mg daily for 3 days, 0.5 mg twice daily for 4 days, 1 mg twice daily thereafter	Too few studies to calculate
Disulfiram	250 mg orally daily; maximum 500 mg daily	Not evaluated[26,]

** Renally-dosed

Suboxone) has been increasingly used in Opioid Use Disorder (OUD) treatment due to its safety, efficacy, relatively high patient adherence, and effectiveness in saving lives – reducing deaths by over 60%.[27] There is no other pharmacologic product on the market as lifesaving. It is vastly safer than full-agonist narcotics and can actually reduce risks associated with these if taken simultaneously, with minimal risk of respiratory depression and tolerance.[28] Though its use for OUD as well as chronic pain where opioids are indicated is appropriately increasing since the X-waiver requirement was absolved, it remains significantly underutilized.

Various evidence-based initiation strategies have been published and can be referenced for more detail including the ASAM Clinical Consideration and California Bridge program (Table 4).[30]

In addition to pharmaceutical and behavioral health approaches, holistic, integrative, complementary, and alternative therapies should be considered, with research showing current use of and interest in these modalities among those seeking buprenorphine for OUD.[31] Evidence has also suggested improvement in cognitive symptoms with vitamin D supplementation in those with OUD.[32]

Opioid Overdose Death Risk Reduction

Opioid overdose reversal medications such as naloxone are life-saving and underutilized. These medications should be prescribed to all those with OUD and considered for any person receiving prescription opioids. Xylazine and fentanyl test strips and reminders to never use alone (www.neverusealone.com) save lives. Additionally, many adolescents who die from opioid overdose do not have OUD, are unaware of what they are ingesting, and die from their first exposure. [33] This highlights the importance of counseling adolescents on the life-threatening risks of ingesting any pill that is not directly prescribed to them. PCPs should counsel all patients with narcotic medication prescriptions on the importance of secure storage to prevent accidental poisonings .[34, 35] Clinicians should screen for development or worsening of problematic alcohol use among those engaging in opioid medication tapers.[36]

Substance Use Disorder in Pregnancy

SUD contributed to 31% of Missouri's pregnancy-related mortality, with only 31% of those cases having a history of SUD treatment, all of which were deemed preventable.[3] Additionally, 42% of pregnancy-associated not-related (PANR) fatalities were due to injury, poisoning, or overdose with 82% of these cases involving a history of SUD. Of the overdose deaths, 90% involved polysubstance use, with 80% including opioids.[3] The ASAM has teamed with the American College of Obstetrics and Gynecology producing guidance on treatment of OUD in pregnancy in their Practice Bulletin 711.[37] Core recommendations include contraception counseling among patients

Table 4. Clinical Decision Support for Buprenorphine Initiation Approaches[28,29]

Initiation Strategy	High-Dose ("macrodosing")	Standard	Low-Dose with Opioid Continuation ("microdosing")
Advantages	Rapid stabilization Helps bridge access barriers to ongoing buprenorphine	Longest used and most well-described	Initial opioid discontinuation not required
Need for withdrawal?	Yes	Yes	No
Premedicate with adjuvant medications?**	Consider	Recommended	Recommended
Initial starting dose (buprenorphine SL)	8-16+ mg	2-8 mg	0.25-1 mg
Duration of initiation until stabilization	≤2 h	1-3 days	3-10+ days
Need for full agonist opioid continuation	No	No	Yes
Level of care coordination required	Moderate	Moderate	High

** These include clonidine, hydroxyzine, acetaminophen, and NSAIDs.

undergoing treatment for SUD, universal screening at the first prenatal visit using a validated screening tool, treatment with opioid agonist therapy during pregnancy, monitoring for neonatal abstinence syndrome for infants born with opioid exposure and encouraging breastfeeding for those without absolute contraindications.[37]

Other Substances

Stimulants

Stimulant use disorder (StUD) rates are increasing, as are stimulant potency and combined use with opioids.[1,2] This has led to a three-fold increase in cocaine overdose deaths and 12-fold increase involving other stimulants (e.g. amphetamine, methamphetamine, prescription stimulants) over the last 10 years. In 2022, such stimulants were involved in half of all overdose deaths. StUD can lead to severe and lasting cardiac, dental, nutritional, infectious, and psychiatric problems. Given this mounting health crisis, the American Society of Addiction Medicine (ASAM) published a recent Clinical Practice Guideline on the management of StUD focused on its identification, diagnosis, treatment, and promotion of recovery.[38] Emphases include: contingency management as the most effective treatment studied and current standard of care; high rates of co-occurring psychiatric conditions that should be identified and simultaneously treated (e.g. treating ADHD with pharmacotherapy including psychostimulants); treatment of stimulant withdrawal to aid treatment engagement and prevention of decompensation and return to use; and secondary and tertiary prevention strategies recommended to reduce overdose, risky sexual practice-, IV drug use, and nutrition-related harms.[38]

Kratom

Kratom (Mitragyna speciosa korth) leaf and extract product consumption has increased in the US since 2015, with estimated lifetime consumption at 0.9% to 6.1%. Its alkaloids act on several central nervous system receptors (i.e., adrenergic, serotonergic, noradrenergic, and opioidergic).[39] Users report doing so for self-management of pain, fatigue, mental health symptoms, and SUD, such as using kratom to attenuate alcohol or opioid withdrawal and/or to replace full-agonist opioids.[39, 40] However, kratom (mitragynine) exposure is associated with adverse effects including physical dependence and SUD; it has also been identified as the single causal agent in dozens of deaths and increases risk of overdose death when used in combination with other substances.[39, 40] Physicians should educate on these harms and recommend caution with use. Research into managing kratom withdrawal and related SUD is ongoing but suggests it can be managed similarly to conditions associated with other opioids.[41]

Benzodiazepines

Those using benzodiazepines are also at risk of developing related sedative use disorder. In 2022, 3.7 million people aged 12 and older misused prescription benzodiazepines.[1] These agents are additionally associated with increased risk of death when used with opioids, falls, physical dependence, cognitive impairment and related accidents and loss of function, and should be initiated and utilized only with great caution and informed consent. Treatment for sedative use disorder includes slow taper with use of other behavioral and pharmacotherapies to help address related symptoms. Taper protocols vary; the ASAM is currently developing a Clinical Practice Guideline on Benzodiazepine Tapering.[42]

Xylazine

Xylazine is a nonopioid alpha-2 adrenergic agonist traditionally used in veterinary medicine and is being increasingly used as an adulterant in unregulated drugs, most commonly fentanyl sharing full-agonist activity at the kappa opioid receptors, prolonging its effects.[43] Typical human effects include sedation, bradycardia, central nervous system depression, and transient hypertension followed by hypotension.[44] Xylazine is associated with wound formation, regardless of consumption, and prolonged use can lead to infection, sepsis, and amputation.[45] Current xylazine-associated wound identification and management is inadequate.[46] Physicians should educate on the risks of xylazine and encourage use of xylazine test kits and appropriately assess for and treat associated wounds.

Conclusion and Call to Action: Integrating Substance Use Disorder Treatment

According to data of available addiction medicine specialists and NSDUH figures, in Missouri, there are more than 2,000 patients per specialist for OUD alone. The extent of opioid use alone in our state necessitates care beyond the reach of our specialist services; hence, state and federal policies have implemented changes that promote treatment of SUD in primary care.

Despite the well-known importance and successful models of such care expansion, primary care integration of SUD/OUD management remains in its infancy in Missouri.[47] Collectively, we must seek to identify evidence-based strategies for implementing necessary, life-saving care for these patients within the primary care clinic setting. While care for these patients in the primary care setting is important, this does not negate the importance of access to specialty services. PCPs should consider consultation with an addiction medicine specialist for difficult cases, specific questions, and for complex patients whose management of their SUD would overwhelm all other preventative care efforts. SUD care should be considered a central method of preventative medicine for affected patients.

SUD and its related rates of death and disability has been rightly, repeatedly stated a public health crisis. To curb this crisis, we must recognize that respectful, person-centered addiction care is primary care and should be considered part of medical care provided by any clinician. Integrating SUD treatment into primary care is essential to closing the gap between the many who need such care, which is proven lifesaving and dramatically effective, and those who receive it. The need is great, and so are the proven tools. Primary care clinicians are uniquely positioned to deliver life-saving interventions, reduce stigma, and promote long-term recovery. By implementing evidence-based practices, fostering trust, and advocating for accessible treatment, we can all can play a pivotal role in reversing the trajectory of the substance use epidemic, saving lives of those in their prime, and returning people to function and fulfillment.

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From Ancient Traditions to Modern Medicine: A Review of the Evolution, Procedural Complications, and Surgical Challenges of Piercings

by Ali Malik, MD & M. Laurin Council, MD

While piercings offer a unique form of self-expression, they also come with medical risks and potential complications.



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Abstract

Piercings have evolved from ancient cultural traditions to a mainstream form of body modification, interweaving personal expression and modern medicine. This review traces the historical origins of piercings, highlighting cultural significances and transformation into contemporary trends. As piercings have become increasingly commonplace, the incidence of medical complications has risen, necessitating medical and surgical intervention. Moreover, the growing popularity of body modifications, including gauges and dermal implants, presents unique surgical challenges in reconstructive procedures following piercing removal. By exploring the intersection of historic cultural practices and medical science, this review aims to provide a broad understanding of the evolution of piercings and considerations for physicians managing piercing-related concerns.

Historical Overview of Piercings

Body piercings have played an integral role in human culture for thousands of years, symbolizing status, beauty, and spirituality. The earliest physical evidence of piercing comes from Ötzi the Iceman, a 5,000-year-old mummy with gauge-style ear.[1,2] In Ancient Egypt, piercings symbolized wealth and status, and ear and nose piercings were common among the elite, including King Tutankhamun.[3,4] In ancient African cultures, tribes like the Maasai and Mursi used large earlobe discs and lip plates, respectively, as markers of beauty, maturity, and social status (Figure 1).[5] Meanwhile, in ancient Rome, soldiers pierced their nipples as a show of strength and solidarity, while the Aztecs and Mayans used lip and tongue piercings as part of religious rituals.[6,7]

From the Middle Ages through the Renaissance, the popularity and meaning of piercings in Europe varied significantly, often reflecting shifting societal and religious attitudes. During the Middle Ages, the Christian Church opposed body modifications, viewing the body as sacred and unalterable.[8,9] However, the Renaissance saw a renewed interest in self-expression, influenced by increasing global trade and cultural exchange. In Victorian England, piercings, particularly among women, were viewed with moral disapproval but persisted as symbols of fashion

and status.[10] European colonial expansion in the 19th century also brought awareness of non-Western body modification practices, occasionally influencing Western styles.

In the early 20th century, industrialization and mass production made jewelry more widely available, leading to broader acceptance of ear piercings across social classes. Following the world wars, jewelry trends became simpler, but ear piercings remained common among women. Social changes after World War II, including the women's liberation movement, brought a shift in attitudes toward personal adornment, paving the way for expanded forms of self-expression and body modification.

The counterculture movements of the 1960s and 1970s transformed piercing practices in Western societies. Hippie and punk movements embraced piercings as symbols of rebellion, and celebrities like David Bowie and Madonna popularized the trend in the 1980s. The 1990s saw the establishment of professional piercing studios, which offered safer environments and increased awareness about aftercare. By by the early 21st century, various types of piercings—such as septum, lip, eyebrow, navel, and dermal piercings—gained traction alongside more extreme modifications like stretched earlobes and dermal implants. Social media platforms played a significant role in normalizing these practices by creating a global community where individuals could share their unique styles and experiences.

Today, body piercings are popular across cultures and are seen as extensions of personal identity, belief, and style. Advances in biocompatible materials, personalized jewelry, and healing techniques have increased safety, reduced complications, and broadened the appeal of piercings.[11,12] These innovations ensure that body piercings will continue to evolve as an essential medium of self-expression and cultural tradition.



Figure 1. African cultures, tribes like the Maasai and Mursi used large earlobe discs and lip plates, respectively, as markers of beauty, maturity, and social status.

Complications from Piercings

Short-term Medical Complications

The most common site of piercings is the ear, with increasing popularity involving the mouth, nose, eyebrows, nipples, navel, and genitals.[11,12] While piercings are generally safe when performed by trained professionals, they can lead to immediate complications, although the absence of regulation and incident reporting, particularly for sensitive or high-risk piercings, results in inconsistent and unreliable estimates of the frequency of complications associated with body piercings.[13]

Immediate complications of body piercings include bleeding, pain, and nausea. The use of firm pinpoint pressure as a form of hemostasis may address most instances of superficial bleeding. In some cases, excessive bleeding can indicate more serious underlying medical issues that require focused medical attention. Materials known to cause allergic reactions—including sanitary products used in the procedure (e.g. nickel-plated items, latex surgical gloves)—should be avoided in sensitive individuals undergoing body piercings.[13,14]

Piercing site infection, including localized cellulitis, is the most common non-immediate complication of piercings.[11,12] The most commonly identified organisms from piercing-related infections are staphylococcus and streptococcus species, although there is a higher rate of incidence of pseudomonas infections when cartilaginous ear and nasal structures are involved in



Figure 2. Various ear piercings through cartilage and ear lobe.

body piercings (Figure 2).[11] Individuals with genital piercings are at increased risk for sexually transmitted infections such as *Neisseria gonorrhea* and *Chlamydia trachomatis*.[12] Culture and gram stain of purulent drainage of piercing-related skin infections can help aid in the diagnosis and treatment of skin and soft tissue infections. If localized infections are not properly identified and treated, they can cause more serious systemic complications such as Ludwig angina, endocarditis, toxic shock syndrome, and Fournier gangrene, although instances are rare.[11,12]

Symptoms of piercing site infection include redness, swelling, pain, and discharge. Preventative measures include proper sterilization of equipment, the use of autoclaves at piercing studios, and appropriate aftercare. Conservative treatment of minor local infections includes warm compress application and over the counter or prescription topical antibiotics, such as mupirocin. Oral antibiotics such as cephalexin or clindamycin provide adequate coverage for streptococcus and staphylococcus. If concerns for methicillin-resistant *Staphylococcus aureus* exist, oral trimethoprim/sulfamethoxazole confers adequate coverage. As discussed, infected piercings involving the cartilaginous structures of the ear are more likely to be caused by Pseudomonas and are treatable with a fluoroquinolone like ciprofloxacin.[11]

Allergic contact dermatitis is the most frequent non-infectious cutaneous complication of piercings. Importantly, nickel is the most common allergen associated with body piercings, and ear piercing is believed to be the most common source of nickel sensitization.[13,14] A 2001 study by Ehrlich et. al demonstrated a 4.0% nickel sensitization rate in males with no piercings compared with 11.1% and 14.% in males with one or multiple piercings, respectively.[14] To minimize the risk of sensitization, the use of hypoallergenic metalware in piercings (e.g. surgical stainless steel, niobium, titanium, or gold) is recommended in lieu of nickel, particularly in the period from piercing administration to resolution of healing.[15] Triple antibiotic ointments like Neosporin should be avoided due to increased risk of allergic contact dermatitis.[16] Irritant contact dermatitis can occur from the cleaning solutions used to clean piercings as well. Symptoms of allergic reactions include itching, redness, and swelling at the piercing site. Treatment involves the removal of the piercing or jewelry piece or cleaning solution and future avoidance of allergic triggers.

Removal of infected piercing jewelry is requisite for most forms of treatment, and the placement of a loose loop suture through the piercing can be used to maintain piercing patency throughout infection treatment. Oral piercings tend to have a lower infection rate but, when present, are treatable with amoxicillin/clavulanate (Figure 3). The recommended duration of treatment for local cellulitis is five days, but extension of therapy should be considered if there is no improvement in symptom burden.[11] The addition of oral alcohol rinses or topical cleaners containing hydrogen peroxide or vinegar can aid in infection healing. Treatment for genital piercing infections should include coverage for *Neisseria gonorrhea* and *Chlamydia trachomatis* with intramuscular ceftriaxone and oral azithromycin in appropriate settings.[11,12] If the patient has not received a tetanus vaccination or booster within the last five years, then this should be updated if a patient presents with an infection after a recent body piercing.[11]

Long-term Medical Complications

Potential complications of piercing-related infections are relatively minor when identified early and treated with appropriate antimicrobials. However, the risk of infectious complications is greater in deep piercings

and those that pierce through mucosal surfaces. A delay in clinical presentation can lead to increasingly severe local skin and soft tissue infections such as abscess formation, cellulitis, chondritis, sepsis, nasal septal perforation, airway compromise as in cases of Ludwig angina, or possible dissemination to distant sites such as infective endocarditis, from oral piercings, or toxic shock syndrome, from genital piercings.[11,12] Long-term complications can arise months or even years after an initial piercing.

Over time, piercings can lead to scarring or the development of keloids or hypertrophic scars, which are raised, overgrown areas of scar tissue. Keloids generally occur four to eight weeks after piercings, increase in size for up to six months, then flatten over a period of a few years.[17,18] Keloids are more common in individuals with a genetic predisposition and can be difficult to treat. There is an increased likelihood of keloid formation in cases of post-procedure complications, such as hematoma, infection, excess skin tension, and/or delayed wound healing. Treatment options include steroid injections, silicone sheets, and in some cases, surgical removal.[17,18] Scar tissue can also cause discomfort and impact the appearance of body piercings.

Some piercings, particularly surface piercings, may migrate or be rejected by the body. This occurs when the body perceives the jewelry as a foreign object and slowly pushes it out. Factors that contribute to piercing migration and rejection include improper placement, excessive movement, and the body's immune response. Migration can result in an unsightly appearance and may require the piercing to be re-pierced or removed. Jewelry can also sometimes become embedded in the skin if the piercing hole closes over it, requiring surgical removal. This complication is more common in piercings subjected to pressure or trauma. Embedded jewelry can cause pain and infection, necessitating prompt medical and/or surgical intervention.

Psychological and Social Complications

While it may be medically necessary to remove piercings, it may also be psychologically traumatic, particularly when piercings were obtained for reasons based on factors of identity, culture, spirituality, or remembrance. Suture material, non-stick posts or non-metal catheters can be used to maintain the body piercing opening if the removal is intended to be temporary to provide the patient or individual with reassurance of patency.[17] The deformity that

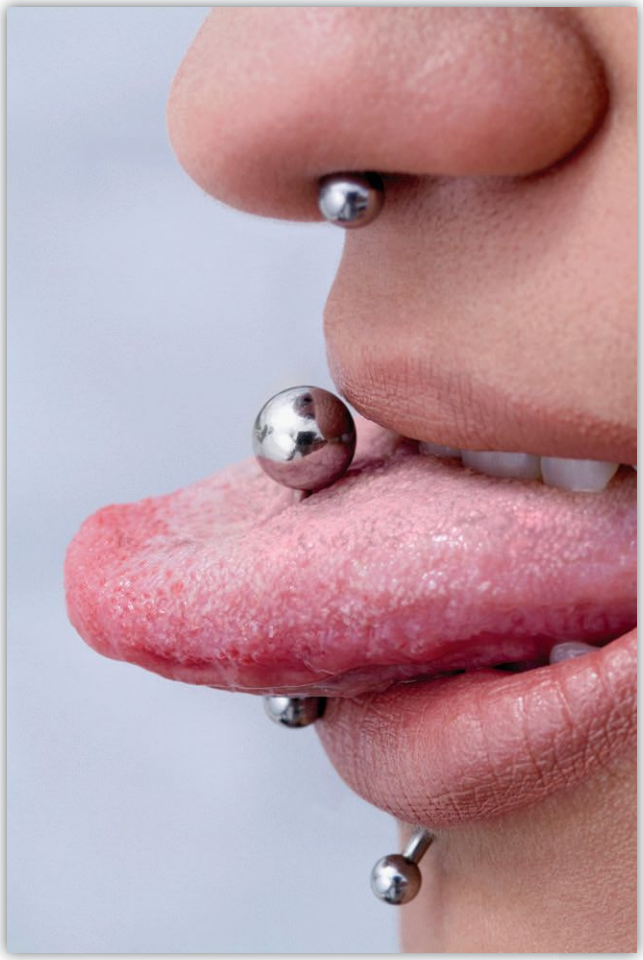


Figure 3. Oral piercings.

can occur from piercings can unintentionally reduce patient self-esteem and body confidence. For example, disinterest leads to the intentional removal of 13–18% of body piercings at body sites other than the earlobes in Western culture.[18,19] Individuals who undergo body piercing procedures may face discrimination and stigma arising from incorrect assumptions about the piercing, differing personal opinions, or non-conformance to staff dress codes and expectations around workplace appearances.[20] Counseling and social support can help individuals navigate these feelings.

Visible piercings can lead to discrimination and ostracization in certain professional environments. Despite growing acceptance, some work environments or industries impose strict appearance and dress code standards. Individuals with visible piercings may face challenges in job interviews or workplace settings where traditional norms prevail. Advocacy for body modification acceptance in the workplace continues to grow.







Figures 3, 4, 5. Removal and managing scar tissue can be challenging for reconstructive surgeons.

Challenges with Surgery and Reconstruction Following Piercing Removal

General Considerations

Along with the growing popularity of body art, there has been a parallel increase in individuals seeking removal and subsequent reconstruction of piercing sites, often due to aesthetic or professional reasons, infection, or other complications. Surgical reconstruction of these piercing sites, especially in cases of expanded piercings such as large-gauge earlobes, presents a unique set of challenges for reconstructive surgeons. These challenges span from managing scar tissue and skin integrity to achieving satisfactory cosmetic outcomes, restoring function, and addressing the patient's expectations.

Reconstructive surgeons must carefully assess the extent of scarring and plan operative procedures to minimize further tissue damage. Techniques to reduce scarring include silicone gel sheets and fractional resurfacing and pulsed dye laser treatments. Managing patient expectations is crucial. Some patients may expect complete restoration of pre-piercing appearance, which may not always be aesthetically possible. Reconstructive surgeons should provide patients with realistic expectations and discuss potential limitations and risks of surgical intervention.

Scar Tissue and Healing Considerations

One of the primary challenges in repairing a site where a piercing has been removed is managing scar tissue that has developed over time. Piercings, particularly those that are in place for long periods of time, create a permanent tract lined with epithelial tissue. When the piercing is removed, this epithelial-lined tract can close but residual scar tissue remains, which can lead to various complications. Scar tissue can result in altered skin elasticity, because scar tissue lacks the same elasticity and tensile strength as normal skin. This makes reconstruction of the natural contour of the surgical site more challenging. Moreover, areas with significant scarring may have compromised blood

supply, leading to slower healing and a higher risk of wound breakdown or post-operative infection. Patients who are prone to hypertrophic scarring or keloid formation may also develop unsightly or painful scars after reconstructive surgery, complicating the aesthetic outcome.

Challenges with Large-Gauge Piercings

Large-gauge piercings, or stretched piercings, particularly in the earlobes or other stretched tissues, pose unique reconstructive challenges These piercings can create large, stretched-out holes or even tears, leaving behind significant tissue distortion when jewelry is removed.[17] The larger the gauge, the more complex the reconstruction. Tissue may be thin, fragile, and difficult to work with. Specific challenges include tissue deficiency, loss of natural contour, and asymmetry and cosmetic concerns.

In some cases, there may not be enough adjacent tissue to properly close the defect without tension, increasing the risk of wound dehiscence or poor cosmetic results. The natural contours of body parts such as the earlobe can be significantly altered by large-gauge piercings. Restoring the natural, rounded shape of the earlobe can be technically challenging and may require flaps, grafts, or multi-step procedures to recreate.

Achieving perfect symmetry between the repaired side and the contralateral, non-operative side is difficult. In bilateral reconstructions, such as reconstructive procedures involving both ears or earlobes, slight differences in tissue thickness, skin texture, or shape may become noticeable. These differences are particularly apparent in operative areas like the face and ears, where symmetry is paramount for aesthetic satisfaction.

Smaller gauge holes can often be closed with less invasive techniques such as simple suturing. This involves removing the jewelry, allowing the remaining hole to shrink, removing the epithelialized tract, and subsequently stitching the edges together. This method is effective for minor stretching associated with smaller gauges but may not be suitable for larger gauges. Larger gauge piercings may require tissue grafting to fill in gaps and restore normal appearance and contours. This technique involves taking tissue from another area of the body and grafting it onto the piercing site. The graft must be carefully matched to surrounding skin to ensure a natural appearance. Advanced flap techniques can be used to reconstruct severely distorted areas, providing better cosmetic results. This involves creating flaps of skin and tissue to cover the defect and restore a more natural appearance. Flap techniques require careful surgical planning and expertise to avoid complications such as necrosis or infection.

Techniques and Surgical Challenges

In summary, several surgical techniques are used to repair tissue after piercing removal, but each comes with its own set of challenges. In some cases, more than one surgical stage may be necessary to achieve the desired cosmetic and functional outcome. However, this can be time-consuming, costly, and inconvenient for the patient.

Infection and Complications Post-Removal

Another major challenge faced by reconstructive surgeons during piercing repair is the risk of infection, both before and after the removal of the piercing. Infected piercings, particularly those involving cartilage, can lead to chondritis and, in severe cases, cartilage necrosis. For instance, in piercings through cartilage (such as the helix of the ear), infection can lead to permanent cartilage destruction, complicating the reconstruction process. Rebuilding cartilage requires specialized techniques, such as cartilage grafts, to restore structural integrity. If the surgical area was infected prior to removal, the infection can persist or recur post-surgery. This necessitates careful infection control and antibiotic management during reconstruction. Piercings that have been in place for an extended period can sometimes form a persistent sinus tract, leading to chronic drainage or infection even after removal. This can complicate healing and require additional surgical intervention.

Functional Considerations

For some piercings, particularly those in sensitive or functional areas such as the nasal septum, tongue, or lip, reconstruction should not only focus on achieving a cosmetic result but also restoring function. Challenges include maintaining airway patency and speech and swallow restoration. Nasal piercings, especially septum piercings, can cause scar tissue formation that may lead to nasal obstruction if not properly repaired. Restoring the nasal airway without causing further scarring or collapse of the nasal septum can be challenging. In cases of oral piercings (tongue, lip, or cheek piercings), improper healing after removal can lead to difficulty

with speech, eating, or swallowing. Reconstructive surgeons must carefully repair these areas to avoid functional impairment.

Patient Expectations and Psychological Considerations

Patients seeking the removal and reconstruction of piercing sites often have high aesthetic expectations. They may wish for the piercing site to disappear or revert to its original appearance prior to its piercing, particularly in visible areas. Despite the best surgical techniques, it is often impossible to completely erase all clinical evidence of a piercing, particularly for large-gauge piercings or those that have been in place for many years. For some patients, removing a piercing may have deeper psychological or emotional implications. Some may feel a sense of loss or regret about removing a body modification that was once an important part of their identity. Balancing the physical outcome with the emotional aspects of piercing removal is an important part of the reconstructive surgeon's role.

Conclusion

Body piercings have evolved from ancient cultural practices to contemporary fashion statements, reflecting broader societal changes in attitudes toward body modification and personal expression. While piercings offer a unique form of self-expression, they also come with medical risks and potential complications. With a growing number of individuals seeking piercing removal and repair, particularly for larger piercings, the demand for advanced surgical techniques and expertise in this area will continue to rise. As society continues to evolve, so too will the practices and perceptions surrounding body piercings.

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Comparative Analysis of Postoperative Visual Outcomes of Light-Adjustable Lens, Toric Monofocal, and Spherical Monofocal Intraocular Lenses

by Marisa Nakagama, BS, Dhruv Nagesh, BS & John Doane, MD

Considering the long-term cost benefits when deciding between different intraocular lens types is important, which can further contribute to overall patient satisfaction.



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Abstract

This retrospective study compares postoperative visual outcomes among 150 eyes treated with Light-Adjustable Lenses (LAL), toric monofocal lenses, and spherical monofocal lenses at Discover Vision Centers in Missouri and Kansas. The study included individuals with an average age of 68.9 years (25-82 years) who had cataract extraction (CE) within the past five years. Patients with prior corneal refractive procedures, including Radial Keratotomy (RK), Photorefractive Keratectomy (PRK), Laser-Assisted In Situ Keratomileusis (LASIK) or Small Incision Lenticule Extraction (SMILE) were excluded. Sixty-four percent of eyes with LALs achieved uncorrected distance visual acuity (UCDVA) better than 20/20 after the final lock-in, 46.0% with toric monofocal lenses, and 32.0% with spherical monofocal lenses. LAL-treated eyes also showed lowest residual refractive error, with a final mean spherical equivalent of 0.0 ± 0.353D, outperforming toric (0.08 ± 0.386D) and spherical monofocal lenses (0.20 ± 0.631D). These results suggest that LALs offer superior outcomes, though further research is warranted.

Introduction

A cataract is the gradual clouding of the normal clear crystalline lens and is the leading cause of vision loss in the United States (US). Most cataracts are intrinsically age-related, affecting more than 20.5 million Americans above the age of 40. Annually, 6.1 million cataract extractions (CE) are performed, making it the most commonly performed ambulatory surgery in the US.[1]

To provide informed consent it is mandatory to educate patients on the various options available to them with respect to the changing landscape of intraocular lens (IOL) technology. When considering lifestyle and personal preferences, understanding the differences between options can play a significant role in pre-operative choice and post-operative patient satisfaction.

Spherical monofocal lenses are the most frequently implanted IOLs in cataract surgery. While these lenses are able to provide clear vision at one focal point, they cannot correct astigmatism or allow for any postoperative adjustments. Patients may have to wear glasses for both near or distance vision to correct residual refractive errors.[2,3] Data shows that spherical monofocal lenses can offer acceptable visual outcomes for the majority of patients, but the inability to address

astigmatism poses limitations for patients with visually significant corneal astigmatism.[4,5]

Toric monofocal lenses incorporate astigmatism correction into the design of the lens.[2,6] Roughly 50% of patients have visually significant astigmatism that must be corrected to optimize uncorrected vision. Toric lenses provide improvement in uncorrected distance visual acuity (UCDVA) and decrease residual astigmatism when compared with spherical monofocal lenses.[7]

The Light Adjustable Lens (LAL) is an IOL design that incorporates technology that is unique in its ability to allow postoperative adjustments to spherical and astigmatic lens power. LALs enable fine-tuning of lens power postoperatively. LALs use photosensitive macromers in the lens, that when presented with specific wavelengths of ultraviolet light, can be reshaped. Adjusting LALs requires up to three sessions following the surgery in which the lens power is modified to effect the desired refractive power.[8] Refraction adjustability after implantation affords improved uncorrected postoperative visual acuity compared to traditional non-adjustable technology. Studies show that patients with LALs display a higher chance of achieving UCDVA better than 20/20 when contrasted with both spherical or toric monofocal lenses.[9] In addition, there is a lower level of residual refractive errors with LALs which enhances overall visual clarity, reduces dependence on any corrective eyewear and increases patient satisfaction with postoperative outcomes.[10,11]

The objective of this retrospective study is to provide a comparative analysis of the outcomes associated with the newer technology of LALs versus the currently available spherical and toric monofocal lenses. Emphasizing efficacy, suitability, and comfort for patient populations, we aim to provide insights of the changing field of cataract surgery. By evaluating monocular UCDVA and manifest refraction spherical equivalent (MRSE), this study seeks to define outcome differences and better understand patient outcomes in cataract surgery.

Methods

Study Design: Pre- and Postoperative Patient Chart Review

This is an observational study of retrospective data obtained from 2019 to 2024 at Discover Vision Centers' surgical outpatient centers in Missouri and Kansas. The study includes a total of 150 eyes of 99 healthy adults, averaging 68.9 years of age (25-82 years), who received LAL, toric, or spherical monofocal IOLs. All individuals in each group were consecutive patients. Exclusion criteria include patients who underwent prior RK, PRK, LASIK and SMILE. Patients with diagnosed comorbidities of macular degeneration and glaucoma were also excluded from this analysis. This study is in accordance with the tenets of the Declaration of Helsinki. Written consent from patients was not required due to the nature of retrospective review and de-identified data.

All patients underwent comprehensive preoperative ophthalmic exams with dilation to confirm diagnosis of a visually significant cataract and relevant measurements prior to CE. Visual acuity was measured with standard visual acuity charts with 100% contrast and reported using 20/20 for standard vision. Topographic values were measured using the ZEISS Atlas Topographer and ZEISS IOL Master. Preoperative refractive measurements were measured with the ZEISS i.Profiler Plus Autorefractor and manual phoropter refractions. Patient biometry values were determined with the ZEISS IOLMaster 500, using Holladay II formulas for calculation of suitable IOL power to a target manifest refraction of plano, or 0.0 diopters.

The primary postoperative outcomes of this study are monocular UCDVA, monocular mean residual sphere and cylinder, and monocular mean spherical equivalent (SEQ) at their appropriate final refractive postoperative exam. The measurements and manifest refractions of patients who received spherical or toric monofocal lenses were obtained from their postop 1-month visit, while LAL patient postop refractive values were measured at their visit status-post their second lock-in treatment.

Surgical Procedure and Lens Types

All procedures were performed by the same surgeon with the same protocols at two ambulatory surgical centers. The patient's surgical eye was prepped in holding with topical anesthesia of proparacaine 0.5% and dilated with phenylephrine 2.5%/ Tropicamide 1%. All patients also received Ofloxacin preoperatively in the surgical eye. Once in the operating room, the eye was prepped with Betadine and draped in a sterile fashion. A lid speculum was placed and proparacaine 0.5% was administered over the corneal surface. Clear corneal entry was achieved with a 3.0 mm temporal incision and 1.0 mm sideport

Table 1. Pre- and postoperative demographic and refractive data of patients.

Pre-Operative Data of Subjects (n = 150)			
	LAL	**Toric Monofocal**	**Spherical Monofocal**
Eyes (n)	50	50	50
Sex (M/F)	18/32	17/33	12/38
Age (Years)	65.5	69.5	71.7
Mean sph (D)	-3.4 ± 5.632	-3.63 ± 3.312	-1.65 ± 3.835
Mean cyl (D)	1.2 ± 0.974	1.86 ± 1.419	0.95 ± 0.645
Mean sph equiv (D)	-2.8 ± 5.356	-2.70 ± 3.186	-1.18 ± 3.924
Post-Operative Refractive Data of Subjects (n = 150)			
	LAL	**Toric Monofocal**	**Spherical Monofocal**
Mean sph (D)	-0.2 ± 0.392	-0.14 ± 0.398	-0.18 ± 0.657
Mean cyl (D)	0.3 ± 0.397	0.44 ± 0.387	0.76 ± 0.609
Mean sph equiv (D)	0.0 ± 0.353	0.08 ± 0.386	0.20 ± 0.631

incision. One percent preservative-free lidocaine was injected intracamerally to prepare for clear corneal phacoemulsification. Once the residual cortex was removed, the appropriate posterior chamber IOL was inserted through the clear corneal incision. Specific lenses and relevant models included in the study are LAL®, LAL+™ (RxSight). Toric monofocal IOLs include: TECNIS® Toric I ZCT 150, 225, 300, 400, TECNIS® Toric II ZCU 150, 225, 300, 375, 450, 525, 600 (Johnson and Johnson Vision) and SA6AT9 AcrySof® Toric (ALCON). The LI61AO Sofport® (Bausch and Lomb) is the spherical monofocal IOL studied.

Postoperative drops of topical steroid and antibiotics were prescribed accordingly depending on patient tolerance, usually Pred-Forte with tapering and Ciprofloxacin. Patients were educated on the importance of compliance with postoperative drop scheduling prior to, and following CE. The imperativeness of wearing RxSight UV protective glasses during their postop phase prior to lock-ins was emphasized to patients with LALs, explaining that UV light sources, including the sun, can modify the prescription of the lens and lead to unexpected visual outcomes. All LAL patients received three different types of RxSight UV protective glasses: one clear, one clear with bifocal and one tinted.

No sooner than 17 days after surgery, LAL patients underwent adjustment treatments with the digital Light Delivery Device (LDD) ultraviolet light at 365 nm to modify the shape of the lens, adjusting refractive power to desired targets. Adjustments were performed until the patient was satisfied with their vision and ready to lock-in. All 50 eyes underwent a primary adjustment. Twenty-six eyes (52%) received at least two adjustment treatments and then proceeded with lock-in. Sixteen eyes (32%) had tertiary and six eyes (12%) had quaternary adjustments prior to lock-in. Patients were instructed that after the final light treatments, there can be no additional refractive changes.

Results

Of the 150 eyes of 99 adults included in the study, 50 eyes received LALs, 50 eyes received toric monofocal, and the remaining 50 eyes had spherical monofocal IOLs implanted. The mean age of eligible patients for this report was 68.9 years, with a gender ratio of 68.7% female (103 eyes) to 31.3% male (47 eyes). Table 1 provides more information regarding patient demographics as well as pre- and postoperative refractive data of mean sphere, cylinder, and spherical equivalent in diopters.

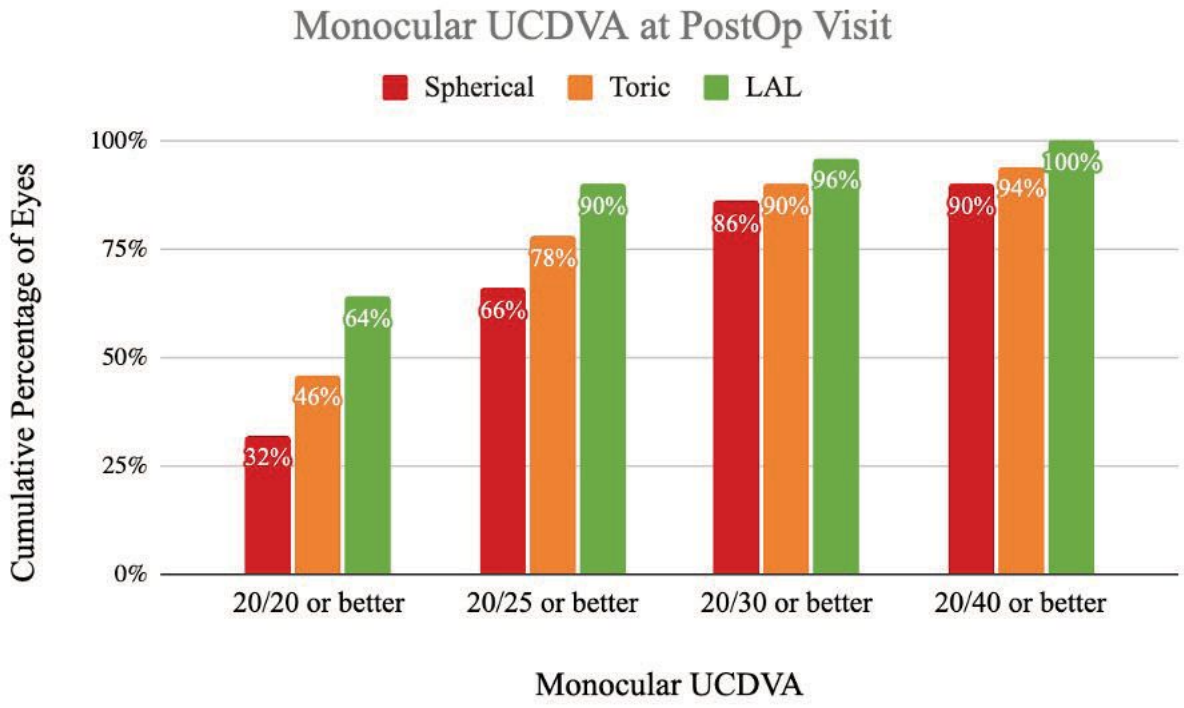


Figure 1. Comparison of monocular UCDVA in the LAL, toric, spherical monofocal treatment groups at their postop visit.

Comparison of Postoperative UCDVA Between Groups

After CE, at least 90% of all eyes, regardless of lens type, reached monocular UCDVA ≥ 20/40. At the stable, finalized postop visit after the second lock-in treatment, 32 eyes (64.0%) of the LAL group had UCDVA ≥ 20/20, compared to the 23 eyes (46%) of the toric monofocal group, and 16 eyes (32%) of the spherical monofocal group (Figure 1).

Comparison of Postoperative Refractive Diopters Between Groups

Seventy-four percent of LAL eyes were within 0.25D of target plano spherical equivalent, higher than that of the toric monofocal (50%) and spherical monofocal (38%) groups. Ninety-two percent of LAL eyes were within 0.50D of plano spherical equivalent, compared to 82% of the toric and 64% of the spherical monofocal groups (Table 1). The bar graph in Figure 2 summarizes the accuracy of spherical equivalent refraction outcomes between each lens type.

LAL patients achieved decreased residual mean cylinder and MRSE (0.3 ± 0.397D, 0.0 ± 0.353D). When looking at the difference between the preop and postop values, there is also a greater change in preop mean residual cylinder values compared to postop (Figure 3). The standard deviation in mean sphere, cylinder, and SEQ are reduced in LAL patients compared to that of spherical and toric monofocal values.

Discussion

With constant evolutions of cataract surgery and IOL technology, physicians continue to explore ways to improve visual outcomes for their patients. Whether that be through improved surgical techniques, Femtosecond laser-assisted cataract surgery (FLACS), or the use of different lens types, the field of ophthalmology continually strives to improve the most commonly performed surgical procedures of cataract extraction with IOL placements. With new advancements, it is important to compare the various surgical treatment options and their respective visual outcomes in an effort to properly validate superiority and to educate patients prior to consenting to surgery.

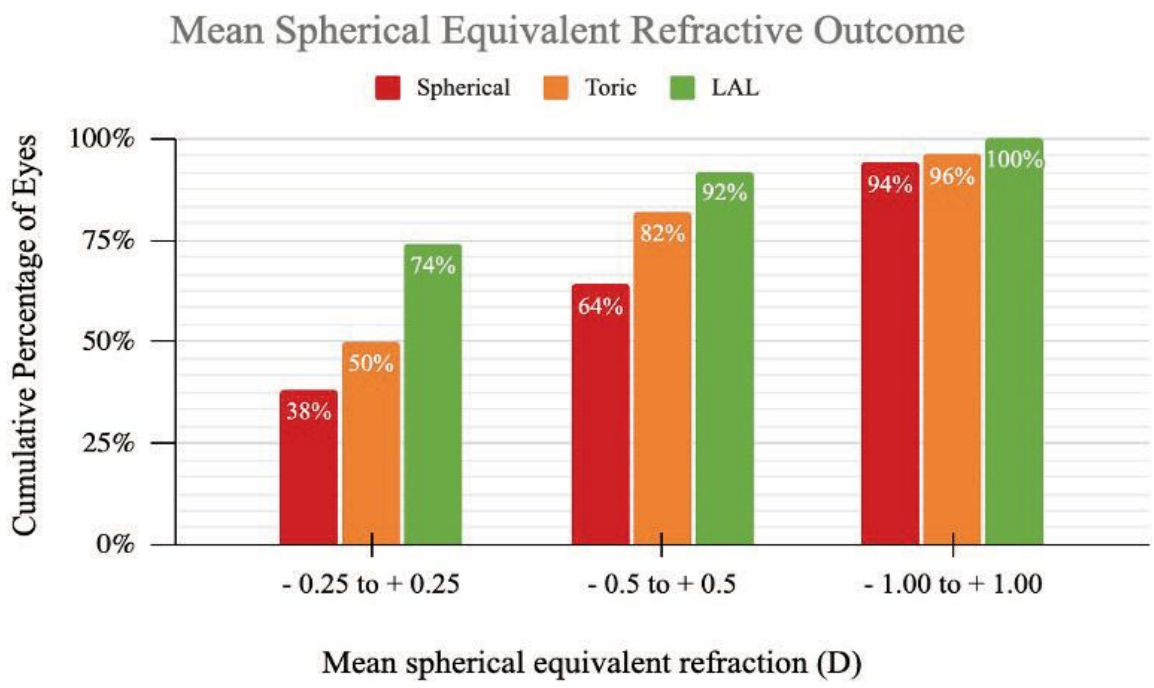


Figure 2. Accuracy of spherical equivalent refraction between different treatment groups status post cataract surgery.

In our study, when looking at monocular UCDVA, compared to the spherical and toric monofocal lenses, the LAL consistently had a higher proportion of eyes reaching better unaided visual acuity. In fact, it was found that LAL patients (64%) were twice as likely to reach 20/20 or better monocular UCDVA compared to the spherical monofocal IOL eyes (32%). This is consistent with the FDA studies of 600 subjects where 70.1% of LAL patients achieved 20/20 compared to 36.3% of the control, spherical monofocal IOL group.[12]

Generally, patients with mild to no corneal astigmatism perform well with a spherical IOL. However, a study of 2,415 patients, all within the prevalent age group for CE, found that on average, 64.4% of patients had corneal astigmatism between 0.25 to 1.25D, and 22.2% had more than 1.50D.[13] Furthermore, astigmatic changes increase with age as much as 10% in a span of a 12-year period.[14] This underlines the importance of astigmatic management with CE by calculating the most appropriate IOL power for each individual, but also choosing the lens type to improve overall visual acuity of the general patient population.

Yamauchi et al. showed that toric monofocal lenses had significantly better postoperative binocular UCDVA, compared to non-toric spherical IOLs of the same material, a finding seen in our results as well as other studies.[15,16] Residual astigmatism is a common refractive error that is observed even after uncomplicated CE and if not addressed, these unexpected outcomes contribute to overall patient dissatisfaction.[17,18] Toric monofocal lenses, compared to spherical monofocal lenses (0.20 ± 0.631D), do remain an effective option to manage corneal astigmatism as seen in our results, achieving MRSE of 0.08 ± 0.386D, but studies have found that residual astigmatism and residual spherical refractive errors are still observed even with toric lenses. This can be due to incorrect preoperative measurements of corneal astigmatism and the inability to predict postoperative astigmatic results, especially in those with low astigmatism. The postoperative residual refractive errors and residual astigmatism can also be due to the misalignment of the lens implanted, postoperative rotation of the toric IOL despite accurate alignment at the time of surgery, or due to surgically induced astigmatism after wound

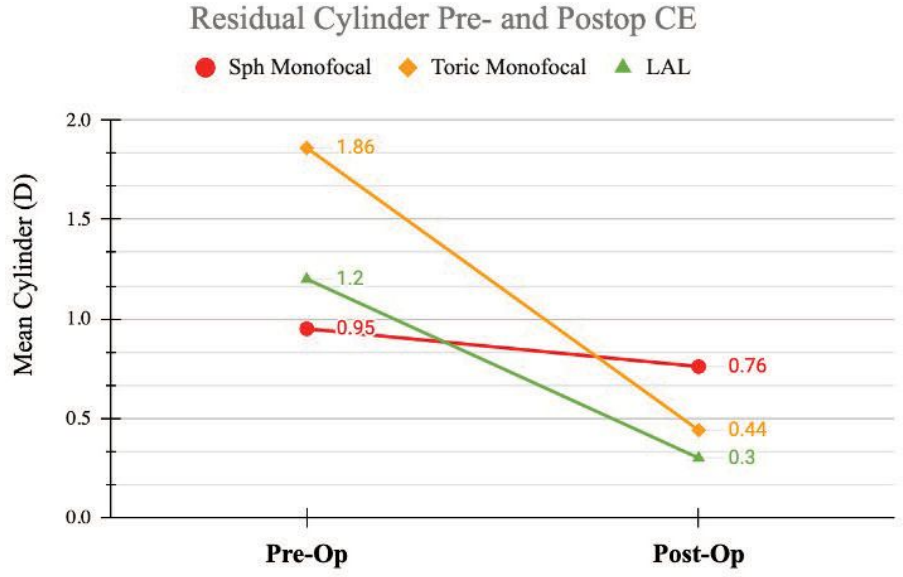


Figure 3. Comparison of change in mean cylinder (D) between pre- and postop CE for different treatment groups.

healing of the incision.[17,19,20] These postoperative results bring up the question of how to adjust the residual astigmatism that can be caused after CE and IOL placement. LAL technology and the ability to adjust the implanted lens even after the procedure can help improve these unexpected visual outcomes.

Our study illustrates that although LAL, spherical monofocal and toric monofocal lenses improve overall visual outcomes in all eyes, LAL lenses excel with the smallest postop mean residual cylinder value of 0.3 ± 0.397D (Figure 3). This data was similar to another study where 100% of patients, who started with 0.75 to 2.0D of corneal astigmatism, achieved MRSE within 0.25D of emmetropia nine months status post LAL adjustments and lock-in.[21] While toric monofocal lenses also improve postoperative MRSE and overall vision, they are still limited to 82% within 0.5 D and 50% within 0.25 D of target, compared to 92% of LALs being within 0.5 D and 74% within 0.25 D of target refraction.

Additionally, LAL lenses had the greatest reduction in mean SEQ, with a beginning preoperative MRSE of -2.8 ± 5.356D to a postoperative 0.0 ± 0.353D of targeted emmetropia, showing not only the smallest MRSE, but also the most efficiency of reducing MRSE compared to spherical and toric monofocal lens types. Hengerer et al. also found similar findings in LAL patients but with an extended follow-up period of 18 months. Their study found a final MRSE of 0.03 ± 0.17 D in LAL patients thus showing the long-term refractive stability of these IOLs.[22]

It is important to understand that the results of LALs rely on patient compliance. Patients are required to wear UV-protective glasses in any presence of ambient outdoor UV light sources for up to four to six weeks or until lock-in is complete. If not, the photosensitive lenses are at risk of photopolymerization and unexpected refractive outcomes. A case study from 2023 discussed a 61-year-old man who required an explanation of his LAL due to self-reported non-compliance of UV glasses wear and resulting uncontrolled polymerization of the LAL.[23] The introduction of ActivShield in the lens has markedly decreased chances of auto adjustment.[24] Patient compliance should be addressed and taken into consideration as physicians recommend the lens to potential candidates.

Conclusion

The visual outcomes of monocular UCDVAs and reduced residual cylinder and MRSE of patients who received LALs objectively exhibit superior results to those of spherical and toric monofocal lenses. A recent study presented at the Association for Research in Vision and Ophthalmology meeting in April 2023 also found that LALs are more cost-effective when compared to surgery with conventional monofocal lenses. The study analyzed the incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted life years (QALY) gained post surgery and found that patients who received LALs, although

more expensive upfront, saw better post-surgical vision outcomes due to its adjustability after implantation. Considering the long-term cost benefits when deciding between different IOL types is important, which can further contribute to overall patient satisfaction.[25] Additional research of increased sample size, long-term postoperative refractive stability are required. Qualitative patient satisfaction studies are also welcomed.

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Adverse Childhood Experiences and Antidepressant Therapy: A Systematic Review

by Dixie Meyer, PhD, LPC, Ali Abid, BS, Awais Paracha, MD, Zohair Siddiqui, MD, Stephanie Chen, MD & McKenna Walsh, MA

If patients confide they have adverse childhood experiences, medical providers will want to consider treatment drug class and establish a plan to monitor the patient carefully for unremitting symptoms, symptoms severity, and suicide risk.



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Abstract

Adverse childhood experiences (ACEs) increase depression risk and may affect antidepressant (ADM) treatment outcomes; however, cumulative research on each ACE in conjunction with ADM outcomes is lacking. This review aims to examine the relationship between ACEs and ADM. We examined PsychInfo and PubMed/MEDLINE databases from 2010-2025 and identified 26 publications that met review criteria (i.e., peer-reviewed and concurrently examined ACEs and ADM). ACEs were associated with an increased propensity to use ADMs, an interaction between DNA methylation and ADM efficacy, an increased risk of suicide while on ADMs, and ADM responsiveness. The majority of the studies show serotonin modulators and stimulators, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors are associated with fewer depressive symptoms in ACE survivors. Multiple ACEs and child abuse impaired ADM effectiveness. Yet, genetic links and age when the ACE occurred may explain this vulnerability. These findings should be interpreted with caution, as cumulatively, the research often had smaller sample sizes in the ACE history groups, research often did not test antidepressants against each other, and reported depression symptom changes in the studies may be organic symptom reduction unrelated to treatment. Before medical providers initiate depression treatment, they should ask their patients about ACE history. If patients confide they have these experiences, medical providers will want to consider treatment drug class and establish a plan to monitor the patient carefully for unremitting symptoms, symptoms severity, and suicide risk.

Adverse Childhood Experiences and Antidepressant Therapy: A Systematic Review

Major depression disorder (MDD) is a debilitating chronic illness that affects 18.5% of adults.[1] Practitioners may focus on depression treatment without considering specific

patient experiences that may disproportionately predict successful outcomes. One specific patient experience, adverse childhood experiences (ACEs)[2] or traumatic incidences such as parental neglect, abuse (psychological, sexual, physical), and household dysfunction (violence, substance abuse, mental health, criminal behaviors) occurring in the first 17 years of life are linked to depression development. In a landmark study, Nemeroff et al.[3] highlighted ACEs may affect depression treatment i.e., antidepressant (ADM) response. Across a 12-week period, Nemeroff and colleagues showed those with a history of childhood trauma responded better to psychotherapy when compared to ADM and combination treatment was only slightly better than psychotherapy alone.

However, prompting more research, the study only used one type of ADM (nefazadone), and the sample sizes representing of specific types of trauma (i.e., parental lose, neglect, and physical or sexual abuse) were small. Since this seminal work, multiple studies substantiated these results showing ACEs predict ADM treatment. A prominent meta-analysis[4] demonstrated that individuals subjected to childhood maltreatment are twice as likely to experience an adverse longitudinal depression course (i.e., persistent, recurrent depression) than those without an abuse history. Furthermore, the meta-analysis reported individuals abused during childhood benefited less from pharmacological, psychotherapeutic, and combined pharmacological/therapeutic intervention than those without a history of maltreatment.[4]

ACEs are associated with depression outcomes,[2] yet research investigating each ACE in conjunction with ADM outcomes is limited. Furthermore, cumulative research to underscore what mechanisms predict the relationship between ACEs and ADM is also scarce. This systematic review aims to expand the childhood maltreatment and ADM research examined in Nanni and colleagues' review[4] (i.e., physical and sexual abuse, neglect, and familial conflict or violence) to include all 10 identified ACEs. To expand the review by Nanni et al.[4], we began our investigation in 2010 to provide current findings examining the relationship between ADM and ACEs. We are not limiting our research to ADM efficacy but rather seek to gain a more comprehensive understanding of the relationship between our variables.

Methods

The protocol was filed with the National Institute for Health Research (PROSPERO) following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols standards.[5] Articles that met initial criteria were discussed in team meetings to establish eligibility. A team-based method was adopted to avoid risk of bias and validate all included studies that evaluated a direct relationship between ACEs and ADM. To examine the quality of the research, we used the Evidence Hierarchy.[6] This tool examines the research design to determine significance of the study in evidence-based practices. Studies are ranked based on research design quality where a rank of one is the highest level reserved for multiple RCTs or a meta-analysis, a rank of two represents RCTs and experiments, level three is for quasi-experimental studies, and a rank of four is the reserved for non-experimental research (Table 1).

Inclusion/Exclusion Criteria

We examined the relationship between ADM and ACEs conjointly in peer-reviewed studies. All research needed to study the direct relationship between ADMs and ACEs. Participants needed a depression diagnosis. Studies that included individuals with bipolar disorders, psychotic disorders, or psychosis were excluded. All medications needed to be classified as antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors).

Searches and Data Extraction

The final article search was completed in January 2025. Seven research team members independently searched journal articles in MEDLINE and PsycINFO, including the dates 2010-current. All searches included the term "antidepressants" concurrently with the following terms: child abuse, child adversity, child maltreatment, adverse childhood experiences, parental divorce and separation, child neglect, physical abuse, sexual abuse, emotional abuse, family mental illness, substance abuse, domestic violence, suicide, grief and loss, and incarceration. The search strategy produced 9,843 results. Duplicate record removal reduced the total records to 7,637. Articles were initially screened by title and abstract, transitioning to full-text analyses as needed. We

Table 1. Rankings in the Strength of the Evidence

Source	Findings	Strength
Björkenstam et al., 2017	8 indicators of Child Adversity were associated with greater rates of ADM drug use (hazard ratio: 1.32, 95% CI 1.25-1.41).	4
Carvalho et al., 2021	After 6-weeks of ADM treatment only parental physical violence was associated with non-remission from depression (x^2=4.348, p= 049)	4
Christensen, et al., 2020	Results showed significant response to vortioxetine on MADRS (10 mg, –2.2, *P* = .025; 20 mg, –4.4, *P* < .001). Participants with trauma more likely to relapse (hazard ratio 2.8, *P* = .0019).	1
González-Chica et al. 2019	ADM use up to over 4x more likely in those who were sexually abused (odd ratio ranged from 2.02-4.53).	4
Harkness et al., 2023	Emotional maltreatment by the mother was a significant and direct predictor or lower odds of remission at 16 weeks (odds ratio [OR] = 1.68, *P* = 0.02).	2
Harkness et al., 2012	Participants with child abuse history in the CBT or ADM group had improved treatment response over the interpersonal psychotherapy group (Odds ratio: 3.61). Those with a child abuse history more likely (Odds ratio: 3.04) to experience depressive symptom reoccurence.	2
Kim et al., 2013	Depressive patients who experienced physical (mean 36, p= .001) or sexual abuse (mean = 35.7, P< .001) had higher BDI scores and suicide attempts (31.6%, p= .019; 35.8%, p= .008) respectively and (39.7%, p=.002; 36.6%, .038) presence of suicidal ideation at endpoint. History of parental separation was not associated with suicidality or depression.	4
Koskenvuo & Koskenvuo, 2015	ADMs were the most likely used drug (17.6%). Psychotropic drug use was most associated with family member fear, which increased risk for multiple antidepressant and psychotropic drug use odds ratio: 3.08 (95% CI 2.72-3.49). History of family conflicts was also associated with increased risk Odds ratio 2.10 (95% CI 1.87-2.35).	4
Medeiros et al., 2021	Participants with childhood maltreatment had more severe depressive symptoms (p < .001) and a larger response to ADM (p= .004) than those without. They had no differences in ADM dosages, they did not have a differential of improvement in depressive symptoms from those without. Neither the type of medication nor the age of the maltreatment impacted the depressive symptoms.	2
Menke et al., 2021	Participants with childhood trauma were not more resistant to ADM treatment.	4
Niciu, et al., 2015	Participants who experienced early life parental loss or separation had greater treatment response while the other indicators of early life stress or trauma was not associated with greater treatment response [F(1,35)=6.65, p=0.01].	4
Nikkheslat et al., 2020	Participants in the non-responder group had higher rates of childhood trauma compared to responders U = 1261.00, z = -2.259, p= 0.024).	3
Quilty et al., 2015	Of the 'low serotonin affinity' medication group β = 0.63, t = 2.97, p<. 01, participants who reported childhood abuse had poorer treatment outcomes when compared to the 'high serotonin affinity' medication participant group. β = 0.24, t = 1.31, p = 0.19.	3
Raghavan et al., 2014	Compared to the sample-matched group of children, children with a history of neglect and abuse were more likely to be prescribed a psychotropic drug. ($82 more, P <.001).	4
Read et al., 2014	Many adults believed abuse or neglect in childhood (85.4%) were the cause of depression.	4
Shamseddeen et al., 2011	Participants who did not experience physical or sexual abuse showed greater efficacy with combination therapy than with medication only (62.8% vs 37.6%). History of sexual abuse unrelated to treatment outcomes. Participants who experienced physical abuse had poorer outcomes to combination therapy (18.4% versus 52.4%).	2
Shen et al. 2020	Interactions between DNA methylation and early-life stress suggests an association with decreased treatment response at two CpG sites (TPH2-5-203, FDR corrected p=0.010; TPH2-10-60, FDR corrected p=0.001).	4
Shi et al., 2012	Variation in genes involved in the CaMK pathway but neither the cAMP-PKA and Ras-MAPK pathways were positively associated with remission. No difference in CTQ and LES scores was found in participants with and without remission. The genes of interest also showed no interaction with childhood abuse and negative life events.	3
Singh et al., 2013	Risk of suicidality was lower in participants without child abuse history (7.6%) when compared to participants with low (38.5%, p = 0.041) or high impact abuse (58.3%, p = 0.009). After controlling for depression severity, the low impact group was not associated with increased suicidality. The high impact group had significantly higher risk of suicidality (OR = 31.5, 95% CI = 1.3 to 748.7, p = 0.03).	3
Singh et al, 2015	No subjects with high impact abuse remitted whereas 77% reporting low impact remitted. Subjects reporting high impact abuse had a 50-fold greater odds of carrying the rs2242446-TT genotype (95% confidence interval=4.85-514.6).	3
Sung, et al., 2013	Differences between early and late-onset MDD were not found regarding treatment response after 12 and 28 weeks.	2
Wang et al., 2022	Interaction between ADM response and childhood trauma score and P11-3-185 site methylation (OR = 0.297, FDR-corrected *P* = 0.023), physical neglect and P11-2-117 site methylation (OR = 0.005, FDR-corrected *P* = 0.033)., and emotional abuse and P11-3-185 site methylation (OR = 0.001, FDR-corrected *P* = 0.023).	3
Williams et al., 2016	Those who were abused between the ages 4-7 years (chi-square=72.769, df=12, *P*<0.0001) were 1.6 times less likely to respond to ADM treatment (*P*=0.034; OR=1.574) or remission (*P*=0.032; OR=1.606).	2
Xu et al., 2016	One polymorphisms TPH2 SNP rs2171363 showed a significant interaction with a history of childhood trauma (β=-2.432, SE=1.060, OR=0.088, 95%CI: 0.011-0.702).	4
Yang et al., 2021	After 12 weeks of antidepressant monotherapy there was a significant difference in rates of remission between participants with ACEs and those without 15.2% and 32.2% respectively	3
Zisook et al., 2019	History of ACEs predicted remission by week 12 (remission mean= 2.9, no remission mean = 3.2, hazards ratio: 0.95 95% CI=0.92, 0.99, p=0.02.	2

removed studies that did not have a relevant discussion of ACEs and ADM within the title, abstract, or keywords (n = 7,526); thus, 113 articles were eligible to be screened. Records were screened for ADM and ACEs conjointly. This review included 26 articles after excluding samples with other mental health diagnoses (n=29) and studies not directly examining the relationship between ACEs and ADM (n=58). At least two reviewers independently analyzed all articles and conferred on eligibility (Figure 1).

Results

This review focused on themes that emerged when analyzing data from relevant studies. Our thematic synthesis[7] followed a three-stage process, beginning with the rote reiteration of results (to maintain proximity to the data), moving on to descriptive coding (to organize shared characteristics), and culminating in analytical themes. Research articles (n=26; combined samples N=520,612) included cohort (n=7), cross-sectional (n=3), case series (n=6), randomized clinical trial (n=7), and quasi-experimental (n=3) designs. Results are organized by five themes emerging from the findings: Epigenetics (total sample size for Epigenetics, n=723), ADM Efficacy (n=6,872), ADM and Counseling (n=587), Suicidality (n=970), and Population characteristics (n=512,274).

Population Studies

Population-based studies show ACEs increase the likelihood of ADM use in adults and children.[8-12] Most of the studies analyzed multiple ADMs alongside various ACEs. Kosenvuo and Kosenvuo[9] found that individuals who experienced parental divorce or separation, financial difficulties, serious family conflict, fear of family members, or a family member who had a severe illness or alcohol-related issues were more likely to use ADMs with the highest odds ratios (OR; threefold greater) reported with individuals who feared a family member followed by those who experienced family conflict (twice as likely). Björkenstam et al.[10] examined three databases to assess childhood adversity (i.e., psychiatric morbidity, public assistance, parental death, substance abuse, separation, residential instability, criminality, and child welfare intervention). All measured childhood adversities predicted depression with a graded association showing hazard ratios (HR) were highest for those with four or more ACEs (HR: 3.05, 95% CI 2.83-3.29) and increased likelihood for ADM usage (HR: 1.32, 95% CI 1.25-1.41). González-Chica et al.[11] assessed ADM trends by sexual abuse. OR for ADM use varied from ranged from 2.02-4.53 for sexual abuse and OR dependent on the age of onset and duration of ADM use. Raghavan et al.[12] examined Medicare expenditures in a sample of children with suspected maltreatment (i.e., physical abuse, sexual abuse, abandonment, and neglect) and a comparison sample. Children with suspected maltreatment were more likely to use ADMs, as demonstrated by average Medicaid expenditures ($82 more/year), than controls. Read et al.[8] investigated antidepressant beliefs using a convenience sample of all ADMs prescribed in the previous five years. Respondents reported beliefs about what factors were related to depression etiology. Most respondents (85.4%) reported that child abuse and neglect contributed to depression.

Suicidality

Studies examining suicidality used adult populations and observed more suicidality in participants with a history of abuse at baseline prior to initiation of ADM treatment.[13,14] Kim et al.[13] investigated changes across 12 weeks of ADM treatment. Singh et al.[14] investigated the first week of treatment. Singh et al.[14] used an SNRI or SSRI only, whereas the Kim et al.[13] study included SSRIs (44.4%), dual-action ADMs (41.1%), a different conventional ADM (3.2%), or nothing (11.3%). Kim et al.[13] examined parental separation, physical abuse, and sexual abuse. Singh et al.[14] generically noted "child abuse," distinguished by abuse intensity. Kim et al.[13] reported that sexual and physical abuse by parents were associated with more depressive symptoms, regardless of ADM type. Individuals who had suffered physical abuse were more likely to require augmentation and a combination of pharmacological treatments following their initial ADM treatment.[13] Singh et al.[14] showed that individuals without childhood abuse had a decreased likelihood of suicidality after ADM treatment in the first week, and those with high-impact abuse showed increased suicidality while on ADMs after controlling for depression severity.

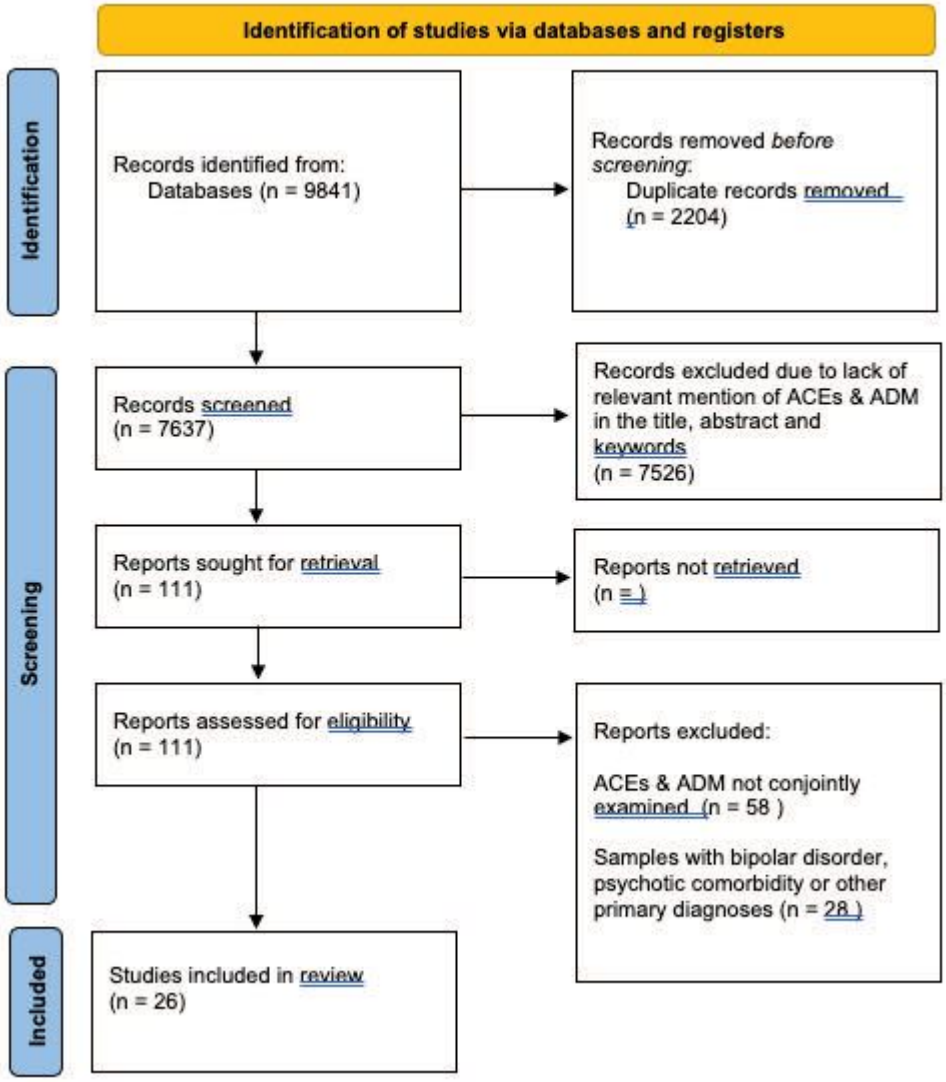


Figure 1. PRISMA 2020 flow diagram of studies in the systematic review

Epigenetics

Five studies examined ACEs and epigenetic changes in DNA to evaluate the course of ADM therapy. The studies examined unique single nucleotide polymorphisms (SNPs), except one study that examined P11 gene DNA methylation at CpG sites.[15] Two studies[16,17] investigated specific SNPs expressed in serotonergic neurons, one study examined the calcium/calmodulin-dependent protein kinase pathway (CaMK),[18] and the final study examined norepinephrine transporter SNPs.[19] ADM treatment included two weeks,[15,17] six weeks,[16] and eight weeks.[18,19] All studies used SSRIs and SNRIs,[16, 18,19] with two studies also including noradrenergic and selective serotonergic antidepressants (NaSSAs) and serotonin antagonists and reuptake inhibitors (SARIs).[15,17] Xu et al.[16] observed interaction effects between TPH2 methylation and ACEs (SNP rs2171363), suggesting associations with ADM response and early life stress. Shi et al.[18] reported that, although there were significant positive gene associations in the CaMK pathway to antidepressant response, there were no observable significant short-term ADM effects related to ACEs. Singh et al.[19] reported that participants with high-impact child abuse were more likely to carry the rs2242446-TT genotype and were less likely to experience depression remission related to ADM treatment. Wang et al.[15] examined methylation at CpG sites of the P11 gene. They found elevated methylation in MDD patients with ACE histories and noted that this might affect ADMs short-term responses. Shen et al.[17] examined the effects of ACEs on tryptophan hydroxylase 2 (TPH2)—a gene involved in serotonin biosynthesis. A high trauma score was associated with DNA hypomethylation in males at TPH2-8-237 and is related to ACEs and ADM treatment outcomes. Hypermethylation at TPH2-5-203 in males and TPH2-10-60 in females, coupled with early-life stress, was associated with a weaker ADM response.[17]

ADM Efficacy

Twelve studies examined the relationship between ACEs and ADM response rates in adults. Treatments ranged from four weeks,[20] six weeks,[21,22] eight weeks,[23-25] 12 weeks,[27-30] 16 weeks,[26] to 26 weeks.[31] One article analyzed a single-blind randomized study testing outcomes from the first 12 weeks.[29] Six studies found a lower ADM response rate in patients with ACEs.[21,23,25,28,30,31] One study reported those with child maltreatment had the highest response rate to ADMs when compared to those without a history of maltreatment and to psychotherapy options.[26] Two studies did not find ACEs were associated with differential response rates,[20,29] and the other three studies did not directly test this outcome.[22,,24,27] Quilty et al.[31] reported that those who experienced overall abuse, neglect, or physical abuse were less likely to respond to low-serotonin affinity medications (e.g., mirtazapine, moclobemide) as compared to high-serotonin affinity medications (e.g., paroxetine, venlafaxine) and had more depressive symptoms following ADM use. Zisook et al.[28], in their sample of initial ADM non-responders, noted that those with remitted depression from subsequent ADM treatment were less likely to report ACEs. Nikkheslat et al.[21] found that more exposures to ACEs were linked to ADM non-responsiveness, regardless of cortisol levels. Harkness et al.[25] reported that when mothers were emotionally abusive, the participant was less likely to respond to escitalopram or escitalopram augmented with antipsychotic medication. When the father was emotionally abusive, and the participant had a history of physical abuse, they were less likely to respond to antidepressant use, which may be indirectly related to anhedonia symptoms. Williams et al.[23] found that physical, emotional, and sexual abuse between the ages of four and seven led to poorer ADM responses in adulthood. Those taking sertraline exhibited more modest improvement than those using escitalopram or venlafaxine-XR. Sung and colleagues[27] found those with a history of ACEs were more likely to experience earlier onset, chronic, and recurrent depression regardless of ADM type (SSRIs, 44.4%), dual-action (41.1%),[13] different conventional ADM (3.2%), or no ADM prescribed (11.3%).[13,26] Christensen et al.[24] reviewed four studies in a meta-analysis and demonstrated that vortioxetine could be more effective than a placebo in preventing depressive symptoms in ACE-exposed individuals. Carvalho et al.'s[22] observational study following depressed outpatients undergoing pharmacological treatment found that, by week six, only physical paternal-related violence was associated with non-remission. Menke et al.[20] did not find ACEs were associated with differential ADM treatment response. Yang et al.[30] examined developmental effects of ACEs on hypothalamic pituitary adrenal (HPA) axis function and ADM strength. The study found depression was higher among those who had experienced ACEs. Cortisol and adrenocorticotropic hormone (ACTH) levels were positively associated with total scores on the CTQ and scales reporting depression and anxiety. After the 12-week ADM monotherapy, remission was much higher in those without ACEs, with cortisol and ACTH levels adjusting accordingly. Initial measurements of ACEs, ACTH, and cortisol predicted long-term ADM treatment.

ADM and Counseling Response

Three studies examined counseling compared to and in conjunction with ADM in those with ACEs. All studies tested cognitive-behavioral therapy (CBT)[25,32,33] and interpersonal psychotherapy (IPT).[25] All studies sampled adults. Niciui and colleagues[33] examined CBT and ADM; Harkness et al.[25] compared CBT, IPT, and ADM; and Shamseddeen et al.[32] compared an SSRI to an SNRI alone and in combination with CBT (four sessions). Treatment length included 12 weeks[32,33] or 16 weeks.[25] Harkness[25] examined emotional abuse, neglect, sexual abuse, and physical abuse and used ADMs (e.g., bupropion, citalopram) determined by a psychiatrist. Participants with ACEs responded less favorably to IPT than CBT or ADM and were more likely to experience recurrent depression sooner than those without ACEs. Response rates between CBT and ADM treatment in those with a history of maltreatment were similar. Participants in the Shamseddeen et al.[32] study were treated with fluoxetine, paroxetine, or venlafaxine. Those with a history of physical or sexual abuse responded more to ADM alone compared to counseling plus ADM. In contrast, those without an abuse history responded more to combination treatment over ADM alone. Niciu et al.[33] found that parental loss or separation was linked to ADM responsiveness in conjunction with CBT.

Discussion

Findings overwhelming support individuals with ACEs are more likely to use and need ADM treatment[9-12] with many individuals attributing depression to ACE history.[8] Cumulative findings suggest that individuals with ACEs history and depression receiving ADMs should be monitored for response concerns. Individuals with ACEs, excluding parental divorce or separation,[13] are more likely to experience chronic, recurrent depression with more severe symptoms irrespective of ADM type,[27,28,31] are less likely to respond to ADM treatment, and are at risk for suicidality.[13,14] Poor trajectories may only be significant for those who experience multiple ACEs,[23] or experienced abuse,[13,14,19,21,23,25,28,31] and it may be dependent on the abuse perpetrator.[25] Previous research shows ACEs reduce ADM efficacy[2,3] and that cortisol dysregulation may contribute to depression,[34,35] possibly affecting ADM efficacy.[36] Recent research, however, did not support a correlation between cortisol and its relationship to outcomes.[19]

While not all ADMs were tested or equally tested, it appears high-serotonin affinity ADMs provide more relief for depressive symptoms for those with ACEs than low-serotonin affinity ADMs.[31] Multiple studies support the efficacy of vortioxetine,[24] venlafaxine, fluoxetine, paroxetine, and citalopram/escitalopram in treating individuals with ACEs.[23,31] Findings should be interpreted cautiously, as few studies compared ADM types. Instead, they often tested against placebo[24] or acknowledged that all tested ADMs indiscriminately showed reduced efficacy in individuals with ACEs.[27] Adults who experienced physical, emotional, or sexual abuse in preschool or early school age may respond better to escitalopram and venlafaxine-XR than sertraline.[23] Experiencing ACEs, when cognitive understanding affects trauma processing, may create a disposition that facilitates helplessness due to vulnerabilities and dependence evident in childhood. Adolescents with a history of physical abuse may respond better to fluoxetine, paroxetine, or venlafaxine over counseling,[32] again showing a developmental predisposition where younger individuals could lack the cognitive capacity to process trauma.

Counseling Findings Are Inconsistent

Research suggests pharmacological intervention may be the best treatment for adults with ACEs, but counseling outcomes could depend on ACE type. Adults who experienced neglect or physical, emotional, or sexual abuse in childhood were more likely to respond to ADM or CBT over IPT, with ADM showing the most benefit.[26] Processing trauma in counseling may facilitate re-exposure, resulting in a reexperiencing of the traumatic event that impedes patients' ability to cope. Other adverse experiences may be linked to a window of opportunity for symptom reduction associated with conjunctive treatment. Adults who experienced parental loss or separation in childhood may experience more symptom reduction from ADM treatment combined with CBT.[33] When viewed from an epigenetic lens, research indicates there may be an interaction effect between ACEs and particular SNPs altering serotonin or norepinephrine expression.[14,16,17] This interaction is expected as research highlights specific ADM-related phenotypic expression and hypo/hypermethylation related to childhood stress.[37]

Psychopharmacology research further substantiated findings noted in the Nanni et al.[4] review (i.e., individuals with ACEs report more severe chronic depression and are less responsive to ADMs). Epigenetics is poised to advance the field as a promising approach to developing therapies that target and treat depression. Researchers have known for years that depression may have genetic etiologies.[38] Several genes may predispose one to depression (for a review, see Jiang et al.).[37] Specifically, epigenetic modifications and gene variations like SERT and TPH2 are linked to ACEs[39] and may affect treatment outcomes (see Xu et al.).[16] Based on cumulative literature analysis, a coherent narrative establishes the chronology that ACES could create an epigenetic gene alteration that may play a crucial role in the pathophysiology of depression and result in varied treatment responses.

Limitations and Future Research

ACEs are prominent in our society, and people need help coping with early childhood experiences that impair daily functioning. A literature review revealed many studies have yet to comparatively investigate all the ACEs concurrently, creating

significant confounding factors that may cloud the results. Many ACEs were rarely investigated or were grouped without differentiating unique experiences to assess depression outcome differences. Additionally, since the assignment of ACE status often relied on self-report, response and recall biases are likely. Finally, many studies reported changes in depression symptoms across a specific timeframe in relation to treatment (e.g., 12 weeks). Yet, we expect that depression scores would change longitudinally, regardless of treatment. Depression score changes could reflect a phenomenon known as regression towards the mean whereby as time passes scores naturally drift toward to an average score.

Future research should extend the ACEs literature to examine less frequently studied ACEs, such as substance abuse in the home, family violence, and parental mental health concerns. As some studies noted, abuse may predict more severe depression than other ACEs, suggesting that ACEs should be tested independently. There was a dearth of research examining the use of counseling, principally in comparison to or in conjunction with ADM. More rigorous research is required to test the synergistic effect of combined counseling and ADM and to compare counseling to ADM types.

Conclusion

Given that individuals with a history of ACEs are more likely to relapse from depression and that ADMs are less effective for those with a history of multiple ACEs or a history of neglect or abuse, the findings warrant a discussion to address best practices for those with ACEs. Vortioxetine, venlafaxine, fluoxetine, paroxetine, and citalopram may be helpful medications for individuals with depression and ACEs. The current data shows that counseling may be helpful in both isolation and conjunction with ADMs for those with an ACE history if child development, risk factors, and counselors and medical providers partner in patient care. If integrated care options are not available, the medical provider may need to provide more mental health support for patients. Medical providers need to assess patients with an ACE history for chronic depressive symptoms, symptom severity, and treatment response as well as for suicide risk. Scheduling more follow-up appointments for high risk patient can give providers opportunities to ensure the patient is experiencing some relief from their depression and are content with their treatment.

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Recent Advances in Rheumatology

by Kent Kwas Huston, MD

The purpose of this review is to broaden knowledge of mechanistic and therapeutic advances in rheumatology and foster a greater appreciation of current management principles related to autoimmune rheumatic disease.



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Abstract

There are too many topics for this article to represent a comprehensive and thorough review of rheumatology. Instead, this paper will focus on advances which would be of interest to a general medical audience. Highlighted are the more commonly encountered rheumatic diseases as well as uncommon disorders that are of significant interest as they expand our understanding of biologic mechanisms of disease. We will take a tour from rheumatoid arthritis to a fascinating new entity called VEXAS. The purpose of this review is to broaden knowledge of mechanistic and therapeutic advances in rheumatology and foster a greater appreciation of current management principles related to autoimmune rheumatic disease.

Rheumatoid Arthritis

As the most common autoimmune disease encountered by rheumatologists it is worth spending some time reviewing advances in rheumatoid arthritis (RA). Referral to a rheumatologist is appropriate whenever a physician is concerned about a patient having inflammatory arthritis based on joint pain and swelling, prolonged morning stiffness, elevated inflammatory markers, erosions on radiographs or positive serologies including rheumatoid factor and anti-citrullinated peptide antibodies (commonly referred to as ACPA or CCP). More recently, additional tests such as anti-mutated citrullinated vimentin, anti-carbamylated protein antibodies and 14-3-3eta are being reported on so called RA panels. Although the underlying biology is fascinating, the clinical utility and exact role of more novel autoantibodies and protein levels in diagnosing RA is still unclear. There is much interest in developing a multiple biomarker assay to diagnose and predict clinical response in RA.[1] Until more data are available, the standard tests to consider are still the rheumatoid factor, CCP, inflammatory markers and radiographs of the hands and feet. Interestingly, a recent study questioned the standard practice of obtaining baseline radiographs in RA.[2]

Upon diagnosis of RA, there are a myriad of treatment options. Fortunately, the American College of Rheumatology has published evidence-based treatment guidelines.[3] Methotrexate remains the standard of care for moderate to severe RA and hydroxychloroquine is recommended for patients with low disease activity. The guidelines recommend against long term glucocorticoids given concerns over potential toxicity although short term steroids are not infrequently used due to the prolonged time it takes to

attain efficacy of methotrexate and related disease modifying antirheumatic drugs (DMARDs). There is significant interest in limiting the use of glucocorticoids for many rheumatic diseases as will be discussed further. For patients who do not reach the target of low disease activity or remission after an adequate trial of methotrexate, the guidelines recommended adding a biologic DMARD over triple therapy (hydroxychloroquine and sulfasalazine added to methotrexate). However, there is still debate in the rheumatology community regarding the utility of triple therapy versus biologics based on numerous studies.[4]

There are now multiple biologic and targeted synthetic drugs to choose from for treatment of RA. These target a variety of immunologic pathways including TNF (infliximab, etanercept, adalimumab, certolizumab, golimumab), IL-6 (tocilizumab & sarilumab), T cells (abatacept), B cells (rituximab) and Janus kinase (JAK) (tofacitinib, upadacitinib, baricitinib). The optimal biologic varies by patient and there is strong interest in developing biomarkers which predict an individual patient's response to inhibition of these pathways. For now, the choice is based on patient characteristics and shared decision making in the clinic. For example, TNF inhibitors are avoided in patients with a history of multiple sclerosis or significant systolic heart failure, abatacept is less favored in those with severe COPD, and IL-6 inhibitors are discouraged in patients with diverticulitis. The FDA placed a black box warning on JAK inhibitors based on a large post authorization study of tofacitinib indicating possible increased risk of major adverse cardiovascular events and malignancies compared with TNF inhibitors.[5] Currently, JAK inhibitors are recommended only for patients who failed at least one TNF inhibitor.

The advent of multiple highly effective treatments for RA has resulted in a major shift in prognosis for this disease. Extra-articular manifestations such as rheumatoid nodules have become less common although mortality remains increased in patients with extra-articular disease.[6] Data suggest that long term functional outcome has improved in the modern treatment era especially in those with good clinical response to medications.[7] However, cardiovascular risk related to chronic inflammation remains a major concern.[8] Cardiovascular complications related to RA have been long recognized and include atherosclerosis, congestive heart failure, pericarditis and arrythmia. Cardiovascular disease is a leading risk of early mortality in RA.[9] Systemic inflammation is now a well-recognized component of atherosclerotic pathogenesis and RA can be considered a risk factor for atherosclerotic heart disease. Indeed, RA disease activity has been associated with risk of cardiovascular events.[10]

The interplay of risk factors for cardiovascular disease in RA is complex. Interestingly, RA patients tend to have low levels of total cholesterol and LDL which tend to increase after initiation of immunosuppressive medications without increasing cardiovascular risk.[11] Initiation of statins and addressing other cardiovascular risk factors is known to reduce the risk of cardiovascular disease in RA. In addition, there is emerging evidence showing that immune modulatory treatment of RA, with either conventional synthetic medications such as methotrexate or biologic therapy including TNF inhibitors, abrogates cardiovascular risk in RA patients.[12,13] Furthermore, anti-inflammatory therapy has now been shown to reduce cardiovascular events in the general population without RA.[14,15] Another potential pathway for reduction of cardiovascular risk relates to emerging interest in exploring the role of glucagon-like peptide-1 receptor agonists in reducing both disease activity as well as cardiovascular outcomes in patients with inflammatory diseases including RA.[16]

Psoriatic Arthritis

Like rheumatoid arthritis, psoriatic arthritis (PsA) can cause irreversible joint damage and deformities. Patients with PsA have varied clinical presentations. PsA can mimic RA with a symmetric polyarthritis of the small joints, present as an oligoarthritis with asymmetric involvement of larger joints, or with axial disease including sacroiliitis and spondylitis. Other clues to psoriatic arthritis include the presence of nail pitting, dactylitis (sausage digits) or enthesitis (inflammation at insertions of tendons and ligaments to bone). Most patients with PsA have a history of psoriasis. However, approximately 10% of patients experience the onset of arthritis prior to skin involvement.

The explosion of immunologic knowledge in the past few decades has led to multiple biologic therapies becoming available for PsA. TNF inhibitors have been successfully used to treat this disease for over two decades. More recently the IL-23/IL-17 axis has been implicated as key driver of PsA via multiple basic science studies.[17] Capitalizing on this research, several molecules inhibiting IL-23 and IL-17 have

been developed and are now approved to treat PsA. Currently approved drugs targeting the IL-23 pathway include ustekinumab, guselkumab, and risankizumab while secukinumab, ixekizumab, and bimekizumab target IL-17. T-cells participate in the pathogenesis of PsA and inhibiting activation of T cells with abatacept is also an effective therapy.[18] The Janus kinase pathway has also been implicated. JAK inhibitors (tofacicinib and upadacitinib) are approved for PsA.[19] Another novel medication now approved for PsA is apremilast.[20] This phosphodiesterase 4 inhibitor is thought to suppress downstream expression of pro inflammatory cytokines and can be used in mild PsA. Interestingly, apremilast is also effective for treatment of oral ulcers in Behcet's.[21] With the advent of multiple targeted medications as well as older conventional synthetic DMARDs, the treatment of PsA has become much more effective and complicated. The American College of Rheumatology has published treatment guidelines for PsA.[22]

Biosimilars

Biologic therapy has revolutionized the treatment of multiple autoimmune diseases. However, this comes with a significant societal cost. These drugs are much more complex than traditional medications. Biologics are made by incorporating DNA into living cells utilizing recombinant technology to transcribe and translate the molecular code into a full-length protein. The function of monoclonal antibodies depends on their three-dimensional structure which in turn is dependent not only on the primary amino acid sequence of the molecule but also on proprietary manufacturing techniques. The three-dimensional structure is altered by post translational modifications dependent on the manufacturing process. Therefore, it is not possible to make a generic version of a biologic drug. Recognizing this, the Biologics Price Competition and Innovation (BPCI) Act of 2009 created a regulatory pathway for approval of mediations deemed biosimilar to the original biologic drug. To reduce development costs, biosimilars are approved based on less data compared with reference products. Initial skepticism regarding safety and efficacy has eased since approval of the first biosimilar in rheumatology in 2016. Clinical experience and mounting data have encouraged continued development and use of biosimilars.[23]

Of note, biosimilars are not more effective than the original product and the decision to use a biosimilar is solely economic and typically driven by a patient's insurer. There are currently biosimilars available for infliximab, adalimumab, rituximab and tocilizumab. The American College of Rheumatology has published a white paper on biosimilars as well as a position statement.[24,25] The ACR supports the use of biosimilars when initiating a new medication and opposes insurance company mandated forced switching of patients on established therapy. Unfortunately, insurance companies commonly force patients to switch therapy even when the patient's autoimmune disease has been under excellent control with an originator product.

Lupus

Systemic lupus erythematosus is a complex autoimmune disease which can affect any organ system. It remains a prime example of autoimmunity for many researchers. Multiple immunologic abnormalities have been described and patients develop a large array of autoantibodies. B cells are heavily implicated in lupus pathology. A monoclonal antibody that targets B cell activation (belimumab) was approved for lupus in 2011 and for lupus nephritis in 2020.[26,27] This was the first biologic therapy approved for lupus and stimulated interest in development of biologics targeting other pathways in lupus.

Type I interferons have emerged as one of the more clinically relevant cytokines over the last several of decades of lupus research.[28] Interferons regulate the immune response to viral infections. There is evidence that upregulation of interferons is also a key factor in lupus pathogenesis. Genetic signatures taken from peripheral blood mononuclear cells of lupus patients show upregulation of the interferon pathway and serum levels of interferon alpha are elevated. This is thought to be a major driver of lupus autoimmunity. Recent immunologic developments have been translated into the clinic with the advent of a drug which blocks type I interferon receptors called anifrolumab. This drug has been shown reduce lupus activity in a phase 3 study using a composite score of lupus activity.[29]

Another recent success in the treatment of lupus is voclosporin, which was approved for lupus nephritis in 2021.[30] This calcineurin inhibitor, used in combination with mycophenolate, has potential advantages over cyclosporin and tacrolimus in that it does not require monitoring of drug levels. Outcomes of lupus nephritis have been frustrating for clinicians and patients for many years. There is now interest in

combining multiple medications targeting different immunologic pathways to prevent end stage renal failure in patients with lupus nephritis.

Scleroderma

Scleroderma is a much-feared autoimmune disease depicted, by Osler as "one of the most terrible of all human ills," causing one to be "beaten down and marred and wasted until one is literally a mummy encased in an ever-shrinking, slowly contracting skin of steel."[31] Clearly, Osler was referencing diffuse scleroderma which causes widespread skin tightness rather than limited scleroderma, which causes tight skin distal to elbows and knees (either can affect the face). The early phase of progressive skin tightness in diffuse scleroderma is now known to respond to immunosuppressive treatment although many patients remain refractory to traditional medications.

Ever since ACE inhibitors were shown to be effective for renal crisis, the major risk of death in scleroderma is related to pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). Monitoring with pulmonary function tests, chest CT and echocardiograms is recommended for scleroderma patients.[32] There are now multiple medications targeting various pathways available for treatment of PAH and combination therapy is typically used. These therapies have likely improved survival in the modern treatment era.[33] There are also several options for patients with scleroderma related ILD. Although cyclophosphamide demonstrated efficacy in the first large, randomized trial of scleroderma lung disease, most clinicians prefer mycophenolate due to comparable efficacy and a more favorable side effect profile.[34,35] Tocilizumab has been approved for scleroderma ILD based on two randomized clinical trials.[36] Antifibrotic therapy has also been shown to have a role in management of scleroderma ILD. Nintedanib, a tyrosine kinase inhibitor approved for idiopathic pulmonary fibrosis, has also shown to be effective in randomized trials of scleroderma ILD.[37] These and future advances will hopefully make descriptions such as Osler's of historic interest only.

Polymyalgia Rheumatic and Giant Cell Arteritis

Polymyalgia Rheumatic (PMR) and Giant Cell Arteritis GCA are distinct but associated entities. Patients with GCA can present with PMR symptoms and clinicians need to query patients with PMR regarding symptoms of GCA such as headaches, vision changes and jaw claudication. Any patient over the age of 50 presenting with a new onset headache should be screened for GCA with a sed rate and c-reactive protein. Both conditions have traditionally been managed with long term glucocorticoids often for more than one year. Because of the significant risk of adverse effects related to glucocorticoids including weight gain, loss of bone density, infections, cataracts, glaucoma, hyperglycemia, elevated blood pressure, avascular necrosis, and increased cardiovascular risk there has been longstanding interest in developing steroid sparing therapies for these conditions. Although there is evidence supporting the use of methotrexate, the results have not been consistent. Based on studies of the proinflammatory cytokine IL-6 in PMR and GCA, clinical trials have now shown that blocking this pathway is an effective treatment for both conditions.[38,39] Although IL-6 inhibitors do not eliminate the need for glucocorticoids, they can significantly reduce the cumulative exposure to steroids and resulting toxicity. Hopefully, future studies will show that other biologics, targeting different immunologic pathways, will also be effective and further diminish our reliance on glucocorticoids in management of PMR and GCA.

ANCA Associated Vasculitis

ANCA (anti neutrophil cytoplasmic antibody) associated vasculitis includes granulomatosis with polyangiitis (GPA, formerly known as Wegener's), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss). ANCA refers to the immunofluorescent test used to screen for these diseases. Autoantibodies targeting proteinase 3 (PR3) and myeloperoxidase (MPO) are more specific for vasculitis compared to the ANCA immunofluorescence test. Clinical presentations vary and can include a migratory polyarthritis, purpuric rash, upper and lower respiratory tract inflammation, scleritis, mononeuritis multiplex, and pauci-immune glomerulonephritis among others. EGPA is a consideration in patients with a history of asthma.

The substantial morbidity and mortality associated with ANCA vasculitis was significantly diminished after a trial demonstrated efficacy of cyclophosphamide.[40] However, may patients suffered adverse effects from long term cyclophosphamide including hemorrhagic cystitis, bladder cancer, and hematologic malignancies.

Interest in alternative treatments for vasculitis lead to a large randomized controlled trial of rituximab which reported noninferiority compared to cyclophosphamide for the induction of remission in GPA and MPA.[41] Nowadays, rituximab is the preferred agent for both GPA and MPA due to it favorable sided effect profile compared with cyclophosphamide. High doses of glucocorticoids are typically used along with targeted therapy to treat vasculitis. Concern for adverse effects of steroids lead to a trial of a complement 5a receptor antagonist called avacopan as a steroid sparing agent.[42] Although steroids are still required, avacopan allows a more rapid taper and decreased cumulative dose of glucocorticoids. Biologic therapy has also been developed for EGPA. Mepolizumab and benralizumab, inhibitors of IL-5 signaling, have been approved for treatment of EGPA.[43,44] Guidelines for treatment of ANCA associated vasculitis have been developed by the American College of Rheumatology.[45]

CAR T cell Therapy

Rheumatology has a long tradition of borrowing therapies from Oncology. Recently, there has been significant interest in CD chimeric antigen receptor (CAR) T cell therapy for treatment of severe autoimmune rheumatic disease. This treatment modality has been successfully deployed for the management of hematologic malignancies. By eliminating pathogenic B cells, it may also play a role in managing severe autoimmune disease. A fascinating trial of CD 19 CAR-T cell therapy in 15 patients with severe lupus, scleroderma and myositis has been reported.[46] The striking results of this trial are likely to spur ongoing interest in developing this therapy for severe rheumatic diseases.

VEXAS

A new disease entity called VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) was described in 2020.[47] This disease linked seemingly disparate clinical features of inflammatory diseases such as relapsing polychondritis, Sweet's syndrome, and vasculitis with hematologic disorders including myelodysplastic syndrome and multiple myeloma. A novel approach analyzing genetic data from a diverse clinical cohort was used to identify a somatic mutation in UBA1. This gene codes for an enzyme involved in ubiquitination, a process marking proteins for degradation. This work connected a previously unrecognized syndrome of varied inflammatory and hematologic findings with a single gene mutation. For anyone interested in chasing zebras, look out for men over 50 with unexplained fevers and inflammation affecting skin, joints, lungs, cartilage, or blood vessels along with hematologic abnormalities such as an elevated MCV and cytopenias. There is now a genetic test available to aid in diagnosis.

Conclusion

As evidenced in this discussion, there have been major advances in rheumatology in recent years. The advent of biologic therapy ushered in a new age of highly effective treatments for otherwise disabling autoimmune diseases. An ever-expanding understanding of various disease relevant immunologic pathways has now been translated into routine clinical care for patients with rheumatic disorders. Scientific advances may now allow even more powerful methods of targeting the immune system with treatments such as CAR T cell therapy on the horizon. Breakthroughs such as this, as well as a deeper knowledge of disease mechanisms, will guide us to ever more successful patient care.

Addendum

Since the submission of this manuscript, two additional therapies have been FDA approved for rheumatic diseases reviewed in this article. Upadacitinib, a Janus Kinase inhibitor, was approved for the treatment of giant cell arteritis in April, 2025. The SetPoint System, a vagus nerve stimulator, was approved by the FDA in July, 2025 for the treatment of rheumatoid arthritis.

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