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Misleading at Best: A Critical Appraisal of "Nurse–Physician Substitution in Hospital Settings"

by Rebekah Bernard, MD & Phillip Shaffer, MD

In February 2026, Cochrane published a review entitled "Substitution of Nurses for Physicians in the Hospital Setting for Patient, Process of Care, and Economic Outcomes." The evidence does not support independent substitution of nurses for physicians in hospital settings and instead reflects delegated care within physician-led teams.

Abstract

Background

A recent Cochrane review concluded that nurse-led care results in little to no difference in outcomes compared with physician-led care in hospital settings. These findings have been widely interpreted as evidence supporting substitution of nurses for physicians.

Objective

To evaluate the studies included in the Cochrane review and determine whether the evidence supports independent nurse substitution for physicians in hospital settings.

Methods

We conducted a structured analysis of the 82 randomized controlled trials included in the review, examining clinical setting, patient acuity, level of supervision, and type of intervention.

Results

Only 10 of 82 studies evaluated inpatient hospital care, all involving stable or selected patient populations within physician-led or supervised systems. An additional 11 studies addressed low-acuity emergency or preoperative settings. The remaining majority consisted of outpatient, protocol-driven care for stable conditions, often with explicit physician oversight. No study evaluated independent



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nurse-led management of hospitalized patients or intensive care settings. Many studies assessed task-specific interventions, additional services, or structured follow-up rather than equivalent clinical roles.

Conclusion

The evidence cited does not support independent substitution of nurses for physicians in hospital settings. Instead, it supports the effectiveness of protocolized, delegated care within physician-led teams. While addressing physician workforce shortages is important, maintaining quality and safety requires preserving physician-led models of care.

Keywords

Physician-led care, nurse practitioner, scope of practice, hospital care, team-based care.

Introduction

On February 12, 2026, Cochrane, an international organization known for producing systematic reviews intended to inform clinical and policy decision-making, published a review entitled "Substitution of nurses for physicians in the hospital setting for patient, process of care, and economic outcomes" (Butler, et al).[1] The review analyzed 82 randomized controlled trials involving 28,041 patients across multiple countries and specialties and concluded that there was "little to no difference between nurse-physician substitution and physician-led care" in mortality, quality of life, self-efficacy, and patient safety outcomes, with "uncertain evidence" regarding cost of care.[1]

These conclusions were rapidly amplified in media coverage, with headlines stating that nurses can deliver hospital care as well as physicians,[2-3] and Cochrane itself asserting that nurses "match doctors" in hospital care.[4] Such interpretations suggest that the review demonstrates the safety and effectiveness of independent nurse substitution for physicians in hospital settings. However, this conclusion is not supported by the underlying evidence. A closer examination of the included studies demonstrates that they primarily evaluate delegated, protocol-driven care within physician-led systems rather than independent nurse substitution in hospital settings.

Methods

This study is a structured critical appraisal of a published systematic review. Two reviewers independently analyzed the Cochrane review by Butler et al.[1] Discrepancies in study classification were resolved by consensus. All studies were examined using data reported in the publication and its supplementary materials. Each study was categorized according to clinical setting (inpatient, emergency department, preoperative, or outpatient), patient acuity (high, moderate, or low/stable), and level of physician involvement (independent, supervision/collaboration, or physician-led team). Descriptive synthesis was used to evaluate patterns across studies regarding type of intervention (comprehensive clinical management, protocol-driven care, procedural task, monitoring/follow-up, or adjunctive service). Studies were also assessed qualitatively for relevance to contemporary US practice, including consideration of publication date and training context. No new data were generated, and no statistical analyses were performed.

Results

Key findings are summarized in Table 1, demonstrating substantial limitations in both scope and applicability.

Limited Inpatient Evidence

Despite the title, only 10 of the 82 studies evaluated inpatient hospital care. Eight studies evaluated minor injuries in emergency department settings, and three studies involved preoperative assessment.

Of the 10 inpatient studies, four involved skilled nursing facility care in which nurses were acting only in a nursing role without making medical judgments.[5-8]

Three studies were of nurses acting as residents in a hospital ward providing care for only 25% to 40% patient hours each week, with additional coverage provided by physicians. Nurses were closely supervised by an attending physician.[9-11]

In one of these studies, Pioro, nurse practitioners (NP) declined to accept 20 patients and attending physicians declined to transfer another 20 patients to the NP service. In fact, 47% of patients randomized to the NP arm were cared for by the resident physician arm.

No inpatient study evaluated independent nurse-led management of hospitalized patients without physician oversight. Instead, these studies reflect narrow, highly selected scenarios within physician-led teams.

Geographic Distribution and Recency of United States Data

Only six of the 82 studies were conducted in the United States (US), with the most recent published in 2011. This limitation is particularly important given substantial changes

Table 1. Key Findings

Domain	Finding
Clinical setting	Inpatient care (n=10); Low risk emergency care (n=8); Preoperative assessment (n=3); Outpatient care (n=61)
Geographic distribution	US (n=6); International (n=76)
Recency of US data	No studies in the United States since 2011
Evidence quality/ Bias	Rated moderate to low overall; 'some concern' or high risk of bias for most studies
Power	Low mortality event rate limits statistical power; self-efficacy a subjective outcome
Nursing categories	No differences in outcomes across RN, NP, or other nursing roles

RN: Registered Nurse; NP: Nurse Practitioner

in nurse practitioner education, including expansion of online programs, growth of direct-entry pathways, and increasing variability in clinical training, none of which are reflected in the included studies.

Rare Events and Outcome Limitations

Outcomes such as mortality were characterized by rare events, with several studies reporting fewer than 10 total deaths, limiting statistical power to detect meaningful differences. Commonly reported outcomes such as self-efficacy reflect subjective patient perception rather than objective clinical measures.

Inappropriate Meta-Analysis

Butler includes claims regarding mortality derived from meta-analysis of the data which disregards Cochrane's own guidance. The Cochrane handbook states that meta-analysis should be done only when 'methods, interventions, participants, and the underlying clinical question [are] similar enough for pooling to make sense' [12] The studies that Butler includes in this mortality meta-analysis are widely disparate, ranging from NICU patients to patients with low-risk breast cancer in follow up clinics. This error has also been noted by other reviewers. [13]

Task Delegation Rather Than Clinical Substitution

The majority of studies (61 of 82) evaluated care typically performed in outpatient settings, including management of stable chronic conditions. Care was delivered using strict protocols, decision-support tools, and predefined pathways, often with physician oversight.

Several studies did not evaluate substitution but instead assessed the addition of nursing services. For example, Allison[14] demonstrated improved outcomes with additional counseling for chest pain patients, and Cargill[15] showed increased screening rates with nurse referral.

Other studies evaluated discrete procedures performed by specially trained nurses, including endoscopy, intraocular injections, and colposcopy, demonstrating task-specific competency in controlled, low-risk settings but not comprehensive medical management.[16-19]

Multiple studies involved structured telephone follow-up or telemonitoring for stable patients, relying on scripted protocols and predefined escalation pathways.[20-23]

Lack of Differences Across Nursing Categories

Cochrane reported no differences across nursing categories, including comparisons between unqualified nurses, registered nurses, and nurse practitioners.[1]

Discussion

This analysis demonstrates that the Cochrane review does not evaluate independent substitution of nurses for physicians in hospital settings. Only 21 of 82 studies involved any hospital-related care, all conducted within

physician-led or supervised systems, and no study examined independent nurse-led management of hospitalized or critically ill patients. The majority of evidence reflects outpatient, protocol-driven care for stable or low-acuity conditions, limiting applicability to complex inpatient medicine.

In addition, the review found no differences among nursing types, suggesting that outcomes were driven by protocolization and system design rather than differences in training level.

These findings suggest that the review primarily captures task delegation within structured systems rather than equivalence in comprehensive clinical management. The absence of contemporary US inpatient data further limits generalizability, particularly given substantial changes in nurse practitioner education and training pathways.

While physician workforce shortages are a legitimate concern, reducing physician involvement in patient care is not an appropriate solution. Policymakers should instead focus on strategies that expand access while preserving quality, including strengthening physician workforce pipelines, optimizing team-based care, and improving system efficiency.

Conclusion

The evidence does not support independent substitution of nurses for physicians in hospital settings and instead reflects delegated care within physician-led teams.

References

1. Butler M, Kirwan M, Mc Carthy VJ, Cole JA, Schultz TJ. Substitution of nurses for physicians in the hospital setting for patient, process of care, and economic outcomes. Cochrane Database Syst Rev. 2026;2(2):CD013616.
2. Cochrane. Nurses can deliver hospital care just as well as doctors, review finds. Medical Xpress. Published February 11, 2026. Accessed March 24, 2026 from https://medicalxpress.com/news/2026-02-nurses-hospital-doctors.html
3. Wilson FP. Physician shortage: give nurses a shot? Medscape. Published February 11, 2026. Accessed March 24, 2026. https:// www.medscape.com/viewarticle/physician-shortage-give-nurses-shot-2026a1000432?ecd=a2a
4. Cochrane. Nurses match doctors in delivering hospital care. News release. February 12, 2026. Accessed March 23, 2026 from https://www. cochrane.org/about-us/news/nurses-match-doctors-delivering-hospital-care
5. Griffiths, P., Wilson-Barnett, J., Richardson, G., Spilsbury, K., Miller, F., & Harris, R. (2000). The effectiveness of intermediate care in a nursing-led in-patient unit p. International Journal of Nursing Studies, 37(2), 153–161. https://doi.org/10.1016/%2520S0020-7489(99)00061-920-7489(99)00061-9%255D
6. Griffiths, P. (2001). Substitution of a nursing-led inpatient unit for acute services: Randomized controlled trial of outcomes and cost of nursing-led intermediate care. Age and Ageing, 30(6), 483–488. https://doi.org/10.1093/ageing/30.6.483
7. Steiner, A., Torgerson, D. J., Walsh, B., Pickering, R. M., Wiles, R., Ward, J., & Brooking, J. I. (2001). Therapeutic nursing or unblocking beds? A randomised controlled trial of a post-acute intermediate care unit. BMJ, 322(7284), 453–459
8. Walsh, M. B., Pickering, R. M., & Brooking, J. I. (1999). A randomized controlled trial of nurse-led inpatient care for post-acute medical patients: A pilot study. Clinical Effectiveness in Nursing, 3(2), 88–90. https://doi.org/10.1016/S1361-9004(99)80036-3
9. Goldie, C. L., Prodan-Bhalla, N., & Mackay, M. (2012). Nurse practitioners in postoperative cardiac surgery: Are they effective? Canadian Journal of Cardiovascular Nursing = Journal Canadien En Soins Infirmiers Cardio-Vasculaires, 22(4), 8–15.
10. Mitchell-DiCenso, A., Guyatt, G., Marrin, M., Goeree, R., Willan, A., Southwell, D., Hewson, S., Paes, B., Rosenbaum, P., Hunsberger, M., & Baumann, A. (1996). A Controlled Trial of Nurse Practitioners in Neonatal Intensive Care. Pediatrics, 98(6), 1143–1148. https://doi.org/10.1542/peds.98.6.1143
11. Pioro, M. H., Landefeld, C. S., Brennan, P. F., Daly, B., Fortinsky, R. H., Kim, U., & Rosenthal, G. E. (2001). Outcomes-based trial of an inpatient nurse practitioner service for general medical patients. Journal of Evaluation in Clinical Practice, 7(1), 21–33. https://doi.org/10.1046/j.1365-2753.2001.00276.x
12. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.
13. Iacobucci, G. (2026). Study claiming that substituting nurses for doctors is safe and effective is flawed, say experts. BMJ, 392, s336. https://doi.org/10.1136/bmj.s336
14. Allison TG, Farkouh ME, Smars PA, Evans RW, Squires RW, Gabriel SE, et al. Management of coronary risk factors by registered nurses versus usual care in patients with unstable angina pectoris. American Journal of Cardiology 2000;86(2):133-8.
15. Cargill Victoria A, Conti M, Neuhauser D, Mcclish D. Improving the effectiveness of screening for colorectal cancer by involving nurse. Care 1991;29(1):1-5.
16.Limoges-Gonzalez M, Mann NS, Al-Juburi A,Tseng D, Inadomi J, Rossaro L. Comparisons of screening colonoscopy performed by a nurse practitioner and gastroenterologists: A single-center randomized controlled trial. Gastroenterology Nursing 2011;34(3):210-6.
17.Schoenfeld P, Lipscomb S, Crook J, Dominguez J, Butler J, Holmes L, et al. Accuracy of polyp detection by gastroenterologists and nurse endoscopists during flexible sigmoidoscopy: a randomized trial. Gastroenterology 1999;117(2):312-8.
18. Austeng D, Morken TS, Bolme S, Follestad T, Halsteinli V. Nurse-administered intravitreal injections of anti-VEGF: study protocol for noninferiority randomized controlled trial of safety, cost and patient satisfaction. BMC Ophthalmology 2016;16(1):1-7.
19. Nessa A, Roy Joya S, Chowdhury Most A, Khanam Q, Afroz R, Wistrand C, et al. Evaluation of the accuracy in detecting cervical lesions by nurses versus doctors using a stationary colposcope and Gynocular in a low-resource setting. BMJ Open 2014;4(11):1-9.
20. Beaver K, Tysver-Robinson D, Campbell M, Twomey M, Williamson S, Hindley A, et al. Comparing hospital and telephone follow-up after treatment for breast cancer: Randomised equivalence trial. BMJ (Online) 2009;338(7690):337-40.
21. de Thurah A, Stengaard-Pedersen K, Axelsen M, Fredberg U, Schougaard LM, Hjollund NH, et al. Tele-health followup strategy for tight control of disease activity in rheumatoid arthritis: results of a randomized controlled trial. Arthritis Care & Research 2018;70(3):353-60.
22.Willems DC, Joore MA, Hendriks JJ, Nieman FH, Severens JL, Wouters EF. The effectiveness of nurse-led telemonitoring of asthma: Results of a randomized controlled trial. Journal of Evaluation in Clinical Practice 2008;14(4):600-9.
23.Kumar R, Teo PS, Tan WB, Choi X, Chia PY, Lee HL, et al. A randomised clinical trial of the safety, cost effectiveness and patient experience of nurse-led telemonitoring of chronic hepatitis B patients. GastroHep 2019;1(5):249-55.

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Teen Vaping: Not Gone, But Forgotten

The harm associated with e-cigarettes or vaping products is not fully appreciated.

by Rebecca Sabates, MD & Gary Salzman, MD

Since their introduction to the United States market in 2007, electronic cigarettes have gained popularity in use, specifically in the youth and young adult population.[1] By 2014, e-cigarettes became the most popular choice of tobacco products among adolescents. Between 2011 to 2018, e-cigarette use in high school students rose from 1.5% to 20.8%; use in middle school students also rose from 0.6% to 4.9% over the same period.[2] Historically, the appeal of vaping products, specifically in youth and young adult populations, has been attributed to several factors such as its discreet delivery system shaped like USB flash drives, high nicotine content and multiple flavors options.[2,3] Another draw to vaping has been the idea that vaping is less harmful than tobacco cigarettes. This has been supported by many scientists for reasons such as the far greater number of chemicals in cigarettes, data that supports that lung function improves when cigarettes are replaced with e-cigarettes and studies that show higher inflammatory biomarkers in cigarette users than vape users.[4] Vaping has also been studied as a successful method for smoking cessation. [4,5] It is important to note, however, that even those that have concluded that vaping is less harmful, acknowledge that vaping is not without its health risks.

The harm associated with e-cigarettes or vaping products was not fully appreciated until 2019 when the Center for Disease Control (CDC) first reported a severe pulmonary illness associated with its use. Cases of e-cigarette, or vaping, product use associated lung injury (EVALI) were tracked by the CDC after it was identified. Given the alarming number of cases reported, the CDC officially declared it an epidemic in 2019. The peak number of cases reported were 215 between August 2019 and September 2019.[6] In February 2020, the CDC discontinued its monitoring of cases which coincided with the start of the COVID-19 global pandemic. Despite this, the attention by public health experts on EVALI prompted a harder look at vaping usage and efforts to regulate vaping products.[1]



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A diagnosis of exclusion, EVALI has no specific clinical features or symptoms; there has been several proposed definitions but the most widely accepted tool for identification has been based on the CDC definition of confirmed cases which includes: 1) e-cigarette use in 90 days before symptom onset; 2) pulmonary infiltrates on plain film chest radiography or ground glass opacities on chest computed tomography; 3) absence of pulmonary infection on initial work up; and 4) no evidence of alternative diagnosis.[1]

The pathogenesis of EVALI is not fully understood but a study published in 2019 identified vitamin E acetate (VEA) in the bronchoalveolar fluid of 48 out of 51 EVALI patients.[7] This supported previous observations that a majority of EVALI patients reported use of tetrahydrocannabinol (THC) containing products and VEA has frequently been used in these products to thicken the liquid.[8] Subsequent studies in both *in vitro* and *in vivo* models also observed cytotoxicity, barrier dysfunction and inflammation to lung tissue that was exposed to aerosolized VEA, as well as other chemical components commonly found in THC containing products.[3] Despite the strong evidence that supports a causal link between VEA and EVALI, other contributing factors are being explored, particularly for nicotine only e-cigarettes that do not contain VEA like cannabinoid e-cigarettes do.

EVALI has prompted responses by public health agencies on both a federal and state level. The US Food and Drug Administration (FDA) began having authority over e-cigarettes and vaping products in 2016 under the Deeming Rule section of the Tobacco Control Act.[9] This rule broadened the FDA's authority to regulate manufacturing of vaping products, requiring manufacturers to submit applications for approval of products to the FDA.[9] This led to several significant changes including the ban on selling vaping products to youth under the age of 21, effective removal of VEA in some vaping liquid products, and restriction of sales on unauthorized flavored cartridge-based e-cigarettes.

In 2020, the Prevent All Cigarette Trafficking Act (PACT Act), a legislative bill regulating the delivery and sales of tobacco products, was amended to include e-cigarette and vaping products, thus attempting to control access for young adults to vaping products and complementing the regulations of the Tobacco Control Act.[10] State level regulations have also attempted to fill gaps in addressing the use of e-cigarettes by either enacting special taxes on e-cigarettes, requiring special licenses for retail distributors and/or restricting product packaging.[11,12] Some states such as Colorado, Massachusetts, New Jersey and California have also banned specific flavors to make vaping less appealing to young populations.[11]

In Missouri, restrictions for vaping have largely mirrored those of other states including the regulations for licensing, packaging, and distribution.[13] More recently, Missouri has introduced legislation to modify the existing Clean Indoor Air Act to ban vaping and marijuana in all indoor public spaces.[14] One study analyzed e-cigarette use and its association with different types of state regulations; these results suggest a decline in e-cigarette use and initiation in states that enacted laws regulating the distribution and licensing of vaping products.[11] The results are promising in the battle against EVALI.

In addition to federal and state regulations on vaping products themselves, several health campaigns have been launched to educate youth and young adult populations to discourage the use of vaping products. Campaigns such as The Truth Initiative and the FDA's Real Cost campaign were originally launched to spread awareness of tobacco use but have since evolved to include e-cigarettes/vaping in their educational focus for young adults. A randomized controlled trial performed in 2021 examined the impact the Real Cost Campaign had on discouraging vaping use and the results showed a lower usage of vaping in adolescents who were shown anti-vaping advertisements three times weekly as compared to the control group.[15] Studies such as this show that public health campaigns can have a large impact on disease prevention like EVALI. At the height of EVALI cases, 20% (5.4 million) of high school and middle school students reported e-cigarette use, by far the most common method of using tobacco products; in comparison, 4.3% (1.2 million) students reported using cigarettes.[16] As recent as 2024, the National Youth Tobacco Survey stated that 5.9% (1.63 million) middle and high school students reported using e-cigarettes and 1.8% students reported using cigarettes; this is the lowest documented use ever obtained by the National Youth Tobacco Survey (Figure 1).[17,18]

Although tobacco is commonly delivered via e-cigarette or vaping systems, nearly one in three students reported using vaping products to deliver marijuana as well (Figure 1).[17,18] The prevalence of cannabis, in general, has been on the rise in the US. In 2022, 15.1% of adults

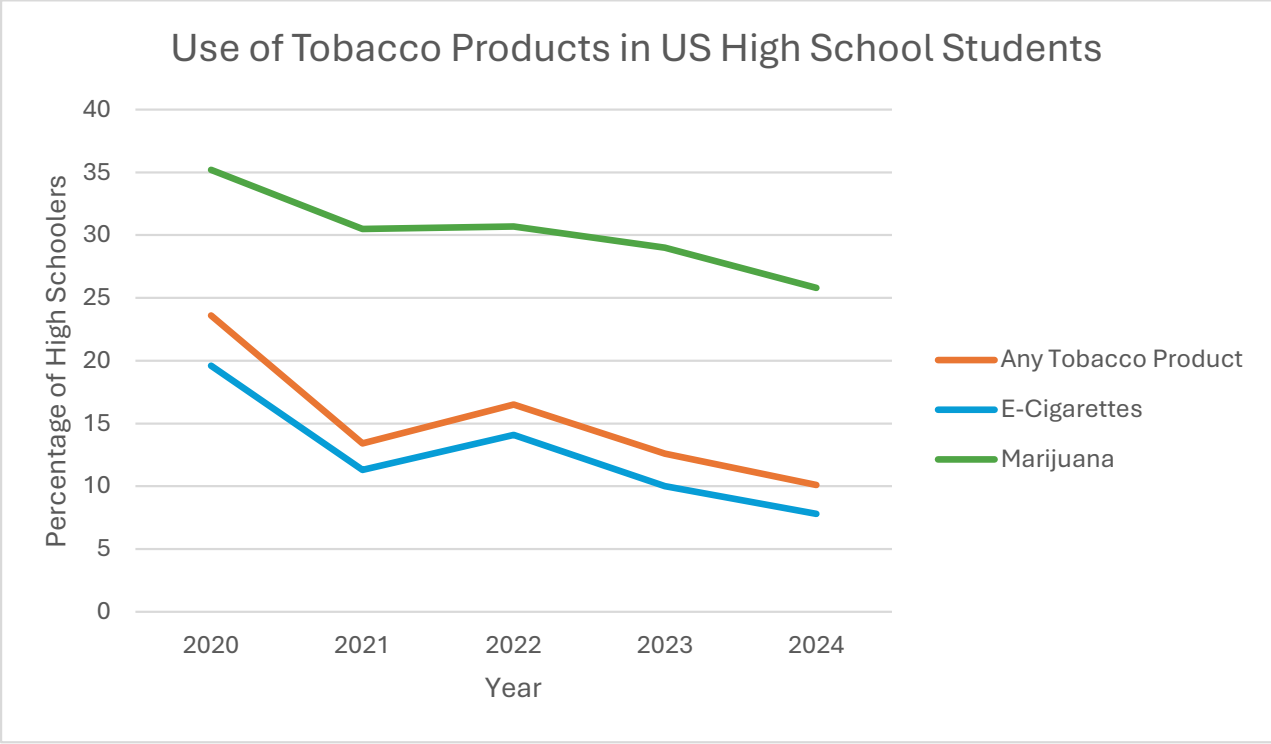


Figure 1. Percentage of United States high school students who report use of any tobacco product, e-cigarettes or marijuana use in the past 30 days from 2020-2024[17,22]

reported using marijuana, an increase from 13.1% in 2021.[19] Approximately one-fourth of these patients reported vaping as the most popular delivery method.[19] Legalization of marijuana has likely contributed to the rise in popularity. A 2023 study surveying over 5,000 Missouri college students across 25 campuses showed a 66.23% increase in use of marijuana between 2013-2023; after legalization in 2023, 10% of cannabis naïve students reported intent to use and 22% of current cannabis users reported intent to increase use.[20] Thus far, most EVALI cases have been reported in patients whose primary use of vaping was for marijuana, so these distinctions are important to track.

The fall in EVALI cases is likely due to multiple factors. Although new public health policies increased awareness and better regulatory measures have contributed to its decline, it is likely that the condition has been under recognized. Prior to the 2019 epidemic, studies of the adverse health effects linked to e-cigarettes first emerged in 2012.[3] In 2014, an acute respiratory condition was described in a case report possibly linking it to e-cigarettes.[3] More cases followed, ultimately leading to the official declaration of the epidemic in September 2019. After discontinuation of monitoring by the CDC, some states chose to continue tracking cases; however, to date there is no official report for the number of EVALI cases since monitoring was stopped in February 2020. The American Thoracic Society in its 2022 workshop report on EVALI noted that although there was useful data obtained during the tracking period of EVALI, this was captured over a period of less than 1 year.[1] Since discussion on EVALI has dulled over the past few years, there is also a component of poor awareness by physicians thereby making it possible that the diagnosis is missed. It begs the question, are EVALI cases truly dropping at the rate we have seen or are patients being misdiagnosed?

A diagnosis of EVALI poses a large challenge for physicians. As previously mentioned, the nonspecific findings and long differential can lead physicians down many different paths, so a thorough exposure history is key. While conversations on tobacco cessation have become a standardized part of practice, vaping has only joined the discussion in the past few years. Guidelines, such as those from the American College of Cardiology, have outlined a systematic approach to counsel

patient through smoking cessation but vaping has yet to receive the same attention.[21] In fact, studies such as those from Hajek et al. has demonstrated higher success in smoking cessation with the use of e-cigarette products over traditional nicotine replacement therapy (NRT) with the caveat being a high rate of continued usage of e-cigarettes at 52 weeks compared to NRT participants.[5] Studies such as these have acknowledged the theoretical health consequences of e-cigarette use itself, so these outcomes should not be considered as an acceptable alternative to the harms of traditional smoking. Therefore, physicians should approach the conversation of vaping usage under the same umbrella of tobacco cessation given what we have learned thus far from the EVALI epidemic.

Although there has been promising strides forward in the education and prevention of EVALI, there is still much to be done. Proposed actions to continue efforts focuses on two major aspects: prevention of vaping by the public and better medical understanding of the condition. For the former, more standardized, federal regulations of e-cigarette distribution and manufacturing should be pursued as it has already been shown to have a positive effect. Limiting flavor options to make vaping less appealing, continued education on health harms, and restricting access to products are cornerstones of this approach.[1] In matters of the study on EVALI itself, a standardized coding system and national case registry should be established to identify cases.[1] In doing so, data could be used to further explore the pathogenesis of the condition and eventually guide treatment management. Physicians should continue to take careful history of vaping use when evaluating patients with acute respiratory distress and consider EVALI in their differential. In the spirit of prevention, they should also encourage and counsel cessation of vaping with the same discrimination that cigarette use has received.

References

1.Rebuli ME, Rose JJ, Noël A, et al. The e-cigarette or vaping product use–associated lung injury epidemic: pathogenesis, management, and future directions: an official American Thoracic Society workshop report. Ann Am Thorac Soc.2023;20(1):1-17. doi:10.1513/AnnalsATS.202209-796ST

2. Cullen KA, Ambrose BK, Gentzke AS, et al. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students—United States, 2011-2018. MMWR Morb Mortal Wkly Rep. 2018;67(45):1276-1277.

3. Barker CK, Ghera P, Hsu B. The evolution of a pediatric public health crisis: e-cigarette or vaping-associated lung injury. Pediatrics. 2024;153(1):e2023063484. doi:10.1542/peds.2023-063484

4. Balfour DJK, Benowitz NL, Colby SM, et al. Balancing consideration of the risks and benefits of e-cigarettes. Am J Public Health. 2021;111(9):1661-1672. doi:10.2105/AJPH.2021.306416

5. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629-637. doi:10.1056/NEJMoa1808779

6. Hartnett KP, Kite-Powell A, Patel MT, et al. Syndromic surveillance for e-cigarette, or vaping, product use-associated lung injury. N Engl J Med. 2020;382(8):766-772.

7. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med. 2020;382(8):697-705. doi:10.1056/NEJMoa1916433

8. Soerianto W, Jaspers I. E-cigarette, or vaping, product use associated lung injury: epidemiology, challenges, and implications with COVID-19. Pediatr Pulmonol. 2025;60(1):e27448. doi:10.1002/ppul.27448

9. Congressional Research Service, "U.S. Secret Service: Selected Issues for the 119th Congress," Congress.gov, published February 25, 2025, accessed February 10, 2026, https://www.congress.gov/crs-product/R48483

10. Bureau of Alcohol, Tobacco, Firearms and Explosives, "Vapes and E-Cigarettes," Bureau of Alcohol, Tobacco, Firearms and Explosives, accessed February 10, 2026, https://www.atf.gov/alcohol-tobacco/vapes-and-e-cigarettes

11. Jun J, Kim JK. Do state regulations on e-cigarettes have impacts on the e-cigarette prevalence? Tob Control.2021;30(e1):e10-e15. doi:10.1136/tobaccocontrol-2019-055287

12. Public Health Law Center, "U.S. E-Cigarette Regulations - 50-State Review," Public Health Law Center, accessed March 9, 2026, https://www.publichealthlawcenter.org/resources/us-e-cigarette-regulations-50-state-review

13. Public Health Law Center, "U.S. E-Cigarette Regulations - 50-State Review: Missouri," Public Health Law Center, accessed March 13, 2026, https://www.publichealthlawcenter.org/resources/us-e-cigarette-regulations-50-state-review/mo#:~:text=%C2%A7%20407.926.4(1),%2C%20407.931.3%20(2025

14. BillTrack50, "MO SB116: Modifies Provisions Relating to the Sale of Tobacco, Alternative Nicotine, or Vapor Products," BillTrack50, accessed March 13, 2026, https://www.billtrack50.com/billdetail/1950138\

15. Noar SM, Rohde JA, Barker JO, et al. Impact of vaping prevention advertisements on US adolescents: a randomized clinical trial. JAMA Netw Open. 2022;5(10):e2236370. doi:10.1001/jamanetworkopen.2022.36370

16. Gentzke AS, Rogers M, Sharapova S, et al., "Tobacco Product Use Among Middle and High School Students — United States, 2011–2018," Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report (MMWR), published December 6, 2019, accessed February 10, 2026, https://www.cdc.gov/mmwr/volumes/68/ss/ss6812a1.htm#T2_down

17. U.S. Food and Drug Administration, "National Youth Tobacco Survey (NYTS)," U.S. Food and Drug Administration, updated September 5, 2024, accessed March 10, 2026, https://www.fda.gov/tobacco-products/youth-and-tobacco/national-youth-tobacco-survey-nyts

18. Centers for Disease Control and Prevention, "Quick Facts on the Risks of E-cigarettes for Kids, Teens, and Young Adults," Centers for Disease Control and Prevention, updated October 30, 2024, accessed March 9, 2026, https://www.cdc.gov/tobacco/e-cigarettes/youth.html

19. Chung JYC, Romm KF, Spindle TR, et al. Examining the relationship of cannabis use patterns, mental health, and sociodemographic factors: a focus on cannabis vaping, smoking and dual-use. Addict Behav. 2025;163:108263. doi:10.1016/j.addbeh.2025.108263

20. McNamara IA, Parnes JE, Stetsiv K, et al. Missouri college students' intentions towards initiating or changing cannabis use in a shifting legal landscape. Cannabis. 2025;8(2):33-50. doi:10.26828/cannabis/2025/000286

21. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment. J Am Coll Cardiol. 2018;72(25):3332-3365. doi:10.1016/j.jacc.2018.10.020

22. Miech RA, Johnston LD, Patrick ME, et al., "Monitoring the Future National Survey Results on Drug Use, 1975–2024: Secondary School Students," Monitoring the Future, published December 2024, accessed March 10, 2026, https://monitoringthefuture.org/wp-content/uploads/2024/12/mtf2025.pdf

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Kratom in Clinical Practice: What Physicians Need to Know

by Mark Gold, MD & Nicole Avena, PhD

As use of kratom-labeled products becomes more common, clinicians may benefit from incorporating routine, nonjudgmental screening into patient encounters.

Abstract

Kratom use is increasingly encountered in clinical practice, yet products marketed under this name encompass markedly different substances with distinct pharmacologic and risk profiles.

Kratom leaf (Mitragyna speciosa) contains a complex mixture of alkaloids, primarily mitragynine, with serving size dependent stimulant and sedative effects, whereas many modern products labeled as kratom contain concentrated, semi-synthetic, or synthetic alkaloids, particularly 7-hydroxymitragynine (7-OH), with substantially greater opioid-like potency.

This review summarizes the pharmacology, clinical effects, and safety data related to natural kratom leaf, contrasts these findings with evidence on high-potency alkaloid products, and examines limitations in adverse event surveillance resulting from exposure misclassification and polysubstance use. Clinical and toxicologic data suggest that severe acute harms attributed to "kratom" disproportionately involve concentrated alkaloid formulations rather than whole-leaf products.

Guidance is provided to assist physicians in screening, counseling, and documentation, emphasizing the importance of distinguishing product type to support risk assessment, harm reduction, and patient safety.



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Why Physicians Are Encountering "Kratom" More Often

Physicians across multiple specialties are increasingly encountering patients who report using natural kratom leaf products or concentrated synthetic substances misleadingly marketed as kratom. These exposures are often grouped together in clinical discussions despite representing markedly different pharmacologic profiles.

While traditional kratom leaf contains a naturally occurring mixture of alkaloids in relatively low concentrations, many modern products sold under the same name are concentrated, enhanced, or synthetically altered to deliver substantially higher doses of isolated compounds. This lack of distinction contributes to confusion among patients and clinicians alike and complicates clinical assessment.

Patients commonly report using natural kratom leaf for a range of self-directed purposes, including pain relief, increasing energy, mood enhancement, or stress. At the same time, physicians have limited standardized guidance on how to evaluate kratom and other synthetic derivative exposures, assess risk, or counsel patients appropriately.

Over-the-counter availability and marketing that purposefully conflates natural kratom and synthetic derivatives further reinforce the perception that all kratom-labeled products share a similar safety profile, which they do not. In practice, however, products marketed as "kratom" vary widely in composition, potency, and effect. Increasingly, adverse events attributed broadly to "kratom" appear to involve concentrated, semi-synthetic, or synthetic alkaloid products, rather than traditional whole-leaf products. Understanding this distinction is essential for accurate clinical evaluation and patient counseling.



Figure 1. *Mitragyna speciosa* (kratom) leaves and common commercial preparations. Kratom is a tropical tree native to Southeast Asia whose leaves are processed into powders, capsules, and extracts for oral consumption.
Original photo- https://www.chhs.colostate.edu/fsi/food-articles/non-produce-plants/kratom/

Natural Kratom Leaf: Botanical and Pharmacologic Overview

Natural kratom leaf comes from Mitragyna speciosa, a tropical evergreen tree native to Southeast Asia. For centuries, kratom leaves have been used in traditional contexts, typically chewed fresh or brewed into teas or tonics. These historical preparations involved minimally processed leaf material, sometimes dried and ground, consumed in modest amounts, and embedded within cultural practices distinct from modern commercial distribution (Figure 1).

The pharmacologic activity of natural kratom leaf is driven by its alkaloid content. More than 50 alkaloids have been identified which all contribute to their functional effects. Mitragynine is the most abundant naturally occurring alkaloid in kratom leaf. It acts as a partial agonist at the μ-opioid receptor and also interacts with certain adrenergic and serotonergic receptors. At lower servings, mitragynine is associated with stimulant effects such as increased alertness and energy. At higher servings, mitragynine can have sedative and analgesic effects. 7-OH occurs naturally in dried kratom leaf only in trace amounts. As 7-OH exhibits significantly greater potency at the μ-opioid receptor than mitragynine, its pharmacologic properties become clinically significant when the compound is isolated, concentrated, or synthetically enhanced. The effects of natural kratom leaf are serving size dependent and variable, influenced by individual metabolism and frequency of use. The absence of standardized serving sizes complicates both patient self-regulation and clinical assessment.

Concentrated and Synthetic Alkaloid Products Marketed as Kratom

A critical distinction for clinicians is the difference between natural kratom leaf preparations and concentrated or synthetic kratom alkaloid

Table 1. Common self-reported uses of kratom and proposed pharmacologic mechanisms. Evidence is primarily derived from observational studies, case reports, and user surveys.

Use/Indication (self-reported)	Proposed Mechanism	Evidence Level	Clinical Notes
Pain Relief	Partial μ-opioid receptor agonism (mitragynine, 7-HMG)	Low- moderate (observational)	Risk of dependence; variable potency
Opioid Withdrawal Mitigation	Opioid receptor activity; adrenergic effects	Low (case reports, surveys)	May delay evidence-based treatment
Mood Enhancement	Dopaminergic/serotonergic modulation	Low	Risk of misuse
Energy/Stimulation (low dose)	Adrenergic activity	Low	Dose-dependent effects
Sedation (high dose)	Opioid-like effects	Low	CNS depression risk

Reference: Prevete E, Kuypers KPC, Theunissen EL, et al. Clinical implications of kratom (Mitragyna speciosa) use: a literature review. Current Addiction Reports. 2023;10(2):317–334. doi:10.1007/s40429-023-00478-3

products marketed under the same name. Many products currently available in US retail settings bear little resemblance to traditional kratom leaf in composition or potency. These formulations may contain concentrated mitragynine, isolated 7-OH, or chemically modified alkaloids designed to enhance opioid-like effects. In some cases, the concentration of 7-OH exceeds levels found naturally in kratom leaf by more than 100 times, exposing users to pharmacologic effects that differ substantially from traditional preparations. Patients are often unaware of these distinctions and may assume that all kratom-labeled products are the same. This misunderstanding can lead to unintentional high-dose exposure and increased risk of adverse effects. From a clinical perspective, failure to distinguish between whole-leaf products and alkaloid concentrates may result in inaccurate attribution of risk and misinterpretation of patient symptoms.

Clinical Effects and Potential Risks

The clinical effects of natural kratom leaf differ from those of concentrated alkaloid products. Commonly reported effects of whole-leaf kratom include increased alertness at lower doses and relaxation or mild sedation at higher doses. High, abnormal doses can cause adverse effects like nausea, vomiting, constipation, dizziness, and headache. Regular use of natural kratom leaf can lead to tolerance and dependence in some individuals, particularly with frequent or high-dose consumption. Withdrawal symptoms have been described and may include irritability, insomnia, myalgias, gastrointestinal discomfort, and mood disturbances.

While kratom leaf withdrawal is often reported as mild to moderate, it remains clinically relevant and may contribute to continued use in susceptible individuals. At the same time, emerging controlled clinical data suggests that dependence and withdrawal are not universal outcomes of regular leaf use. A recent human laboratory study published in Therapeutic Drug Monitoring evaluated the safety and tolerability of escalating single doses and repeated daily doses of dried natural kratom leaf powder administered over several weeks. Across the doses tested, investigators reported no serious adverse events, no evidence of clinically significant withdrawal, and no meaningful abuse potential.[1] These findings are consistent with prior controlled studies indicating that, when consumed in measured amounts and in whole-leaf form, natural kratom leaf may exhibit a lower risk profile than is often assumed based on aggregated adverse event reports. Additional clinical studies support these findings. A Food and Drug Administration single-ascending-dose study of natural kratom leaf evaluated doses up to 12 grams, approximately four times greater than amounts typically reported by consumers, and found no concerning adverse effects and overall good tolerability.[2] A separate clinical trial in healthy adults found no serious adverse effects after 15 days of administration of 0.5, 1, 2, and 4 grams of natural kratom leaf.[3] Taken together, these data suggest that,

under controlled conditions and at measured doses, whole-leaf kratom may exhibit a more favorable safety profile than is often inferred from aggregated adverse event reports.

By contrast, concentrated or synthetic alkaloid products appear to carry much higher risks. Preclinical and translational studies have demonstrated that isolated or enhanced kratom-derived alkaloids, particularly with concentrated synthetic 7-OH, exhibit markedly greater μ-opioid receptor potency than that observed with natural kratom leaf, with pharmacologic profiles more closely resembling classical opioids. Experimental models have linked these high-potency alkaloids to dose-dependent respiratory depression, as well as increased reinforcing effects and greater abuse liability compared with mitragynine-dominant whole-leaf preparations. These risks are further amplified at higher doses and when such products are used in combination with other central nervous system depressants, underscoring the clinical importance of distinguishing natural kratom leaf from concentrated or synthetic alkaloid formulations.[4,5]

Interpreting Adverse Event and Toxicology Data

Reports of adverse events attributed to kratom have increased in recent years, drawing greater attention from clinicians and public health agencies. Interpretation of these data, however, warrants caution. Many reported cases involve inconsistent classification of exposures, with natural kratom leaf often conflated with concentrated or synthetic alkaloid products, as well as frequent concurrent use of other substances, making causal attribution challenging. Surveillance systems and poison control datasets often fail to distinguish between whole-leaf kratom preparations and high-potency alkaloid formulations. In the absence of this differentiation, adverse outcomes associated with concentrated products may be inaccurately generalized to natural kratom leaf, limiting the clinical interpretability of aggregated reports.

Available poison center data illustrate this challenge. Between 2017 and 2023, calls to America's Poison Centers involving natural kratom leaf accounted for a relatively small proportion of total substance-related exposures and were markedly fewer than calls involving opioids or alcohol, suggesting a lower likelihood of acute medical emergencies. During this same period, only 23 reported deaths were associated with "kratom" ingestion, and more than one-third of these cases involved documented polysubstance use.

By comparison, more than 2,000 deaths were reported in association with opioid-related poison center calls.[6] Without clear differentiation between product types and co-exposures, such figures risk being misinterpreted. Data from other surveillance systems show similar patterns. FDA Adverse Event Reporting System (FAERS) data indicate a decline in reports of deaths involving kratom alone between 2019 and 2021, and analyses of fatal cases from 2019 to 2022 demonstrate that the majority involved multiple substances rather than isolated exposure to natural kratom leaf.[7]

These findings further underscore the difficulty of attributing severe outcomes to kratom leaf in the absence of comprehensive toxicologic information. Recent toxicologic analyses further reinforce these limitations. A 2024 review published in Frontiers in Pharmacology examining adverse events associated with kratom use found no consistent pattern of organ-specific toxicity attributable to natural kratom leaf. Across reported cases, no single organ system was reliably or preferentially affected. The authors noted that interpretation was substantially constrained by incomplete toxicology testing, frequent absence of data on dose, serving size and use patterns, and the common presence of additional substances in the individual's system.[8] Taken together, the available evidence was deemed insufficient to support a causal association between natural kratom leaf alone and severe acute adverse effects, and such an association was considered unlikely.

Patterns of use and dependence similarly suggest a more nuanced risk profile. While natural kratom leaf can be habit-forming in some individuals, comparative analyses indicate that the severity of kratom use disorder more closely resembles that associated with substances such as caffeine, tobacco, alcohol, and cannabis, rather than illicit opioids or stimulants such as heroin, methamphetamine, or cocaine. Consistent with this assessment, the World Health Organization Expert Committee on Drug Dependence concluded in 2021 that there is limited evidence of kratom abuse liability in humans, noting that while serious toxicity may occur at high doses, such cases likely represent a small proportion of total users.[9] The National Institute on Drug Abuse similarly reported in 2023 that a very small number of deaths have been linked to kratom

products, with nearly all cases involving other drugs or contaminants.[10] Toxicologic assessment is further complicated by product mislabeling and adulteration. Products marketed as kratom have, in some instances, been found to contain additional pharmacologically active compounds. Accordingly, clinicians should interpret adverse event reports with careful consideration of product formulation, dose, and co-use with other substances.

Regulatory Landscape and Patient Misunderstanding

In the United States, growing concern regarding the increased availability, misuse, and reported adverse effects of concentrated and synthetically enhanced alkaloid products, particularly those containing concentrated synthetic 7-OH, has driven heightened regulatory scrutiny. In response, several states and localities have pursued overly broad scheduling actions that apply to all kratom-labeled products, rather than regulatory frameworks that distinguish between high-potency alkaloid formulations and natural kratom leaf. The absence of standardized terminology and clear product definitions has further contributed to this lack of regulatory differentiation. Patients frequently interpret over-the-counter availability as evidence of safety or quality oversight. Physicians therefore may need to clarify that commercial availability does not imply standardization, regulatory review, or established clinical benefit, particularly in the case of high-potency alkaloid products.

Practical Guidance for Physicians

As use of kratom-labeled products becomes more common, clinicians may benefit from incorporating routine, nonjudgmental screening into patient encounters. Open-ended questions about supplement and substance use can facilitate disclosure and support trust. When patients report kratom use, physicians should inquire specifically about product type, distinguishing between natural kratom leaf and concentrated or synthetic alkaloid formulations, as well as frequency, approximate dose, and route of administration. Clinicians should ask whether the patient is using whole-leaf powder, an extract, or a product marketed as 7-OH or 7-hydroxymitragynine. This distinction may be more clinically relevant than the patient's use of "kratom" alone. Understanding the patient's reason for use, such as pain management, mood symptoms, or self-treatment of opioid withdrawal, can further inform risk assessment. Clinicians should also review concurrent medications or substance use and assess for a history of substance use disorder or prior withdrawal symptoms.

Recent case reports highlight the clinical importance of these distinctions. A published case described a near-fatal overdose involving concentrated synthetic 7-OH products in a patient with a history of opioid use disorder. The individual presented to the emergency department following cardiopulmonary arrest and required cardiopulmonary resuscitation and naloxone administration for successful reversal. The authors concluded that the presentation was consistent with opioid-like respiratory depression attributable to ingestion of high-potency synthetic 7-OH, underscoring the markedly different risk profile of such products compared with natural kratom leaf.[11]

Additional clinical reports have emphasized the complexity introduced by concurrent substance use. A separate case analysis published in the Journal of Addiction Medicine highlighted that kratom-related adverse events frequently occur in the context of polysubstance exposure, underlying medical conditions, or use of concentrated formulations, complicating attribution and management. The authors further cautioned that products marketed as "kratom" may obscure exposure to potent synthetic agents, increasing the risk of misdiagnosis or inappropriate treatment.[12] These findings suggest a practical need for improved clinical documentation. Where feasible, clinicians may consider modifying patient intake forms and substance-use histories to allow separate identification of natural kratom leaf and concentrated or synthetic alkaloid products, particularly 7-OH.

Several states have accelerated efforts to regulate or prohibit concentrated 7-OH products while treating natural kratom leaf differently. Missouri has become a leading example. In 2026, the Missouri Attorney General brought enforcement actions against major retailers of 7-OH products, and one of the state's largest distributors agreed to suspend sales in Missouri. These actions were directed largely at concentrated alkaloid products rather than traditional whole-leaf kratom and

illustrate the rapidly changing regulatory landscape facing physicians and patients. More broadly, state approaches to kratom have become increasingly varied, ranging from total bans on kratom products to restrictions on concentrated alkaloids such as 7-OH. Other states have enacted Kratom Consumer Protection Acts that provide a regulatory framework for quality, labeling, and consumer protection. Since the legal and regulatory status of kratom and 7-OH is rapidly changing, referencing current Missouri statues and applicable guidance from state and local authorities when counseling patients is advised.

Distinguishing these exposures at intake may enhance clinical recognition, guide appropriate monitoring and treatment, and improve the quality of data available for surveillance systems that currently struggle to capture emerging synthetic substances accurately.[13] Counseling should therefore emphasize uncertainty, variability, and individualized risk. Recognizing the difference between whole-leaf kratom and high-potency alkaloid products can help physicians provide more nuanced guidance and avoid unnecessary generalizations.

In patients using concentrated or synthetic alkaloid products, particularly those with a history of opioid use disorder, heightened vigilance for signs of respiratory depression, overdose risk, and withdrawal may be warranted. Documenting kratom-related exposures in the medical record supports continuity of care and may aid future clinical decision-making. Ensuring accurate documentation of a patient's kratom use, with specific distinction between whole-leaf kratom and 7-OH products, will improve risk assessment and guide appropriate monitoring and treatment strategies.[13] As the marketplace continues to evolve, clinicians are best served by maintaining an evidence-informed approach grounded in pharmacology rather than assumption. Careful attention to product type, dose, and co-use can help physicians navigate patient conversations with clarity and clinical confidence while supporting harm reduction and patient safety.

References

1. Institute of Emerging Health Professions, Thomas Jefferson University; JB Pharma Consulting; AlaBiopharma Consulting; PinneyAssociates; NP Pharma. Safety and tolerability of single and multiple daily oral doses of dried kratom leaf powder in a randomized trial in healthy volunteers. Ther Drug Monit. Published online January 5, 2026. Accessed January 8, 2026. https://journals.lww.com/drug-monitoring/fulltext/9900/safety_and_tolerability_of_single_and_multiple.435.aspx.
2. Altasciences Company Inc. Adaptive Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of Kratom in Healthy, Nondependent, Adult Recreational Polydrug Users With Opioid Experience; Clinical trial registration NCT06072170; clinicaltrials.gov, 2025. https://clinicaltrials.gov/study/NCT06072170.
3. Huestis, M. A.; Bothmer, J.; Hudzik, T.; Henningfield, J. E.; Swift, S. Safety and Tolerability of Single and Multiple Daily Oral Doses of Dried Kratom Leaf Powder in a Randomized Trial in Healthy Volunteers. Therapeutic Drug Monitoring 2022, 10.1097/FTD.0000000000001427. https://doi.org/10.1097/FTD.0000000000001427.
4. Kruegel AC, Grundmann O. The respiratory depressant effects of mitragynine are limited by its conversion to 7-hydroxymitragynine. J Med Chem. 2018;61(6):2665-2675. Accessed January 8, 2026. https://pmc.ncbi.nlm.nih.gov/articles/PMC9314834/.
5. Hemby SE, McIntosh S, Leon F, Cutler SJ, McCurdy CR. Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. Addict Biol. 2019;24(5):874-885. Accessed January 8, 2026. https://pubmed.ncbi.nlm.nih.gov/29949228/.
6. O'Malley Olsen E. Notes from the field: unintentional drug overdose deaths with kratom detected—27 states, July 2016–December 2017. MMWR Morb Mortal Wkly Rep. 2019;68(14):326-327. Accessed January 8, 2026. https://www.cdc.gov/mmwr/volumes/68/wr/mm6814a2.htm.
7. FDA Adverse Event Reporting System (FAERS) Public Dashboard for Drugs and Biologics - FDA Adverse Event Reporting System (FAERS) Public Dashboard for Drugs and Biologics | Sheet - Qlik Sense. https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis.
8. Kratom safety and toxicology in the public health context: research needs to better inform regulation. Front Pharmacol. 2024;15:1403140. Accessed January 8, 2026. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1403140/full.
9. World Health Organization Expert Committee on Drug Dependence. Pre-review report: kratom. Published 2021. Accessed January 8, 2026. https://cdn.who.int/media/docs/default-source/controlled-substances/unedited--advance-copy-44th-ecdd-review-report_kratom.pdf.
10. National Institute on Drug Abuse. Kratom. Updated March 25, 2022. Accessed January 8, 2026. https://nida.nih.gov/research-topics/kratom.
11. Pullman MK, Kanumuri SRR, Leon JF, Cutler SJ, McCurdy CR, Sharma A. Cardio-pulmonary arrest in a patient revived with naloxone following reported use of 7-hydroxymitragynine. Clin Toxicol (Phila). Published online August 11, 2025. Accessed January 8, 2026. https://www.tandfonline.com/doi/full/10.1080/15563650.2025.2565428.
12. Smith KE, Siva S, Sharma A, Rattenni R, LeComte R, McCurdy CR, Boyer EW, Strain EC. Complicating factors surrounding concurrent use of kratom and a novel 7-hydroxymitragynine product among a participant enrolled in a kratom clinical trial. J Addict Med. Published online 2025. Accessed January 8, 2026. https://journals.lww.com/journaladdictionmedicine/abstract/9900/complicating_factors_surrounding_concurrent_use_of.600.aspx.
13. Kopczynski A, Song W, Wu A, Suzuki J. Kratom use trends within the Mass General Brigham system from 2017 to 2024. JAMA Netw Open. 2026;9(3):e262037. doi:10.1001/jamanetworkopen.2026.2037.

Disclosure

NA is a consultant for the Global Kratom Coalition. **MM**



Physician Involvement in Healthcare Litigation: What to Do and What to Expect

by Liz LaFoe, JD & Scott Martin, JD

"The law and medicine should be very serious professions to undertake, should they not? People's lives and fortunes depend on them."
— George Eliot

Introduction

Practicing as a physician is not without legal risk. Even the best among the profession can become entangled in a healthcare litigation matter, sometimes of their own volition. Healthcare litigation can be civil, criminal, or administrative and can take place in state or federal court, or before an administrative tribunal, such as Missouri's Administrative Hearing Commission (AHC). Criminal cases typically arise from alleged violations of laws against waste, fraud, and abuse. Civil cases can include alleged medical malpractice—among the most common type of healthcare litigation—as well as contract disputes and labor and employment matters. Administrative cases typically involve a government board or agency. Examples are physician's professional license matters, an appeal of an audit finding, or a survey of a health care institution such as a hospital or nursing home.

This article is designed to provide a practical guide for physicians who find themselves involved in a case, whether as a defendant, witness, or as a plaintiff bringing their own claim. A physician who reads this article should come away feeling prepared and confident in their ability to navigate common legal situations with expert help from experienced counsel.





Liz LaFoe, JD, and Scott Martin, JD, are Senior Counsels with the firm Husch Blackwell. The information contained in this article should not be construed as legal advice or a legal opinion on any facts or circumstances. The contents are intended for general informational purposes only, and readers are urged to consult their own attorney concerning their own situation and any specific legal questions.

Part I: When You Are the Defendant or Respondent

Physician entanglement in healthcare litigation is common, as physicians are generally seen by attorneys and judges as the leaders of patient care. Being named as a defendant or respondent in a legal proceeding is understandably stressful, but it is a manageable situation when approached with the right preparation and the right legal team. The right legal team includes a lawyer experienced in the specific area of law of the matter (e.g., medical malpractice defense for a medical malpractice case, a government investigation of claims submitted for medically unnecessary care, or an investigation by a professional licensing board).

This section addresses common scenarios in which a physician may find themselves a defendant or respondent: medical malpractice cases, professional license matters, and government investigations and audits.

A. Medical Malpractice Cases

Medical malpractice cases in Missouri are brought under the common tort law. This is also governed by medical malpractice reform provisions under state law. Generally, these cases must be filed within two years of the date the complained of conduct occurred, but there are exceptions.[1] Hundreds of medical malpractice cases were brought against physicians in Missouri in 2025 alone. Most medical malpractice cases take considerable time to resolve, often years. Working closely with defense counsel and knowing what to expect in a case at each stage can ease the mental and emotional toll on the provider.

How You Will Be Notified

If a physician is named in a malpractice lawsuit, they will be formally served with a copy of the complaint or petition outlining the allegations involving them together with a summons describing the number of days by which a responsive pleading must be filed. In state court that is 30 days; in federal court 20 days from the date of service. Therefore, prompt attention should be given to these documents.

Immediate Steps

When served, the physician should immediately notify their insurance carrier of the lawsuit. This is crucial because responses to a lawsuit are due in as little as 20 to 30 days from the date it was served. It is important that the attorney handling the defense have time to analyze the lawsuit and prepare a response. Even before service of a formal petition or complaint, it is important to notify one's employer (if applicable) and the insurance carrier if there is a reasonable likelihood of a potential claim—for example, after a letter is received from an attorney seeking records concerning an alleged significant medical incident or error.

When to Consider Private Counsel

In very rare situations where a verdict may reasonably exceed a physician's insurance coverage, the physician should consider hiring their own medical malpractice counsel. If the alleged claims include punitive damages or claims that likely fall outside the scope of what the insurance covers, the insurer will generally send a "reservation of rights" letter to the physician, requiring the physician to consult private counsel since punitive damages as a matter of public policy are generally not covered by insurance. Private counsel may also be able to negotiate on the physician's behalf to resolve coverage disputes in advance of settlement discussions or a verdict.

Preserving Evidence and Preparing Your Defense

If the physician is a named defendant and has control over the medical or other records, there is a duty to preserve all documentation that may be relevant to the case—the patient's file, the electronic health record, and any associated records, whether in digital or paper form. Records should never be altered or destroyed after the fact without a legitimate need. If there is a need to do this after a claim is filed or demand letter received, the physician should first consult with defense counsel before attempting to make any change. This avoids a claim of spoilation of evidence, which itself can result in sanctions by the court. A revised document can turn an otherwise defensible case into a liability.

Often, healthcare litigation is filed a long time after the events giving rise to the claim actually occurred. If the case involves care personally given or overseen by a physician, that physician should take some time to reflect on the care provided and may even want to prepare a diary or notes of recollections. Ideally, anything prepared should be in the form of correspondence to the physician's attorney so it will be considered a privileged document and protected from disclosure.

The Discovery Process

Once a lawsuit is underway, the case will enter the discovery phase, during which both sides exchange relevant information. Physicians should expect to encounter written interrogatories (formal questions that must be answered under oath), requests for production of documents, and depositions. A deposition is sworn, out-of-court testimony where opposing counsel asks the physician questions, typically with a court reporter present. Depositions can feel adversarial, but preparation with defense counsel beforehand is the best way to approach them with confidence. Defense counsel will help the physician understand the types of questions to expect, how to answer clearly and concisely, and when it is appropriate to say: "I don't recall."

Key Advice: Protect Privileged Communications

When a physician has received formal notice of their involvement in a case, investigation, and even in cases where it seems likely a lawsuit will be filed, it is crucial to avoid discussions of the matter with anyone other than the physician's counsel, insurer, or, in some cases, the risk management or in-house legal department of one's employer. As Will Rogers famously said, "Never miss a good chance to shut up." It can be tempting to discuss cases, especially medical malpractice claims, with coworkers or staff, but physicians should resist because those conversations are not protected by attorney-client or other privileges, and they are often discoverable in the lawsuit. Even a seemingly innocent conversation seeking reassurance about care provided could be misconstrued by a plaintiff's lawyer and prove detrimental to the physician's defense.

B. Professional License Matters

How You Will Be Notified

If a physician's license is being investigated—whether due to a patient complaint or because a physician was a named defendant in a medical malpractice lawsuit or government investigation for fraud, the Board of Healing Arts (BHA) will typically send a letter to the physician. It may merely request a response from the physician to a complaint filed with the BHA, or one notifying the physician that a complaint may be filed under the physician practice act and offering a settlement. Normally, the BHA cannot place restrictions, such as suspension or probation, on a physician's license without providing them with notice and the opportunity for a hearing before the Administrative Hearing Commission (AHC).[2] That would be initiated through a formal complaint filed with the AHC sent to the physician by registered mail.

Relationship to Malpractice Cases

BHA investigations are frequently triggered by a physician being a named defendant in a medical malpractice lawsuit, though they can also arise independently from patient complaints, mandatory reporting by hospitals or other healthcare facilities, or referrals from other state or federal agencies. If an investigation derives from the physician being named as a defendant in a lawsuit, their defense counsel for the lawsuit will typically assist them with responding to and handling the corresponding BHA investigation, if that is covered by the applicable insurance policy. Nevertheless, it is important that the physician inquire of insurance defense counsel about their experience with regulatory cases. The physician should also be aware that BHA investigations and civil malpractice cases proceed on separate tracks with different timelines, standards of proof, and potential outcomes, and a favorable result in one does not guarantee a favorable result in the other.

Retaining Experienced Regulatory Counsel

BHA proceedings operate under different rules and procedural standards than civil litigation, including medical malpractice, and an attorney experienced in this area will understand the nuances of the process, the range of possible outcomes, and how best to protect the physician's license. Lawyers have specialized areas of practice just as physicians do so it is important to ensure the physician's counsel has the requisite experience to handle the matter.

What's At Stake

The consequences of a BHA proceeding can be significant. Possible outcomes range from a letter of concern or reprimand to probation, suspension, or, in the most serious cases, revocation of the physician's medical license. Conditions may also be placed on the physician's license, such as mandatory continuing education, supervised practice, or restrictions on the types of procedures performed. Because these outcomes directly impact a physician's livelihood and professional

reputation, it is prudent to consult counsel experienced in professional license defense promptly.

C. Government Investigations and Audits

Types of Investigations

Government investigations can arise from alleged violations of federal or state healthcare fraud laws, including the Federal Anti-Kickback Statute (AKS), which prohibits knowing and willful remuneration to induce or reward patient referrals, and the Stark Law, which prohibits physicians from referring Medicare/Medicaid patients for health services to providers where they or their immediate family have a financial relationship or the Federal False Claims Act.[3] Physicians may also face audits related to Medicare or Medicaid billing, where the government alleges that an overpayment has been made and seeks to recover funds. Government investigations and audits often overlap with one leading to another in many cases.

How You Will Be Notified

Notification of a government investigation can take several forms. A physician may receive a formal letter, a subpoena for records, or, in some cases, a visit from government agents.

An audit finding—such as an alleged Medicare overpayment—will typically be communicated through written correspondence from an agency of the US Department of Health and Human Services (HHS), one of their contractors. Audit results that lead to overpayment demands can be appealed administratively, and these administrative cases can also end up in federal court, as the losing party typically has the right to appeal an adverse decision.

Criminal Exposure and the Importance of Counsel

Some healthcare law violations carry criminal penalties, including substantial fines and imprisonment. Because the stakes in government investigations can be extraordinarily high, early involvement of experienced healthcare regulatory and fraud defense counsel is critical. A physician who receives any indication of a government investigation should not wait to see how the matter develops before consulting an attorney.

Further, early settlement of an audit of a handful of claims for a few thousand dollars can be interpreted later as an admission of a billing error triggering the need to self-audit to refund additional money for the alleged errors. It might be better to challenge even a claim for a few thousand dollars to avoid a later larger claim. Contacting experienced healthcare regulatory counsel early even for a small audit can help.

Key Advice

If contacted by government investigators, a physician, if possible, should not provide statements or answer questions without counsel present, who can advise the physician of their rights and obligations in such situation. While the instinct to cooperate is understandable, even well-intentioned statements can be used against a physician in subsequent proceedings. Physicians should preserve all relevant billing, financial, and medical records and retain experienced healthcare fraud or healthcare regulatory counsel immediately.

Part II: When You Are a Witness

Fact Witnesses and Expert Witnesses

Even if a physician is not a party to a case, their opinion in a matter can often make or break the case. Physicians may become involved as either fact witnesses or expert witnesses. A fact witness is a physician who played a direct role in the patient's care or the events underlying the litigation. An expert witness, by contrast, is retained by one side for their specialized and technical knowledge—typically their understanding of the standard of care—and provides an opinion on the evidence in the case. Expert witnesses are typically paid at reasonable fair market rates for their review of the evidence, opinion, and testimony. Physicians who are approached about serving as an expert witness should carefully consider the time commitment involved, as the role typically requires a thorough review of medical records, preparation of a written opinion, and potentially testifying at a deposition and at trial. Expert witnesses should also be mindful that their opinions and testimony become part of the public record, and their credibility may be scrutinized in future cases. Expert witnesses should present honest opinions within their area of expertise, without regard to compensation for their testimony.

How You May Be Contacted

If a physician is going to be called as a witness, attorneys on either side may first reach out informally to request information and potentially solicit the physician's opinion and testimony. This is true for all different types of cases, including administrative matters. If a physician is going to be formally called as a witness, they may also be subpoenaed. A witness subpoena is a court (or administrative tribunal) order compelling an individual to give testimony. Cooperation with informal communications may avoid the need for a subpoena. Subpoenas can also be issued for records within the physician's possession. A subpoena can be contested with a motion to quash, but courts are generally inclined to allow subpoenas if they are seeking witness testimony or documents that are relevant to the case.

Key Advice

Although not always necessary, the best practice is for a physician to consult their own counsel before or in conjunction with serving as a witness in a case where they are not a party. This is particularly important for treating physicians, who could potentially be added as a defendant in a case where the statute of limitations has not expired. Even as a non-party witness, physicians should avoid discussing the matter outside of privileged communications with their own attorney or the attorney retaining them. When giving testimony, whether in a deposition or at trial, the physician should be truthful, precise, and responsive only to the questions asked. Preparation with counsel beforehand will help ensure the physician presents their knowledge clearly and confidently.

Part III: When You Are the Plaintiff

When Physicians Bring Cases

Physicians involved in healthcare litigation may also be the ones bringing the case. Nothing prohibits a physician from being a plaintiff in healthcare litigation, whether the case arises from an employment or contract dispute, or even if the physician was a patient on the receiving end of poor care or malpractice and suffered an injury due to that. A physician may also act as a "whistleblower" in uncovering fraud and become the plaintiff in a fraud case. In the employment context, disputes may arise from wrongful termination or a breach of a non-compete agreement. In whistleblower or qui tam cases, the physician may be entitled to a share of any recovered funds, but these cases can be complex and lengthy, and the physician should be prepared for the possibility that the government may not intervene in the case.

Key Advice

A physician considering bringing a claim should seek out an attorney experienced in the specific area of law involved. Litigation as a plaintiff requires a significant investment of time, energy, and often money, and the physician should carefully weigh the costs and benefits before proceeding. Many of the same principles discussed throughout this article apply equally to a physician plaintiff: document everything early, maintain confidentiality about the case, and work closely with experienced counsel.

Conclusion

Involvement in healthcare litigation is an entanglement most physicians seek to avoid because aspects of it are foreign to physicians who have not yet experienced it. However, given the volume of healthcare litigation, and the importance of a physician's opinions to the outcome of most healthcare cases, it is something that may happen in any physician's practice. Knowing what to expect and how to prepare may ease the burden of litigation entanglement considerably.

Finally, physicians involved in healthcare litigation should note that, although the legal world can be intimidating, the physician is the true expert in patient care. Judges, attorneys, and jurors highly value and rely on the perspective, experience, and opinions of physicians in healthcare cases. Physicians who can effectively communicate and advocate for care provided often find their testimony is the most believable evidence in a case.

References

1. See e.g., RSMo. Sections 516.105; 538.225.
2. RSMo. Chapter 536; RSMo. Section 334.100.
3. See 42 U.S.C. Section 1320a-7b(b); 42 U.S. Code Section 1395nn. **MM**

The Future of Care: Augmented Intelligence as a Partner in Patient Care

by Kevin D. Weikart, MD

Too often, we are staring at a computer screen frantically typing notes, trying to capture every detail for the electronic health record. The screen has become a barrier between us and the person we are trying to heal.

Today, we physicians are overwhelmed. The administrative burden of medicine has grown so profound that doctors often spend more time with their keyboards than with our patients. This has led to profound burnout and cuts into the spirit of why we entered medicine: to care for people. Time spent in the evenings and weekends updating the notes are crushing to family time. I remember looking through the doors of my study, at my children, in the other room, as a distant eight-paneled window separated me from their life. Augmented intelligence is entering the clinic—not as a replacement for the physician—but as a silent assistant ready to bear the administrative weight and give doctors their time in real time.

Ambient AI

The most immediate impact AI is having in the exam room is through ambient medical transcription. Imagine an AI system that quietly sits in the background listening to the natural conversation between a doctor and a patient, using advanced speech recognition and natural language processing, It instantly translates the conversation into accurate, structural clinical notes. We're just not saving a few minutes of typing. It's about restoring the doctor-patient connection.

When physicians do not have to act as their own documenter, we can look our patients in the eye, and follow nonverbal cues, patient's expressions, show empathy, and engage more deeply with our care. Studies have shown that when doctors use ambient AI scribes, face-to-face time with patients can increase by over 50%, while time spent wrestling with the electronic health records drop significantly.

Improving Writer's Block with Enhanced Empathy

Beyond the exam room, AI is tackling another major source of physician burnout: the endless flood of patient messages. Between appointments, patients use online portals to ask questions, request refills, or report side effects.

Health systems are now piloting generative AI tools to help doctors manage this inbox. When a patient sends a message, the AI reviews it and drafts a response. It doesn't send it automatically—the doctor must review, edit, and approve it. Surprisingly, researchers at US San Diego Health found the AI doesn't save just effort. It actually helps draft more compassionate, detailed responses. At the end of an exhausting 12-hour shift, an AI doesn't get tired. It provides an empathy-infused starting point that breaks the doctor's writer's block, allowing them to make a thoughtful, crafted reply more easily.

A Collaborative Future

Clearly, AI cannot make medical decisions. There is no diagnosing patients or deciding a treatment plan. AI is a collaborative tool. It is handling the data processing, summarizing, and the formatting so that the physician can focus on the human in front of them in real time.

There are still challenges ahead. We must ensure these systems protect patient privacy, eliminate biases, and maintain absolute accuracy. The potential is undeniable. By adopting AI, we are not making medicine more robotic. We are using technology to automate the paperwork so that we can bring humanity back to healthcare. **MM**



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Report of the American Medical Association Annual Meeting

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

The 2026 Annual Meeting of the American Medical Association (AMA) House of Delegates (HOD) was June 5-10, in Chicago, Illinois.

As the policy-making body of the AMA, the HOD considered issues in particular artificial intelligence (AI), public health concerns, Medicare payment reform, and Medicaid eligibility restrictions. Other issues considered were scope of practice, physician burnout, and corporate practice of medicine.

Elections were held. Sandra Fryhofer, MD, was elected to be President-Elect. Lisa Egbert, MD, and John Armstrong, MD, were re-elected, respectively, as Speaker and Vice-Speaker of the HOD.

Bobby Mukkamala, MD, the outgoing President, spoke at the Organization of State Medical Association Presidents (OSMAP). He focused on increasing physician reimbursement under Medicare and Medicaid, fixing Medicare, and reforming prior authorization. At the opening session of the HOD, he recounted the story of his being operated upon for a brain tumor two years ago. He spoke of access to medical care and of getting patients the health care that they need.

John Whyte, MD, the new AMA Executive Director, talked about the role of physicians as essential leaders of change in the health care system. Physicians, working through the AMA, must become the "architects" of medicine's future.

He cited the "Your Care is at Our Core" campaign. The AMA has opposed changes in vaccine policies, called for regulation of AI in medicine, and advocated for physicians. We must be stewards of patient care and the profession.

On June 9, Willie Underwood, MD, was inaugurated as the 181st President of the AMA. In his inaugural address, he focused on patient care and on the role of physicians to change and improve the lives of their patients. He recounted his inspiring personal story. He said that our AMA has a long legacy. We must preserve the good parts, while acknowledging mistakes made in the past. As we lead medicine into the future, we must ensure a health care system, with dignity, which works for all of us and leaves no one behind. He said the AMA must be an ally for physicians, fighting to reduce barriers to physician practice and against barriers to patients.

The HOD sets AMA policy in two ways. First, delegates submit resolutions proposing policy changes or action. Second, the Board of Trustees (BOT) and one of the Councils submit a report containing recommendations for policy or actions. Resolutions and recommendations may be adopted, modified, or rejected.

Medicare reform, particularly of the physician payment system, remains an important goal. See https://fixmedicarenow.org.

There was concern over the recent Medicaid cuts in funding and restrictions on eligibility, particularly work requirements. BOT Report 24 called for the AMA to try to mitigate such cuts. Resolution 116 asked for a study of cost implications of Medicaid Advantage versus state administered Medicaid.



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Moving to Medicare, Resolution 107 asked for better oversight of Medicare Advantage programs. BOT Report 23 advocated changes in assignment to Medicare Advantage. Resolution 105 called for opposing autoenrollment in Medicare Advantage.

Medical education is always a concern of the AMA. There are not enough physicians in practice. Even though medical schools have expanded, new GME positions have not kept up. The Council on Medical Education (CME) Reports 3 and 4 discussed proposals to establish indigenous-led medical schools. Resolutions 312, 316, and 318 dealt with various aspects of residency training.



MSMA physicians attending the 2026 AMA Annual Meeting in Chicago. Front row, L-R: Jay Devineni, Betty Drees, Peggy Barjenbruch, Joe Corrado, Ravi Johar, and Samantha Shuster. Back row, L-R: Brian Biggers, Joanne Loethen, Ellie Azrak, and David Barbe. Not pictured: Charles Van Way and Kevin Weikart.

Nutrition is a traditional concern of the AMA. BOT Report 29 discussed providing educational materials on ultra-processed foods. The Council on Science and Public Health (CSPH) Report 3 discussed the public health implications of food subsidies. Resolution 402 asked for stricter regulations of raw milk. Resolutions 401 and 409 asked for restrictions on toxic materials in food. Resolution 426 asked for incorporating nutrition to reduce cardiovascular risk. Resolution 610 advocated plant-based diets at AMA meetings.

Kansas and Missouri resolutions were of particular interest. Resolutions 202, 203, and 505 were from Missouri. Resolution 202 asked to define "unsupervised practice of medicine." A BOT Report will be forthcoming. Resolution 203 asked for support of outcomes associated with unsupervised nurse practitioner practice. Resolution 218 was from Kansas, opposing the practice of "jury anchoring" in medical liability cases.

Scope of practice remains a serious issue. Non-physicians are constantly trying to gain privileges formerly reserved for physicians, most commonly at the state level. But there is a bill before Congress that would enable pharmacists to provide evaluation and management services for patients with COVID-19, influenza, and other infectious diseases. The AMA opposes this legislation. In a related issue, Resolution 229 called for the AMA to stop using the term "providers," as it blurs the distinction between physicians and non-physicians.

BOT Report 25 advocated for federal legislation to prohibit the corporate practice of medicine. Resolution 709 called for restrictions on the use of utilization review as an administrative back door into corporate medical practice. BOT Report 20 discussed mitigating the excessive use of prior authorization.

The increasing role of AI in health care is an increasing concern. The AMA defines AI as "augmented intelligence" rather than the more commonly used "artificial intelligence," but the terms are interchangeable. Resolutions 003, 007, 238, 246, 248, 505, 515, and CSPH Report 7 all dealt with the use of AI in clinical practice. BOT Report 28 dealt with the use of AI in prior authorization.

Drug use continues to be an issue. Resolutions 201 and 233 asked for restrictions on 7-Hydroxymitragynine (7-OH) derivatives of kratom. Resolution 502 asked for better support of inpatient methadone treatment.

There was concern over the protection of health care in wars around the world. Resolution 602 strongly advocated for the protection of health care facilities, physicians, and other health workers. While directed initially towards the Israel-Gaza war, it was modified to include all such armed conflicts.



Left, Charles Van Way receives recognition as the 2025-2026 President of the Organization of State Medical Association Presidents.



AMA Past President David Barbe and MSMA President Elect Joanne Loethen.



Deepu Sudhakaran was elected Chair of the AMA International Graduate Medical Section.

The HOD continues to grow, reaching 793 at this meeting, and is becoming unwieldy, not to mention expensive. A special report from the Council on Long Range Planning and Development contained strategies to limit growth, including diminishing the number of delegates, changing the formula for allocating delegates by number of members, and others. There will be further virtual "town meetings" to test out the concepts. It appears inevitable that there will be an adjustment in the next year or two. Probably, the AMA will limit the HOD to around 600.

The meeting of OSMAP, the Organization of State Medical Association Presidents, takes place just before the AMA meeting. Bobby Mukkamala, MD, AMA President, David Atzuss, MD, Chair of the BOT, and Todd Askew, AMA Senior VP for Advocacy, participated in a panel discussion on current AMA initiatives. Gary Price, MD, gave an update on the activity of the Physicians' Foundation. He pointed out that 82% of physicians are now employed, a dramatic decrease over the past 25 years.

A panel at OSMAP was convened to discuss unionization of physicians, specifically the role of state medical societies, The moderator was Molly Reese, JD, from the AMA Advocacy Resources Center; speakers were Jeff Howell, EVP of Missouri State Medical Association, Richard Long, JD, General Counsel of Pennsylvania Medical Society, Richard Levenstein, Esq, of Nelson Yager. Unions represent only 8.5% of physicians. The consensus of the panel was that unionization may solve problems for physician-employees, BUT there is no generally accepted model for unionization of physicians and there may be unintended consequences, both short-term and long-term.

Physicians from Missouri continue to serve in leadership roles. David Barbe, MD, is Past President of the AMA. Jerry Kennett, MD, serves on the Board of the AMA Foundation. Marc Mendelsohn, MD, serves on the Council on Science and Public Health. Deepu Sudhakaran, MD, was elected Chair of the AMA International Graduate Medical Section. Charles Van Way, III, MD, has been President of OSMAP, the Organization of State Medical Association Presidents, and has now moved to Past President. Jeff Howell, JD, MSMA's EVP, serves on the Board of Directors for the American Society for Medical Association Counsel, and also on the Executive Committee for AMA's Advocacy Resource Center.

This meeting considered more than 250 reports and resolutions. With so much going on, this summary is necessarily incomplete. The proceedings of the meeting, as well as summaries of addresses by Drs. Mukkamalas, Whyte, Underwood, and others, are available on the AMA website. More information can be found https://www.ama-assn.org/house-delegates/annual-meeting/highlights-2026-ama-annual-meeting. The Interim Meeting of the HOD will be in Orlando, Florida, November 6-10, 2026. **MM**

The Making of a Physician and Politician

by George J. Hruza, MD

A history that started with the unimaginable horror of the Holocaust, and the privation and terror of socialism led us to the United States to live the American Dream.

It was a chilly morning in Mauthausen Concentration Camp, Austria, in the Fall of 1944. The Jewish prisoners were ordered outside to line up for their daily roll call. The prisoners got in line—all but two: a patient and his Jewish surgeon. The SS officer came up to the doctor and yelled: "RAUS," (everyone must get in line for roll call.) The surgeon calmly told the SS officer: "I will be out shortly. I am almost finished amputating this man's gangrenous leg. If I don't finish, the man will die." The SS officer told the surgeon: "Come out and get in line now and I will let you live or finish your surgery and I will shoot you." The surgeon briefly looked up at the SS officer and then proceeded to complete the amputation. The SS officer came up to the surgeon, put the gun to his head and shot him. A 19-year-old young woman heard and watched this standing in line. She thought to herself, "I don't know what this physician has, but I want that." That young lady was Judita Ilkovics Hruza, my mother.

After being liberated by Patton's 71st infantry on May 4, 1945, weighing all of 67 pounds and afflicted with typhus, Judita recovered with the help of the brave American GIs. She moved to Czechoslovakia where she became a pediatrician. She instilled that desire to make a positive difference in other people's lives in me and my sister. We both became physicians; Eva became a radiologist and I a dermatologist and micrographic dermatologic surgeon.



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Judita Hruza after her Holocaust talk at Shaare Emeth, Creve Coeur in 2012 with a photo of her taken after the war in 1945 at age 21.

Growing up in socialist Czechoslovakia was very different from the United States (US). There were shortages of everything including toilet paper. Fresh fruit and vegetables were almost non-existent except for what we were able to pick in the forest. If there was a line in front of a store, my parents would get in it without knowing what was for sale. Oranges were a true luxury. I remember we got one orange once every two to three months that my mother would cut in half and let us alternate picking which half we would get. My older sister picked the smaller half. When it was my turn, as the bratty younger brother, I picked the larger half. The wait list for a car (if one could afford one) was eight years; for an apartment—21 years. I got firsthand experience with government-run healthcare. At age 8, I needed my adenoids removed. My mother took me to the hospital. I was taken to the OR, laid down, and my adenoids were taken out with any anesthesia. Apparently, anesthesia for adenoidectomy was not in the national health service budget.

Our telephone was bugged. Mail from the West was opened by the security apparatus. Censorship was complete and propaganda incessant telling us that the West consisted of fascists that were amassed on our border ready to attack at any time. My mother even had a taste of "cancel culture." In 1956, during



10-year-old Jiri (George) on the train station platform in Prague ready to escape to the West from socialist Czechoslovakia in 1966.

the Soviet invasion of Hungary, my mother, being Hungarian, listened to radio-free Hungary and shared with her friend, another pediatrician, what was actually going on. That 'friend' reported the conversation to her communist party supervisor. My mother immediately lost her position as a professor at Charles University and was sent to work at an elementary school in the suburbs. My mother's 'friend' ultimately became the minister of health. Neither my sister nor I would be allowed to attend University as we would have 40 demerits on a 100-point scale due to both parents being part of the intelligentsia.

I got my seriousness and perseverance from my mother. My father was a brilliant scientist but also had a daring streak, a playful sense of humor, and skepticism of government, which I share. In Spring 1945, Patton's army was heading east into Czechoslovakia. My father, 16 at the time, joined the Prague resistance and subsequent uprising against the Nazis. He was involved with running firefights on Prague's cobblestone streets saving his helmet as a souvenir with a round depression in the left front from a German bullet. I captured some of his daring traits by going helicopter skiing and seeking out the steepest ski pitches or 'butterfly runs.' However, I am also rationally cautious. When we were cross country skiing in the Krkonose mountains in Czechoslovakia, we skied up to a sign with a skull and crossbones and AVALANCHE DANGER. I was eight-years old and refused to go down that way, turned around and started walking around the danger area adding hours to the trip. My father reluctantly agreed to follow me. At Charles University, his team was required to hold communist indoctrination meetings. He thought that was stupid, so he wrote minutes of the non-existent meeting. The communist party apparatchiks thought they were so good that they sent a party supervisor to attend the meeting to learn how to do it. My father organized and rehearsed the meeting ahead of time; a Potemkin village type effort.

My parents hatched a plot with the help of my uncle, Denes Ilkovics, who escaped from Hungary to Sweden in 1956, to get to the West. My father was in New York as part of a cultural exchange program. The rest of the family were kept as hostages to make sure that my father would return. Being 10, I was kept in the dark about the plot. My mother told me to bring my favorite stuffed bear and stamp collection to show to my uncle. Denes arranged a visa to Sweden to be picked up in Yugoslavia, which was not fully behind the Iron Curtain. Of course, we did not have permission to get the visa from the Czech Department of the Interior. We traveled to Yugoslavia and went to the Swedish embassy in Belgrade. The Swedish consul asked where our permit for the visa was. My mother showed him our permanent permission to go to Hungary and Bulgaria. The only word he recognized was 'permanent.' The rest was in Czech. He accepted the 'permit!' We then crossed to Austria at about 5:00 a.m. at the smallest border crossing hoping the guards would be sleepy and had likely never seen a Czech passport. My parents were tried in absentia in Czechoslovakia for escaping. My father would have spent 12 months in prison, my mother 18 months. We arrived in Stockholm on December 31, 1966, and celebrated with my first taste of champagne.

At the time of our escape, I was indoctrinated to be a good little communist. It took six weeks of being in the West that I realized that I was being fed lies upon lies by the communists. I declared that I was no longer a communist and have been a free market capitalist ever since. In Sweden, I learned Swedish, became a solid downhill and cross-country skier, and learned orienteering. After three and a half years, we finally got a visa to come to the US to join my father in New York.

We traveled by ship. When I saw the Statue of Liberty, I instinctively knew that this was the place for me. We started out in a four-story walk-up studio apartment on the Lower Eastside. All of us took full advantage of the incredible opportunity that the US has to offer. My father became a prominent professor at NYU doing NIH

research on aging before it became popular and later practiced pathology. My mother switched to forensic psychiatry treating the criminally insane at Manhattan Psychiatric Center (having done both pediatric and psychiatric residency). My sister became a radiologist.

A few months after arriving in the US, I took the admissions test for Stuyvesant High School, a math and science public high school in Manhattan. I found the math part easy, but in the English part I would go for pages where I recognized only a few words. Fortunately, my math score was high enough to get me admitted. I spent 11 years at NYU as an undergraduate majoring in physics, then medical school followed by dermatology residency with a detour to New York Hospital-Cornell for internal medicine internship.

I found dermatology appealing because I could see the disease (when I tried to listen to the heart and I was supposed to hear S3 or S4 or a murmur, all I heard was bump-bump-bump-bump) and make a diagnosis and help patients get better. I never thought surgery would be something for me after a traumatic rotation in general surgery where I never seemed to measure up to the chief resident's liking. I did not know that my left-handedness using instruments made for right-handed individuals would be a handicap. I had the opportunity during my dermatology residency, to do surgery at the VA. After my first case, I realized that surgery was going to be my passion. It is quick, elegant, requires manual dexterity, a bit of artistic flair and the patient is usually cured. I enthusiastically applied for dermatologic surgery fellowships that were in their infancy at the time. I applied to a dozen programs, all that had an open spot, got several interviews and … was rejected by all. This was quite disheartening for a guy who was top of his class in both college and medical school.

I picked myself up off the ground and, with the help of my Chairman, Irwin Freedberg, got a laser surgery fellowship at the Wellman Lab at Massachusetts General Hospital under the tutelage of John Parrish, MD, and R. Rox Anderson, MD. Just about every laser, light source, or energy-based device we use in dermatology and several other fields were conceived by Dr. Rox. Because of his contribution to dermatology and medicine at large, I awarded him the American Academy of Dermatology's (AADs) highest honor, the Gold Medal, when I was national President. We did the early work with Q-switched laser for benign pigmented



Dr. Hruza (left to right) graduation from New York University School of Medicine in 1982 with Drs. Judita Hruza, Eva Horn (nee Hruza) and Zdenek Hruza.

lesions and tattoos and short pulse carbon dioxide laser, an early version of resurfacing lasers

With my physics background, I found the research fascinating, but I missed surgery. I applied again for dermatologic surgery. This time to only two programs that still had available spots (I was a bit late). Lo and behold, I got offered both. I chose to go to University of Wisconsin-Madison where Fred Mohs, MD, was still operating. After a great three months in the summer sailing, windsurfing, waterskiing and lots of surgery followed by nine months of Wisconsin winter, I accepted a position at Washington University (WU) in St. Louis to run their dermatologic surgery program. While there, I realized that teaching and clinical research made my practice a lot more fulfilling. I trained countless residents in dermatologic surgery and trained 21 fellows in dermatologic surgery. More broadly, I have been an author on 200-plus papers and book chapters and have written four textbooks on lasers in dermatology. I have been the section editor of the dermatologic surgery section of Bologna's Dermatology for the last four editions (it is the bible for dermatology residents) and have presented on and lectured on dermatologic surgery on five continents.

I have always been interested in business and finance, so I earned my MBA at WU in Saint Louis. I then realized that I could do things better on my own. I left WU after 11 years and set up a solo private practice

in Mohs and laser surgery in Chesterfield. It quickly became clear that I made the right move. I had the same number of patients with lower reimbursement than WU, yet my collections doubled. As my practice grew, we needed more space and I wanted to improve the quality of patient care. I joined forces with one of my prior residents, Dan Ring, MD, and, after a two-year search, we found suitable land and built a 20,000 square foot medical building with an Ambulatory Surgery Center in Chesterfield. I'd say that has been one of my best investments with a tangible impact on patient care.

My desire to make a positive difference in people's lives drove me to expand my horizons beyond my practice and I got involved in organized medicine and served on many committees, boards of directors, and editorial boards. This culminated in presidencies of American Society for Laser Medicine and Surgery, American Society for Dermatologic Surgery, American Academy of Dermatology (AAD), St. Louis Metropolitan Medical Society, and Missouri State Medical Association.

The AAD presidency taught me crisis management. During my tenure I had to call for a recall election of a board member (first time ever), cancel our 20,000-attendee meeting at the start of COVID-19 and help members navigate the pandemic safely for their patients and keep their offices solvent. Next, I expanded my impact on the international arena with my election representing North America on the International League of Dermatology Societies representing dermatology societies from more than 110 countries. Our mission is global skin health, especially in low resource settings.

I have been advocating for dermatologists and their patients for 25 years. My first advocacy visit to DC was in September 2001. We concluded our Hill visits and left DC on September 10, 12 hours before 911. When United Healthcare drastically narrowed their network in Missouri, eliminating about three-fourths of their private practice dermatologists, leaving patients with longstanding relationships with their dermatologists stranded. We sprang into action, getting publicity on all the local TV stations and the *St. Louis Post Dispatch* as well as getting patients involved writing letters to their members of Congress. I took several handwritten patient letters with me to DC to meet with legislators and regulators demanding that Centers for Medicare Services (CMS) enforce rules for network adequacy. We found that network directories for dermatologists have more than a 50% error rate including one dermatologist that had passed away, orthopedist listed in the dermatology section, dermatologists that had not been in network for years or that had moved away years ago etc. Our efforts paid off with legislation and regulatory reform insisting on accurate regularly updated network directory. Since 2001, I have travelled to Washington two to three times per year advocating for our patients and testified numerous times in Jefferson City on behalf of MSMA.

In 2022, I decided that to make a more significant impact for our patients, practices and Missourians at large, I had to be on the other side of the table. I am thankful for three things that the US has done for my family: 1) Patton's 71st infantry liberated my mother from Mauthausen. I would not be here without the brave GIs. 2) The incredible freedom and opportunity afforded to my family by the US. 3) President Reagan (along with Margaret Thatcher and Lech Walesa) liberated the Czech Republic from Soviet socialist oppression.

Carrie Hruza, my wife, was all in on this next chapter in our lives. I ran for the Missouri Senate. We jumped in with both feet and gave it our all, knocking on almost 50,000 doors, raising and spending lots of money, and meeting voters from all walks of life. It was an intense and exhilarating experience. Carrie was with me every step of the way, being far more effective than me to convince voters to vote for me. We won the primary and lost the general. It was definitely a big letdown, but we picked ourselves up, stopped moping and ran for Missouri House of Representatives in 2024. We went all in again, but also wiser and more effective winning the general 57% to 43%,and outperforming the President and all statewide candidates. Carrie was again the star campaigner. I credit her for our convincing margin of victory.

My first two sessions did not disappoint. I passed (along with Rep. Chad Perkins) a capital gains tax elimination in 2025. In 2026, I passed a bill to fight antisemitism in public schools, colleges, and universities as well as five healthcare related pieces of legislation to improve access to care and ability of physicians to provide care. I was so encouraged by all the good stuff that we were able to pass and just as importantly, bad legislation we were able to block, I decided to run for re-election in 2026.

None of these accomplishments would have been possible without the partnership, support, encouragement, and positive attitude that Carrie brings to our marriage. Carrie is a powerhouse in her own right, being an accomplished optometrist, appointed to the Missouri Board of Optometry and the most prolific fundraiser for Eye Thrive, a nonprofit that provides free glasses to inner city children using a mobile optometry bus to go to schools. The positive impact this has on the children who can now see in class is immense for them academically and socially.

We have a merged family; Carrie's daughters are Hope and Rose and my children are Stephanie and Paul. Merged families often experience challenges. In our case, the kids figured a great way to bind us together. They convinced Carrie to enter the Mrs. Missouri pageant in 2010. They became her biggest cheerleaders. Carrie won the Mrs. Missouri America title, and the kids and I went to Tucson to see her compete for the title of Mrs. America. To get good seats, they all sat together doing their homework on the floor in front of the venue doors all day rather than hanging out by the pool.



Campaigning for the Missouri State Senate with Carrie at the 2022 Greentree Festival in Kirkwood.



Expanding Hruza clan in Costa Rica 2025.

Seeing our children thrive is what makes it all worthwhile: Hope worked at the West Wing of President Biden's White House appointing boards, commissions, and ambassadors. Rose, after a stint of working for Congresswoman Ann Wagner in DC, is now an L-3 at Washington and Lee Law School. Stephanie is a practicing psychologist in the Tampa area and Paul is heroically handling his many challenges related to his intractable epilepsy. Our family is growing. We took all the kids and their significant others to Costa Rica in 2025. Seeing how they all supported Paul and bonded, our growing, family was great to see. The icing on the cake is our first grandchild, a Cinco de Mayo baby named Graham,was born this year

I feel truly blessed. A history that started with the unimaginable horror of the Holocaust, and the privation and terror of socialism led us to the United States to live the American Dream. I feel so privileged to have been able to make a difference in tens of thousands of skin cancer patients' lives and now expanding my positive influence on more than six million Missourians. **MM**

CORRESPONDENCE

AI in US Healthcare: Changing How, Not Why, We Practice

A compelling editorial by John C. Hagan, III, MD, in the March/April 2026 *Missouri Medicine* issue emphasizes the potential role of artificial intelligence (AI) in healthcare, especially in addressing the growing problem of physician inaccessibility.[1] Physician shortages and increasing administrative burden have strained the healthcare system, ultimately preventing patients from receiving care in a timely manner.[1,2] The Association of American Medical Colleges (AAMC) estimates a national shortage of up to 86,000 physicians by 2036, and this barrier to access will only deepen as the population continues to age.

Dr. Hagan's editorial explores how AI can meet this challenge.[1] Since its origins in the 1950s, the field has expanded rapidly over the past decade. AI's ability to perform computational analyses and use adaptive language to communicate concisely has the potential to improve efficiency, allowing physicians to increase both the quality and quantity of care delivered.[3] This vision is rapidly becoming reality.

A 2025 American Medical Association survey found that 81% of physicians now use healthcare AI, up from 66% just one year earlier, a 15-percentage-point jump in a single year.[4] From risk screening and diagnostic imaging to electronic health record (EMR) integration and treatment decision-making, these examples only scratch the surface of what AI will be capable of doing, and its applications in healthcare will be specialty dependent. As machine learning algorithms and language models advance, the ways in which AI can be incorporated into healthcare are both endless and uncertain.

Formal education in artificial intelligence should be a standard part of medical training to best prepare future clinicians. Medical schools are already moving in this direction; the proportion of institutions offering AI curricula rose from 53% in 2023 to 77% in 2024.[5] The challenges AI poses are precisely why the future of healthcare should not be framed as a choice between humans and AI, but as an opportunity to strategically combine both in ways that strengthen the core values of medicine. AI in clinical practice must operate under physician supervision at every stage, positioning it as a valuable resource rather than an autonomous replacement.[6] Its most compelling application lies in bridging communication gaps. When a patient speaks a language or dialect for which no interpreter is available, AI can counsel them in their native tongue with clarity and cultural sensitivity, ensuring that no one receives a lesser standard of care because their dialect falls outside existing interpreter services.

AI may change how we practice, but it should not redefine why we practice. Empathy remains the cornerstone of patient-physician trust and rapport, and AI can protect it.[6] By reducing time spent on unproductive clicking within the EMR, AI gives clinicians back the time to be present at the bedside, where that trust is built. The true promise of AI is not to replace empathy but to make room for it, freeing physicians to focus on the person sitting in front of them. Equally important is acknowledging AI's disadvantages, including the potential for clinician over-reliance and the many ethical and legal questions that remain unresolved. And just as complex as navigating those challenges will be the task of educating frontline clinicians on how to use these tools effectively, without eroding the clinical reasoning and practical wisdom that remain at the heart of what it means to be a physician. Dr. Hagan draws parallels to the introduction of the World Wide Web and how it revolutionized healthcare.[1] His excellent anecdote reminds us

that the internet, now so essential to our everyday lives, was once beyond our imagination, just as AI is today.

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References

1. Hagan JC. A New Paradigm to Put US Healthcare Back on Track. Mo Med. 2026; 123(2):84-86.
2. Hoque F, Corralyn J, Shields S. The Travesty of Physician Unavailability—A Triage of Concern. Missouri Medicine 2025;122(6):467-468.
3. Hoque F, Poowanawittayakom N. Future of AI in Medicine: New Opportunities & Challenges. Mo Med. 2023;120(5):349.
4, American Medical Association. More than 80% of physicians use AI professionally: AMA survey; March 12, 2026. [Accessed April 25, 2026]. https://www.ama-assn.org/practice-management/digital-health/more-80-physicians-use-ai-professionally-ama-survey.
5. Farmakidis, Anne & Singh, Asmita & Rossi, Alexis. (2025). Artificial Intelligence Curricula in U.S. and Canadian Medical Schools. 10.15766/datasnapshot_AI_0625.
6. Hoque F. Empathy in healthcare: Harmonizing curing and caring in healthcare. J Hosp Med. 2025;20(5):517-520. doi:10.1002/jhm.13540 **MM**

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The Critical Pediatric Obesity Window: Pre-Pubertal Metabolic Disease and the Fallacy of Delayed Intervention

by Matthew Lindquist, DO & Brooke Sweeney, MD

The "waiting it out" approach to pediatric obesity is a biological and clinical fallacy that ignores the advanced state of metabolic disease present in many children under the age of 12.



Matthew Lindquist, DO, FAAP, DABOM, (pictured), is CEO, MoKan Weight Loss and Metabolic Health LLC, Prairie Village, Kansas, USA. Brooke Sweeney, MD, FAAP, FACP, DABOM is Medical Director, Children's Mercy Hospital Weight Management, Kansas City, Missouri, USA,and Professor of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA.

Abstract

Despite increasing recognition of pediatric obesity as a chronic disease, many clinicians continue to rely on "watchful waiting," assuming pubertal growth will mitigate excess weight and metabolic risk. Current evidence contradicts this approach. Children under 12 years of age with obesity frequently demonstrate clinically significant metabolic disease, including insulin resistance, dyslipidemia, dysglycemia, and metabolic dysfunction–associated steatotic liver disease (MASLD), often before symptoms emerge. Puberty does not reverse these processes; rather, physiologic pubertal insulin resistance amplifies preexisting metabolic dysfunction and accelerates disease progression. Delayed intervention allows potentially irreversible injury during a critical period of metabolic plasticity. This article reviews contemporary biologic and longitudinal data challenging the pubertal correction paradigm, highlights the concept of metabolic memory, and discusses limitations of lifestyle-only interventions. Drawing parallels to integrated pediatric mental health care, we propose a primary care–centered model emphasizing earlier metabolic screening, coordinated multidisciplinary care, and timely intervention to improve long-term cardiometabolic outcomes.

Key Words

Pediatric obesity, metabolic disease, and metabolic plasticity.

Introduction

The management of pediatric obesity has reached a critical inflection point where biological evidence and clinical practice must converge to abandon the long-standing "watchful waiting" approach. For decades, a pervasive clinical myth suggested that the rapid linear growth and hormonal shifts of puberty might naturally attenuate excess adiposity or resolve metabolic derangements.[1] However, contemporary data and our daily clinical experience show that children under the age of 12 frequently manifest advanced metabolic disease—including metabolic dysfunction-associated steatotic liver disease (MASLD), insulin resistance, and

Table 1. Clinical Assumptions vs Biological Reality of Pediatric Pbesity

Clinical Assumption	Biological Reality
Growth spurts dilute fat mass.	BMI and metabolic markers track from age 7 into adulthood.[2]
Hormonal shifts correct metabolism.	Puberty is a state of physiologic insulin resistance that is exaggerated in obesity and exaggerates obesity-related pathology.[3]
Waiting avoids early medicalization.	Delay allows for advanced fibrosis in MASLD and beta-cell exhaustion.[5]

dyslipidemia—well before they reach the ages for which pharmacological interventions are currently approved by the Food and Drug Administration (FDA).[2] In fact, the physiology (particularly insulin resistance) that naturally accompanies puberty acts not as a corrective force, but as an additive metabolic stressor that can push pre-existing subclinical pathologies into overt chronic states.[3] This report deconstructs the fallacy of pubertal correction, details the early-onset metabolic burden, and calls-to-action early intervention in a primary care-centered model of care for metabolic disease and obesity, inspired by the successful integration of pediatric mental health services.[4]

The Persistence of the Pre-Pubertal Myth: Deconstructing 'Waiting It Out'

The "waiting it out" strategy is a passive approach based on the assumption that a child's body composition will naturally "even out" as they grow taller during the pubertal transition. This perspective is frequently reinforced by societal norms and perhaps worsened by parents reluctant to discuss a topic loaded with historical stigma and trauma manifested in internalized weight bias and experienced weight bias still frequent in medical encounters. The metaphorical "can" of weight concerns is subsequently kicked down the road often until a crisis point, in the form of often preventable metabolic or mental health complications, is encountered in adolescence or pre-adolescence. Yet, research into the natural history of pediatric obesity demonstrates that adiposity tracks with high fidelity from early childhood into adulthood, with continued progression of metabolic disease and development of an increasing number and severity of co-morbidities over the lifespan.[2] This should be unsurprising, though, given obesity's high heritability.

The belief that puberty resolves obesity is contradicted by longitudinal tracking of the Body Mass Index (BMI). While some children may see a temporary reduction in BMI z-score during a growth spurt, the underlying metabolic dysfunction, particularly insulin resistance, does not necessarily remit. In fact, prospective studies show that children who enter puberty with overweight/obesity often maintain their fat mass and show a failure to recover insulin sensitivity at the end of the pubertal process, whereas their normal-weight peers return to baseline sensitivity levels.[3]

The risks of this delay are profound. Childhood obesity increases the risk of premature mortality three-fold before the age of 30, a statistic that underscores the urgency of pre-pubertal intervention.[6] Table 1 is a summary of clinical assumptions vs biological realities.

The Silent Burden: Metabolic Disease in the First Decade

The metabolic burden of obesity in children under 12 is often underestimated because it is largely asymptomatic. However, the prevalence of clinical cardiovascular and hepatic risk factors in this age group is alarmingly high. Among children with obesity, nearly 90% have at least one feature of metabolic syndrome.[7] Additionally, in US children with class 3 severe obesity (BMI >/= 140% of the 95th percentile), the prevalence of metabolic syndrome is 50%.[8]

Metabolic Dysfunction-Associated Steatotic Liver Disease

An alarmingly frequent occurrence in our tertiary referral clinics, MASLD is now recognized as the most common chronic liver disease in children. This is driven primarily by obesity, in whose presence the prevalence of MASLD is estimated between 34 and 70%.[9] In addition, MASLD, defined as chronic hepatic steatosis (fat content >5%) not secondary to other metabolic or genetic disorders, is now the leading indication for liver transplant in childhood.[10]

A critical nuance is pediatric MASLD presents in a different and more aggressive histopathological pattern than the classic adult pattern.[11] The progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) involves hepatocyte injury and cell death, which can lead to advanced fibrosis and even cirrhosis before a child reaches adulthood.[9]

The diagnostic markers for MASLD in the pre-pubertal population are often overlooked. While elevated liver enzymes (ALT and AST) are used as indicators, many children with significant hepatic fat accumulation remain within "normal" enzyme ranges.[12]

Early-Onset Dyslipidemia and Cardiovascular Risk

Dyslipidemia in children is not merely a marker of future risk; it is a current physiological derangement. Pre-pubertal children with obesity often present with an atherogenic lipid profile: elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and slightly elevated low-density lipoprotein cholesterol (LDL-C).[13]

Studies indicate that between 42.9% and 56.7% of children with obesity meet the criteria for dyslipidemia.[14] This is significantly associated with central adiposity, as measured by waist circumference. This clustering of comorbidities suggests a unified failure of metabolic homeostasis that begins well before the onset of secondary sexual characteristics.

Dysglycemia and Insulin Resistance

Dysglycemia, which encompasses impaired fasting glucose, impaired glucose tolerance, prediabetes, and diabetes mellitus, is a common complication seen in children with obesity and is an independent risk factor for cardiovascular disease. While quite variable depending on race, ethnicity, and other factors, prevalence studies show even pre-pubescent children with obesity as young as 4-10 years-old have rates of dysglycemia up to 30%, with class 2 or 3 obesity being associated with the highest risk.[15] The added physiologic insulin resistance of puberty described above often results in overt prediabetes and diabetes mellitus type 2 in adolescence. While checking a hemoglobin A1c (HbA1c) is commonly recommended, data on norms for youth are still not as accurate for diagnosing dysglycemia, and therefore lack clarity on timing of intervention and intensification of treatments, especially with pharmacotherapy. Additionally, anemia, including iron deficiency, can cause a falsely low HbA1C result and results below the prediabetes cutoff of 5.7% do not rule out pathologic insulin resistance.

While fasting insulin levels are currently not recommended for diagnosis of prediabetes or DM2, a study with up to 19 years of follow-up showed IR (measured by HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) or fasting insulin) doubled the risk of future dysglycemia while fasting glucose was not predictive. Addressing previous concerns about age- and puberty-dependent reference ranges, they validated and showed superiority of age-related insulin-based indices for predicting future dysglycemia, and thus cardiometabolic risk, in children with obesity.[16]

Importantly, we have treatment options that directly address this disease state such as liraglutide and semaglutide but also metformin, which remains inexpensive and has a favorable risk profile.[17] However, current evidence suggests its benefits are greater for prepubertal children than pubertal.[18]

The Regulatory and Clinical Treatment Gap

The current therapeutic landscape for pediatric obesity is marked by a significant void for children under 12 years of age. While the 2023 American Academy of Pediatrics (AAP) guidelines emphasize early, evidence-based treatment, they also highlight the limitations of current pharmacological approvals.[19]

Table 2. Current Medications FDA Approved for Pediatric Obesity

Medication	FDA Approval Age	Indication
Setmelanotide	2 years	Rare genetic obesity (POMC, LEPR, PCSK1)[20]
Semaglutide (Wegovy)	12 years	Obesity[21]
Liraglutide (Saxenda)	12 years	Obesity[22]; Currently off label for obesity in younger children[23]
Phentermine/Topiramate	12 years	Obesity[24]
Orlistat	12 years	Obesity[25]
Metformin	10 years (Diabetes mellitus type 2) (DM2)	Off-label for obesity[18]
Tirzepatide	10 years (DM2)[26]	Off-label for obesity

The AAP 2023 Guidelines and Pharmacotherapy

The 2023 AAP guidelines, led by one of Missouri's own, Sarah Hampl, MD, continues to recommend intensive health behavior and lifestyle treatment (IHBLT) as a foundational component of intervention for children aged two and older. The evidence supports a minimum of 26 contact hours over three to 12 months to achieve meaningful health benefits. The interventions must focus on skills and support for consistent implementation of lifestyle and parenting changes, not simply offer education on didactic nutrition and physical activity changes. However, the reality of limited access to quality interventions that meet these standards prevents wide adoption and access. The need for coordination with a multidisciplinary medical team to evaluate and deliver advanced obesity treatments can itself limit families' access to the full spectrum of guideline-recommended management. In our respective referral centers, implementing these recommended contact hours is extremely difficult from both an operational and a family standpoint despite appropriate staffing. Reflecting the state of the evidence in 2023, the guidelines established age-based distinctions between populations with sufficient evidence to support broader use of obesity pharmacotherapy and those for whom evidence remained limited. Additionally, bariatric surgery evaluation was recommended for children 13 and older with a BMI percentile >= 120% of the 95th percentile but rarely are children referred at this stage.[19]

Adolescents (Age >/= 12 years): Clinicians are recommended to offer anti-obesity pharmacotherapy as an adjunct to IHBLT.

Children (8–11 years): Pharmacotherapy "may be considered" on a case-by-case basis, but it is not a general recommendation due to a lack of sufficient evidence from randomized controlled trials (RCTs).

The limits of the guidelines and the state of the evidence, as well as FDA approvals of current obesity medications often limited to patients 12 years and older all contribute to barriers for the clinician workforce to treat those younger than 12 years old (Table 2). Further, the rapid development of the field of obesity medicine and state of the science over the last 10-15 years necessitates additional education for pediatric primary care and

subspecialty physicians to be able to care for patient with obesity using advanced therapies, especially in children under 12 years of age when medications are off label and guidelines are less definitive. This article is an additional step to support enhanced treatments for younger children with evidence of metabolic disease and earlier onset overweight and obesity. Currently, children who may already show metabolic disease at age 10 or 11 are often told to wait until age 12 to access any pharmacotherapy, let alone the most efficacious like GLP-1 receptor agonists.

The Limitation of Lifestyle-Only Interventions

While IHBLT is the gold standard for children under 12, its implementation is fraught with challenges. The absolute weight reductions seen in lifestyle-only programs are often modest. Furthermore, access to the required 26 hours of face-to-face counseling needed in research trials to lead to clinically meaningful weight change is limited, particularly outside of major urban centers. Attrition rates are high due to the logistical and financial burdens placed on families. Successful clinical applications of the guidelines focus on coordination led by the medical home, and can even offer embedded services in the medical home including behavioral health, dieticians, and supports for identified social needs as well.[27] By the time many children reach the age of 12, their obesity has progressed to a more severe class, and their metabolic dysfunction has deepened, making subsequent treatment more difficult.

Puberty as a Metabolic Stressor: Physiologic and Pathologic Shifts

The onset of puberty introduces a complex array of hormonal changes that naturally alter glucose and lipid metabolism. In healthy, lean children, these changes are transient and reversible; however, in children with obesity, they are often pathological and persistent.[3]

Physiologic Insulin Resistance (IR)

During normal puberty, children experience an approximately 50% decrease in insulin sensitivity. This state is compensated for by a doubling of insulin secretion, ensuring that glucose tolerance remains within normal limits.[3] As we know, children remain great physiologic compensators. In this setting, even children with pre-existing IR typically have adequate beta-cell function to compensate for the worsened IR.

Exaggeration in Obesity

In children with obesity, this physiologic shift is superimposed on a baseline of pre-existing, obesity-induced IR. This creates a "double hit" to the metabolic system. Children with obesity exhibit significantly lower insulin sensitivity and higher insulin secretion at every stage of puberty compared to their normal-weight peers.

One of the most concerning findings in recent longitudinal studies is the failure of metabolic recovery. While lean children return to pre-pubertal levels of insulin sensitivity by the time they reach Tanner stage V (puberty completion), youth with obesity often do not.[3] This lack of recovery contributes to a progressive decline in beta-cell function and is a major factor in the emergence of DM2 in mid-to-late adolescence. Incident-risk of DM2 over five years dramatically increases as HbA1c rises, with incidence of 3.8% at baseline HbA1c levels of 5.9-6.0 then jumping to 11 and 28.5% at baseline HbA1c's of 6.1-6.2 and 6.3.-6.4%, respectively.[28]

Metabolic Memory and the Rationale for Early Intervention

The concept of "metabolic memory" suggests that the metabolic environment to which a child's cells are exposed prenatally and early in life can have persistent, long-term effects on gene expression and tissue function.[29] This phenomenon is driven by epigenetic modifications.

Epigenetics and Longterm Metabolic Health

Transient exposure to a metabolic inducer, such as high glucose/insulin or increased free fatty acids, may produce a permanent or semi-permanent change in gene expression. This can lead to "bistable" behavior, where the metabolic system remains in a pathological state even after the initial stimulus is removed. For example,

Table 3. Parallels of Pediatric Mental Health and Obesity Management in Primary Care

Mental Health Integration Milestone[4]	Proposed Obesity Management Parallel[19,32]
Use of validated screening tools (PSC-17).	Routine metabolic screening (ALT/Lipids/FG/HbA1c) with BMI > 85th percentile
Task-shifting of counseling to PCPs.	Implementation of "brief pulse" IHBLT in primary care.
Co-location of specialists in medical homes.	Integration of behavioral health, Dietitians and Exercise Specialists in clinics.
Addressing social determinants within clinic flow.	Using community health workers for culturally appropriate ongoing support, e.g. improved food and park access.

hyperinsulinemia in early childhood can program pancreatic beta-cells and peripheral tissues, including adipose cells, into a state of dysfunction that is difficult to reverse through weight loss alone later in life, therefore establishing independent chronicity and resistance.[30]

The Case for "Radical" Early Action

The existence of metabolic memory provides a powerful biological argument for treating obesity and its metabolic comorbidities as early as possible. Early intervention can potentially "reset" metabolic set points before they become entrenched through DNA methylation and other epigenetic markers.[30] This is particularly relevant for MASLD, where early treatment can prevent the transition from simple steatosis to irreversible fibrosis and cirrhosis. Each decrease in BMI z-score of 0.25 equates to an odds ratio of 2 for resolution of NASH.[31] The need for early identification of increasing weight and more subtle metabolic changes necessitates support for primary care clinicians to access tools and specialty obesity care support and referral when needed to assure seamless and coordinated patient messaging and care.

Lessons from the Integration of Pediatric Mental Health

The challenges of pediatric obesity care—high prevalence, specialist shortages, and a historically fragmented treatment system—closely parallel those of pediatric mental health care (Table 3). The successful integration of behavioral health services into primary care pediatric offices over the last two decades offers a validated framework for a new model of obesity management.[4]

The Collaborative Care Model

Historically, children with mental health concerns were referred out to external specialists, leading to massive gaps in care and long untreated durations. The shift toward integration involved several key strategies:

Task Shifting

Equipping primary care physicians (PCPs) to deliver behavioral health screenings and initial interventions, supported by on-site or readily accessible specialists.

Universal Screening

Incorporating mental health screening tools (e.g., PSC-17) into routine well-child visits to identify concerns earlier.

The Medical Home

Establishing the primary care office as a multidisciplinary hub where medical and behavioral needs are addressed simultaneously, reducing the stigma and fragmentation of care.[4]

Applying the Parallel to Obesity Care

Integrating obesity management into primary care

allows early identification with appropriate clinician and patient support to avoid the "waiting it out" fallacy and normalizes metabolic monitoring from a younger age.

1. Metabolic Screening in the Primary Office: Much like mental health screening, metabolic markers (lipids, ALT, fasting glucose, HbA1c, and fasting insulin) should be part of the routine evaluation for children with a BMI >85th percentile.
2. Integrated Care Teams: The "Obesity Medical Home" would include a pediatrician, a registered dietitian, and a behavioral health clinician working in tandem.[7] This allows for the simultaneous treatment of the biological, behavioral, and psychological factors that drive obesity and consistent coordinated care with clear messaging to avoid confusion and delays in care.
3. Family-Based Behavioral Treatment (FBT): Research demonstrates that FBT, which targets both the parent and the child, is more effective and cost-efficient than treating the child alone. Primary care is the ideal setting for FBT, capitalizing on the long-term trust between PCPs and families.[32]

Practical Pointers for the Pediatric Practice

Based on the synthesis of metabolic, longitudinal, and organizational data, the following recommendations are proposed for a more proactive approach to earlier identification and advanced intervention for pediatric obesity.

Early Metabolic Evaluation

Clinicians should not wait until the age of 12 or the onset of puberty to screen for obesity-related comorbidities. Given the prevalence of silent MASLD and IR, any child with a BMI-for-age >/= 95th percentile should undergo an initial metabolic workup noted in the table above.[2]

Off-Label Pharmacotherapy

For children under 12 years old with severe obesity (Class II or III with BMI >/= 120% of the 95th percentile) or indication of metabolic disease, medications should be considered in addition to traditional IHLBT in the context of their disease and family history.

A family history of obesity, prediabetes/diabetes mellitus, or especially cardiovascular disease suggests more advanced early intervention should be considered. While medication options are more limited in younger age groups, metformin shows a favorable risk profile and modest but favorable results on BMI, BMI z score, and HOMA IR allowing it to be a good consideration for earlier utilization.[33] As always, any medication should be layered as an adjunct to behavioral therapy, ideally provided in a coordinated fashion in the obesity medical home proposed above.[32, 34]

Focus on "Metabolic Fitness" over BMI Reduction

The primary goal of pre-pubertal intervention should be the improvement of cardiometabolic parameters—such as lowering LDL cholesterol, normalizing ALT levels, and improving insulin sensitivity—even if BMI change is modest. Focusing on these biomarkers can motivate families and ensure that the "metabolic clock" is being slowed or reversed during the critical developmental window before and during puberty.

Conclusion: The Urgency of the First Decade

The "waiting it out" approach to pediatric obesity is a biological and clinical fallacy that ignores the advanced state of metabolic disease present in many children under the age of 12. By the time many children reach the pubertal years, they have already sustained significant hepatic, cardiovascular, and endocrine dysfunction that the physiologic shifts of puberty only serve to worsen.[2]

The pre-pubertal years represent a unique window of potential plasticity where metabolic memory can be positively influenced and the trajectory toward adult chronic disease can be diverted. Inspired by the successful integration of mental health care, the transition toward a multidisciplinary, primary care-centered model of obesity management is the most viable path to addressing this public health crisis. Delaying intervention until the "correction" of puberty is not only scientifically unsound but is a missed opportunity for secondary prevention with potential lifelong benefits, a great example of the key preventative care that is the hallmark of effective pediatrics.

References

1. Putri RR, Danielsson P, Ekström N, et al. Effect of pediatric obesity treatment on long-term health. JAMA Pediatr. 2025;179(3):302-309.

doi:10.1001/jamapediatrics.2024.5552.
2. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. J Pediatr. 2007;150(1):12-17.e2. doi:10.1016/j.jpeds.2006.08.042.
3. Kelsey MM, Pyle L, Hilkin A, et al. The impact of obesity on insulin sensitivity and secretion during pubertal progression: a longitudinal study. J Clin Endocrinol Metab. 2020;105(5):e2061-e2068. doi:10.1210/clinem/dgaa043.
4. Wissow LS, van Ginneken N, Chandna J, Rahman A. Integrating children's mental health into primary care. Pediatr Clin North Am. 2015;62(6):1437-1454. doi:10.1016/j.pcl.2015.08.005.
5. Xanthakos SA, Lavine JE, Yates KP, et al. Progression of fatty liver disease in children receiving standard of care lifestyle advice. Gastroenterology. 2020;159(5):1731-1751.e10. doi:10.1053/j.gastro.2020.07.034.
6. Marcus C, Danielsson P, Hagman E. Pediatric obesity-Long-term consequences and effect of weight loss. J Intern Med. 2022;292(6):870-891. doi:10.1111/joim.13547
7. Jankowska A, Brzeziński M, Romanowicz-Sołtyszewska A, Szlagatys Sidorkiewicz A. Metabolic syndrome in obese children—clinical prevalence and risk factors. Int J Environ Res Public Health. 2021;18(3):1060. doi:10.3390/ijerph18031060.
8. Münte E, Zhang X, Khurana A, Hartmann P. Prevalence of Extremely Severe Obesity and Metabolic Dysfunction Among US Children and Adolescents. JAMA Netw Open. 2025;8(7):e2521170. doi:10.1001/jamanetworkopen.2025.21170
9. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr. 2017;64(2):319-334. doi:10.1097/MPG.0000000000001482.
10. Younossi ZM, Germani G, Wong R, et al. Steatotic liver disease is the dominant indication for liver transplantation in both Europe and the United States: Trends and outcomes in the past 2 decades. Liver Transpl. Published online July 18, 2025. doi:10.1097/LVT.0000000000000688
11. Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. Hepatology. 2005;42(3):641-649. doi:10.1002/hep.20842.
12. Scapaticci S, D'Adamo E, Mohn A, Chiarelli F, Giannini C. Non-alcoholic fatty liver disease in obese youth with insulin resistance and type 2 diabetes. Front Endocrinol q(Lausanne). 2021;12:639548. doi:10.3389/fendo.2021.639548.
13. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115(14):1948-1967. doi:10.1161/CIRCULATIONAHA.107.181946
14. Estrada E, Eneli I, Hampl S, et al. Children's Hospital Association consensus statements for comorbidities of childhood obesity. Child Obes. 2014;10(4):304-317. doi:10.1089/chi.2013.0120
15. Pedicelli S, Fintini D, Ravà L, et al. Prevalence of prediabetes in children and adolescents by class of obesity. Pediatr Obes. 2022;17(7):e12900. doi:10.1111/ijpo.12900
16. Hammel MC, Stein R, Kratzsch J, et al. Fasting indices of glucose-insulin-metabolism across life span and prediction of glycemic deterioration in children with obesity from new diagnostic cut-offs. Lancet Reg Health Eur. 2023;30:100652. Published 2023 May 23. doi:10.1016/j.lanepe.2023.100652
17. Yanovski JA, Krakoff J, Salaita CG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes. 2011;60(2):477-485. doi:10.2337/db10-1185
18. Pastor-Villaescusa B, Cañete MD, Caballero-Villarraso J, et al. Metformin for Obesity in Prepubertal and Pubertal Children: A Randomized Controlled Trial. Pediatrics. 2017;140(1):e20164285. doi:10.1542/peds.2016-4285
19. Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics. 2023;151(2):e2022060640. doi:10.1542/peds.2022-060640.
20. U.S. Food and Drug Administration. IMCIVREE (setmelanotide) injection prescribing information. Updated 2024. Accessed January 28, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213793s007lbl.pdf.
21. U.S. Food and Drug Administration. Wegovy (semaglutide) injection prescribing information. Updated August 2025. Accessed January 28, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215256s024lbl.pdf.
22. U.S. Food and Drug Administration. Saxenda (liraglutide) injection prescribing information. Updated 2025. Accessed January 28, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/206321s020lbl.pdf.
23. Fox CK, Barrientos-Pérez M, Bomberg EM, et al. Liraglutide for Children 6 to <12 Years of Age with Obesity - A Randomized Trial. N Engl J Med. 2025;392(6):555-565. doi:10.1056/NEJMoa2407379
24. U.S. Food and Drug Administration. Qsymia (phentermine and topiramate extended-release) capsules prescribing information. Updated 2025. Accessed January 28, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022580s029lbl.pdf.
25. U.S. Food and Drug Administration. Xenical (orlistat) capsules prescribing information. Updated 2022. Accessed January 28, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020766s038lbl.pdf.
26. Hannon TS, Chao LC, Barrientos-Pérez M, et al. Efficacy and safety of tirzepatide in children and adolescents with type 2 diabetes (SURPASS-PEDS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2025;406(10511):1484-1496. doi:10.1016/S0140-6736(25)01774-X
27. Epstein LH, Wilfley DE, Kilanowski C, et al. Family-Based Behavioral Treatment for Childhood Obesity Implemented in Pediatric Primary Care: A Randomized Clinical Trial. JAMA. 2023;329(22):1947–1956. doi:10.1001/jama.2023.8061
28. Hoe FM, Darbinian JA, Greenspan LC, Lo JC. Hemoglobin A1c and Type 2 Diabetes Incidence Among Adolescents With Overweight and Obesity. JAMA Netw Open. 2024;7(1):e2351322. doi:10.1001/jamanetworkopen.2023.51322
29. Umano GR, Bellone S, Buganza R, et al; Street ME. Early roots of childhood obesity: risk factors, mechanisms, and prevention strategies. Int J Mol Sci. 2025;26(15):7388. doi:10.3390/ijms26157388.
30. Dong H, Sun Y, Nie L, et al. Metabolic memory: mechanisms and diseases. Signal Transduct Target Ther. 2024;9(1):38. Published 2024 Feb 28. doi:10.1038/s41392-024-01755-x
31. Xanthakos, Stavra A.1; Ibrahim, Samar H.2; Adams, Kathryn3; Kohli, Rohit4; Sathya, Pushpa5; Sundaram, Shikha6; Vos, Miriam B.7; Dhawan, Ashish8; Caprio, Sonia9; Behling, Cynthia A.10; Schwimmer, Jeffrey B.11,12. AASLD Practice Statement on the evaluation and management of metabolic dysfunction–associated steatotic liver disease in children. Hepatology 82(5):p 1352-1394, November 2025. | DOI: 10.1097/HEP.0000000000001368
32. McSweeney ZC, Antonelli RC, Ebbeling CB. Treating childhood obesity: building and evaluating evidence-based models of integrated care. J Endocr Soc. Published online June 13, 2025. doi:10.1210/jendso/bvaf109.
33. Masarwa R, Brunetti VC, Aloe S, Henderson M, Platt RW, Filion KB. Efficacy and Safety of Metformin for Obesity: A Systematic Review. Pediatrics. 2021;147(3):e20201610. doi:10.1542/peds.2020-1610
34. Dutton WP, Paddu N, Braddock A, Sweeney B. Clinician's Guide for Pediatric Anti-obesity Medications. Pediatr Clin North Am. 2024 Oct;71(5):957-980. doi: 10.1016/j.pcl.2024.07.006. PMID: 39343504.

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Two Patients, One Plan: Redesigning Transitions of Care in High-Risk Pregnancy with Mom-Baby Dyadic Models

by Johana Mejias-Beck, MD & Kaitlin Wittler, MD

The postpartum period is a critical and vulnerable transition time, especially for mothers with high-risk pregnancy complications and socioeconomic disparities.



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Abstract

Maternal and neonatal care in the United States (US) is often delivered separately, creating gaps during the critical transition from hospital to home. Fragmented maternal and neonatal care contributes to missed postpartum visits, delayed recognition of complications, and suboptimal outcomes, particularly in high-risk populations. Mom-Baby dyad care models integrate transitions of care by approaching the mother and infant as a single care unit. Evidence from high-risk obstetric populations, including patients with preeclampsia, gestational diabetes, and infants requiring NICU care, suggests that dyadic care approaches are associated with improved care continuity, earlier identification of complications, and enhanced engagement in postpartum care.[17] Implementing structured, coordinated Mom-Baby Dyad care has the potential to reduce disparities and improve patient-centered outcomes in vulnerable populations.

Key Words

High-risk pregnancy, maternal postpartum, dyadic model.

Introduction

Family Medicine and Internal Medicine/Pediatrics (Med-Peds) primary care physicians are well equipped to care for patients across the lifespan, from infancy through adulthood. This scope uniquely positions them to provide continuity of care in which both mothers and infants may be cared for by the same physician. Redesigning transitions of care for high-risk mothers through Mom-Baby dyad models offers an opportunity to reduce postpartum morbidity and mortality while simultaneously supporting comprehensive pediatric care. To fully appreciate the value of dyadic models, it is important to understand the complexity of maternal and infant care following delivery.

An important consideration in discussing dyadic postpartum care is understanding its significance. In 2015, the Centers for Disease Control (CDC) began categorizing maternal deaths according to timing across a 21-month period from conception through one year postpartum. Most deaths occur after delivery during the first year postpartum.[4] This data demonstrates the critical need for comprehensive integrative models of care for these mothers.

High-Risk Maternal Transitions and Health Disparities

High-risk pregnancies involve factors that impact the mother, the infant, or both. These include chronic conditions such as diabetes,

hypertension, heart disease, obesity, autoimmune disorders, and HIV; social and demographic factors including adolescent pregnancy and advanced maternal age; pregnancy-specific conditions such as preeclampsia, gestational diabetes, multiparity, and fetal growth restriction; and environmental and social barriers, including substance use, smoking and mental health conditions.

Cardiovascular disease, including hypertension-related complications and cardiomyopathy, has been recognized as the leading cause of pregnancy-related deaths in the US.[3] Emerging data from the Society for Maternal-Fetal Medicine suggest that mental health-related conditions and violence also represent leading causes of pregnancy-associated death overall, underscoring critical gaps in postpartum care and follow-up.[1]

Despite advances in public health, the US has the highest pregnancy-related mortality rates of all developed nations. Approximately 700 women die annually in the US from pregnancy-related complications.[2] States in the deep south report disproportionately high maternal death rates, thought to likely reflect historical underinvestment in maternal health.[3] Rural areas of the US have a higher number of maternity care deserts, or regions with limited or no access to obstetric services. These areas face higher rates of pregnancy-related mortality. Mortality rates in the US also differ greatly depending on race. Black mothers are three to four times more likely to die in childbirth than white mothers and are also more likely to suffer from other pregnancy-related conditions (preeclampsia, eclampsia, and postpartum cardiomyopathy) that can lead to maternal morbidity and mortality.[8]

Morbidity and mortality in these circumstances could be preventable with good healthcare system models that care for mothers before, during, and after pregnancy. In 2021, Maternal Mortality Review Committees determined that three in five pregnancy-related deaths could have been prevented.[2]

Additionally, expanding Medicaid coverage for pregnant women to one year postpartum has been a beneficial healthcare response, but it remains essential to ensure that women have adequate and comprehensive access to health care during this high-risk period.[3] A Mom-Baby dyadic care model facilitates high-risk, complex postpartum care, simultaneously addressing the needs of both mother and child while also hopefully addressing critical health disparities.

Maternal Clinical Considerations Postpartum

Hypertensive disorders

Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, and eclampsia. Gestational hypertension is defined as new onset, nonproteinuric hypertension occurring after 20 weeks gestation. Preeclampsia is a multiorgan disease process characterized by new onset hypertension with either proteinuria or other evidence of end-organ dysfunction after 20 weeks gestation. HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) syndrome is a form of severe preeclampsia. Some patients with HELLP syndrome lack hypertension or proteinuria, and many present in the postpartum period. Eclampsia represents a severe manifestation of pregnancy-related high blood pressure disorders and is defined as seizures not caused by another condition. Eclampsia can occur without classic signs of preeclampsia, and many eclamptic seizures occur during the postpartum period. These disorders are associated with high rates of maternal and neonatal morbidity and mortality. These disorders can present new or worsen during the postpartum period. Adverse pregnancy outcomes related to preeclampsia are primarily due to the need for preterm delivery.[12, 15]

While well-established antepartum guidelines provide detailed protocols for managing hypertensive disorders during pregnancy, including specific blood pressure targets, antihypertensive regimens, timing of delivery, and maternal/fetal monitoring schedules, postpartum management recommendations are notably less specific and evidence-based.[15]

After delivery of the placenta levels of vasodilatory placental hormones decline, resulting in systemic vascular resistance that causes a rise in blood pressure. Systolic blood pressures typically peak on postpartum days three to five, and diastolic blood pressures peak on days five to seven.[6] The risk of morbidity and mortality due to hypertension is highest during the first one to six days postpartum.[16] A Mom-Baby dyad model would provide the opportunity to closely follow these mothers during the frequent newborn visits in the first few weeks of life. There are recent publications demonstrating the benefits of closely monitoring blood pressure postpartum.[11] The POP-HT (Physician Optimized Postpartum Hypertension Treatment) trial showed that close self-monitoring and physician-guided antihypertensive medication management improved blood pressure at nine months postpartum and resulted in more favorable cardiovascular, vascular, and neurovascular outcomes.[11]

Implementation of a similar comprehensive program for managing mothers with hypertensive disorders of pregnancy in the postpartum phase could be uniquely done in a Mom-Baby dyadic model.

Cardiac Disorders

Peripartum cardiomyopathy (PPCM), a form of systolic heart failure, is a major contributor to maternal deaths occurring in the late postpartum period.[4] PPCM can develop during pregnancy and during the postpartum period. Postpartum management requires close specialty follow-up, initiation of guideline-directed therapy (most HF medications are compatible with breastfeeding), and contraception counseling. Diagnosis can be delayed because the symptoms of heart failure overlap with those of normal pregnancy. Many women with PPCM are diagnosed after delivery. This diagnosis, along with preexisting cardiomyopathy, valvular heart disease, and preeclampsia-related cardiac dysfunction, can cause varying forms of heart failure and all require close monitoring in the postpartum phase.[13]

Substance Use and Mental Health-Related Disorders

Emerging data is recognizing mental health conditions and substance use disorders as critical drivers for maternal mortality in the US.[1] While antepartum efforts exist to identify and manage these conditions, pregnancy and the postpartum period remain times of heightened vulnerability with increased risk of suicide and unintentional overdose. Opioid use disorder in pregnancy is associated with severe adverse outcomes including preterm birth, stillbirth, neonatal abstinence syndrome and maternal mortality.[14] Care models that do not integrate routine postpartum maternal assessment for these disorders place women at increased risk of adverse outcomes, including death.

Pediatric Wellness Visits

Pediatric well-child visits are the foundation of primary care pediatrics. During the first three years of life, infants are seen every two to three months for preventive care, including growth and developmental surveillance, anticipatory guidance, and immunizations. This results in almost 20 visits the first years of life, which become the most frequent points of contact with the healthcare system for families. This visit frequency fosters strong longitudinal relationships with families and creates repeated, reliable points of healthcare contact. These visits are particularly critical in pregnancy and the first five years of life, when the architecture of the developing brain is established and neural connections grow at the fastest rate of a person's lifetime.[10] Addressing concerns about behavior, developmental delays, caregiver mental health (postpartum depression), and family needs such as food/housing instability are essential elements of preventative pediatrics.[10] Within a Mom-Baby dyad model, these established visits offer structured opportunities for ongoing postpartum maternal assessment and surveillance, particularly for individuals requiring complex or high-risk postpartum care. By minimizing separate care visits, these models may reduce structural barriers such as transportation, childcare, and scheduling constraints, improving adherence to and continuity of postpartum care particularly among underserved populations.

Infants and mothers are interdependent and interconnected and their care deserves to be treated as such. Supporting healthy interactions between mothers and infants improves social-emotional health, bonding, and positive mental health outcomes.[9] Pregnancy-related mortality and infant mortality are closely linked.[3] This re-emphasizes the critical role that dyadic models can provide to maintain balance of maternal health and infant health, and a stark reminder that these two cannot be separated.

Our Dyadic Model at University Health

At University Health (UH), initial steps have been taken to pilot a Maternal Transitions (MT) Clinic in which our Med-Peds physicians serve as the primary care physicians for both newborns and their mothers. Mothers are screened for high-risk pregnancy features and scheduled for an initial visit in our MT clinic following delivery. This screening and identification allow us to prioritize mothers with high-risk pregnancies, including those complicated by preeclampsia, cardiomyopathy, diabetes mellitus, hypertension, and mental health disorders.

Following delivery, mother and infant are seen together for the initial visit. An extended appointment duration allows sufficient time to address newborn care and anticipatory guidance while simultaneously establishing postpartum maternal care and risk stratification. We are then able to continue to schedule joint visits in our already established frequency of infant well child checks, allowing for ongoing maternal surveillance during the postpartum period.

While appointment attendance rates have posed a challenge, 51 mothers with their newborns have been

Figure 1. Maternal-Child Dyadic Model

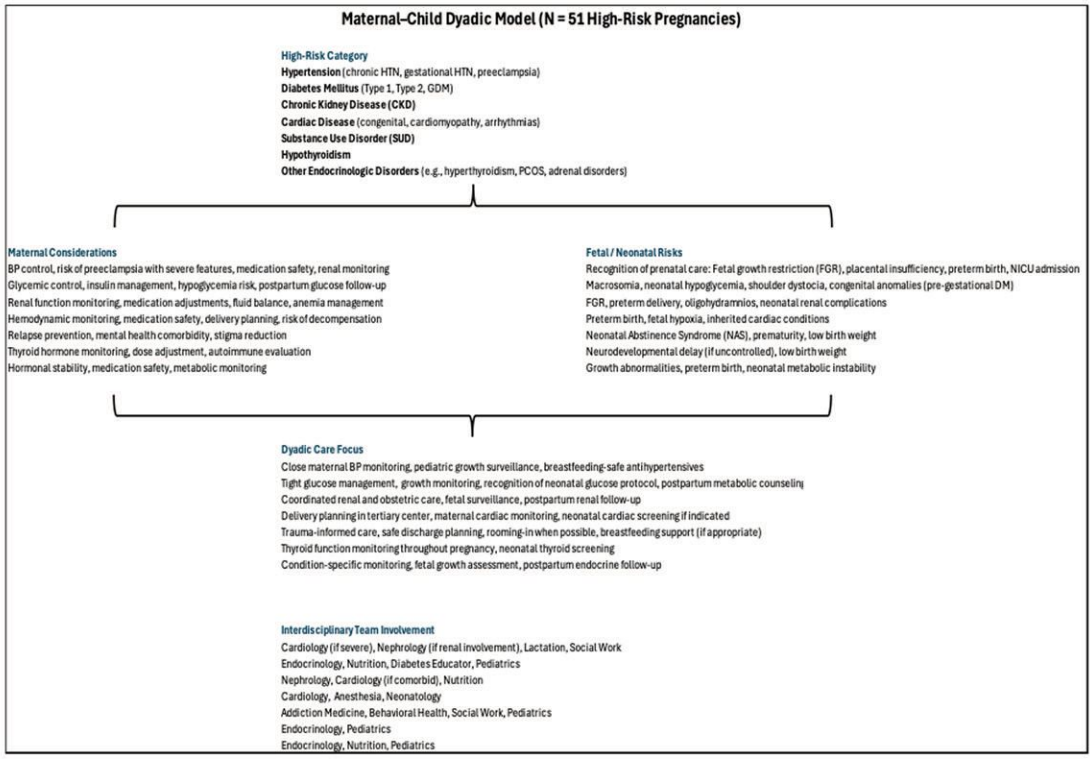


Figure 2. Dyadic Model Components

Cross-Cutting Dyadic Model Components (All 51 Mothers)

Domain	Maternal Component	Infant Component	Dyadic Integration Strategy
Care Coordination	High-risk OB follow-up	Pediatric continuity care	Warm handoffs before discharge
Mental Health	Screen for perinatal mood disorders	Monitor bonding and attachment	Integrated behavioral health referral
Social Determinants	Transportation, housing, food access	Safe sleep environment	Social work + community resource linkage
Lactation	Medication safety review	Feeding monitoring	Lactation consultant involvement
Postpartum Transition	Chronic disease optimization	Newborn follow-up within 48–72 hrs	Combined postpartum-newborn visits when feasible

seen in our MT clinic in 2025 among four Med-Peds physicians (Figures 1 and 2). Medical conditions managed for these patients have included uncontrolled diabetes mellitus, uncontrolled hypertension, preeclampsia, chronic kidney disease, postpartum cardiomyopathy, and substance use.

While some have required additional consultation with specialists like cardiology, addiction specialists, and nephrology, our Med-Peds physicians at UH are well-suited to care for these medically complex conditions in the outpatient setting.

Current Limitations

Bundled Payment Models

While evidence specific to Mom-Baby dyadic bundles remains limited, incorporating structured postpartum maternal surveillance into pediatric care within existing bundled frameworks may represent a feasible strategy to reduce preventable complications and improve value. Bundled payment models combine all services provided during a defined episode of care into a single, fixed rate.[7] Currently, more is known regarding maternity care re-imbursement in various bundled payment models, and these are already being used across the country by state Medicaid agencies, health plans, and others.[8]

One can imagine a bundled payment model that encompasses prenatal care, labor and delivery, and postpartum care, bundled with pediatric well-care visits. The complexity of bundled payment models is beyond the scope of this paper, but we briefly discuss it as we recognize the importance of acknowledging the work that needs to be done around bundled payment models and guidance on reimbursement as an alternative to fee-for-service payment models.

Already established bundled payment models help address preventable complications in maternity care and offer a potential framework to support Mom-Baby dyad care by incentivizing greater coordination of care around both mothers and infants, improving quality and access to care, and emphasizing the importance of continuity across the postpartum period. [8]

Obstetric Education

One challenge is that Med-Peds physicians are not specifically trained in obstetric conditions. Partnership was established, and education was provided in this area by high-risk obstetric physicians during the initiation of our MT clinic. Future education interventions will allow longitudinal medical education for our Med-Peds physicians at UH.

Multidisciplinary Needs and Scheduling

While the introduction of our MT clinic has shown promise in maintaining close care simultaneously for mom and baby, this dyadic approach has come with challenges. Many mothers have already scheduled pediatrician visits in their community prior to enrolling in our program. With their infants already scheduled elsewhere, many mothers are not attending the MT clinic establish care appointment. When our clinic staff reached out to mothers who did not attend appointments, there was a lack of understanding of why the appointment would be needed. Mothers have shared that they already had their post-partum appointment scheduled with their established obstetric physicians. This has been identified as a significant opportunity to improve our MT clinic. Better education regarding the importance of these visits may lead to better adherence.

Another challenge is that a successful dyadic model requires significant multidisciplinary staff (administrative, clerical, social work, case management, physicians, and nursing) to ensure appropriate complex management, continuity, and support. These appointments require significant time. Rooming requires obtaining vitals and pre-visit concerns for both mom and baby. Visit time includes focused evaluation of both patients, lab draws, immunizations, and often social work consultation. Additionally, there are currently no implemented bundled payment plans for our Mom-Baby MT clinic. Irrespective of the limitations we face, our end goal is to improve morbidity and mortality outcomes for both mothers and infants. With continued engagement, funding, and support, we believe that this is possible.

Summary

The postpartum period is a critical and vulnerable transition time, especially for mothers with high-risk pregnancy complications and socioeconomic disparities. Our Mom-Baby dyad care model has provided a patient-centered approach, reduced fragmented care, and improved postpartum outcomes for a small group of mothers at greatest risk within UH.

References

1. Adis K. New National Study Finds Homicide and Suicide is the #1 Cause of Maternal Death in the U.S. Society for Maternal-Fetal Medicine. Smfm.org. Published 2017. https://www.smfm.org/news/new-national-study-finds-homicide-and-suicide-is-the-1-cause-of-maternal-death-in-the-us
2. Petersen EE, Davis NL, Goodman D, et al. Vital Signs: Pregnancy-Related Deaths, United States, 2011–2015, and Strategies for Prevention, 13 States, 2013–2017. MMWR Morbidity and Mortality Weekly Report. 2019;68(18). doi:https://doi.org/10.15585/mmwr.mm6818e1
3. Declercq E, Zephyrin L. Maternal Mortality in the United States, 2025. Commonwealthfundorg. Published online July 29, 2025. doi:https://doi.org/10.26099/kdfd-fc19
4. Centers for Disease Control & Prevention. Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees. Maternal Mortality Prevention. Published August 28, 2025. https://www.cdc.gov/maternal-mortality/php/data-research/mmrc/?CDC_AAref_Val=https://www.cdc.gov/maternal-mortality/php/data-research/index.html
5. MacDorman MF, Thoma M, Declcerq E, Howell EA. Racial and Ethnic Disparities in Maternal Mortality in the United States Using Enhanced Vital Records, 2016–2017. American Journal of Public Health. 2021;111(9):1673-1681. doi:https://doi.org/10.2105/ajph.2021.306375
6. Phelps AJD, Liu J, Lindley KJ, et al. Comprehensive blood pressure management to improve early postpartum blood pressure parameters: A randomized controlled trial. Pregnancy. 2025;2(1). doi:https://doi.org/10.1002/pmf2.70145
7. Lally S. Transforming Maternity Care: A Bundled Payment Approach.; 2013. https://iha.org/wp-content/uploads/2020/10/Issue-Brief-Transforming-Maternity-Care-A-Bundled-Payment-Approach.pdf
8. Bree R. Maternity Bundled Payment Model; 2020. https://www.qualityhealth.org/bree/wp-content/uploads/sites/8/2020/08/Maternity-Bundle-FINAL-2020-1.pdf
9. ChildrenFirstPa. Strategies for advancing dyadic care models actions needed; 2024. https://childrenfirstpa.org/wp-content/uploads/2024/11/Dyadic-Care-Models-One-Pager.pdf
10. HealthySteps. Infographic: Dyadic Services. HealthySteps. Published November 5, 2025. https://www.healthysteps.org/resources/infographic-dyadic-services/
11. Alisse Hauspurg, Kripa Venkatakrishnan, Collins L, et al. Postpartum Ambulatory Blood Pressure Patterns Following New-Onset Hypertensive Disorders of Pregnancy. JAMA Cardiology. 2024;9(8). doi:https://doi.org/10.1001/jamacardio.2024.1389
12. Leeman L, Fontaine P. Hypertensive Disorders of Pregnancy. American Family Physician. 2008;78(1):93-100. https://www.aafp.org/pubs/afp/issues/2008/0701/p93.html
13. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum Cardiomyopathy. Journal of the American College of Cardiology. 2020;75(2):207-221. doi:https://doi.org/10.1016/j.jacc.2019.11.014
14. Centers for Disease Control & Prevention. Substance Use During Pregnancy. Maternal Infant Health. Published May 20, 2024. https://www.cdc.gov/maternal-infant-health/pregnancy-substance-abuse/index.html
15. Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. Longo DL, ed. New England Journal of Medicine. 2022;386(19):1817-1832. doi:https://doi.org/10.1056/nejmra2109523
16. Countouris M, Mahmoud Z, Cohen JB, et al. Hypertension in Pregnancy and Postpartum: Current Standards and Opportunities to Improve Care. Circulation. 2025;151(7):490-507. doi:https://doi.org/10.1161/circulationaha.124.073302
17. Molly E. McAdow, Josefa L. Martinez-Brockman, Alyssa A. Grimshaw, Courtney C. Choy, Julia Rosenberg; Dyadic Care Interventions and Outcomes for Mothers and Their Infants: A Scoping Review. Pediatrics December 2025; 156 (6): e2025073023. 10.1542/peds.2025-073023

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Not Just a Pediatric Condition: Down Syndrome Across the Lifespan

by Emily Haury, MD, Jacqueline Kitchen, MD & Brenda Rogers, MD

While commonly viewed as predominantly affecting children, there are increasing numbers of Down Syndrome patients in their 40s-60s who require comprehensive primary care that considers their unique health risks as well as standard age-related disease risks.



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Abstract

With increasing life expectancy for individuals with Down Syndrome (DS), there are growing numbers of adult DS patients needing care from primary care physicians who are knowledgeable regarding their health needs and risks. The Global Down Syndrome Foundation (GDSF) Medical Care Guidelines for Adults with Down Syndrome identify important areas of focus: mental health, dementia, diabetes, cardiovascular disease, obesity, osteoporosis, atlantoaxial instability, hypothyroidism and celiac disease. Additionally, there are unique considerations regarding cancer risk and screenings, as well as vaccination. Young adults with DS should have a structured transition from pediatric to adult care like any patient with chronic illness or intellectual disability. This article highlights several organizations and programs that provide social, vocational, legal, and family support for Missouri patients with Down Syndrome.

Key Words

Down Syndrome child and adult health care, disabilities, disease risks screeening.

Introduction

Adults with DS have unique health risks, yet due to limited evidence, the first clinical guideline for primary care of adults with DS was published by the GDSF in 2020.[1] With increasing childhood survival rates, the number of people living in the United States (US) with DS has more than quadrupled since 1950s, such that it is no longer considered a rare disease.[2] Based on US population prevalence, we estimate that there are around 5,000 Missouri residents with DS. While commonly viewed as predominantly affecting children, there are increasing numbers of DS patients in their 40s-60s who require comprehensive primary care that considers their unique health risks as well as standard age-related disease risks. Yet one insurance claims analysis showed that more than 40% of adults older than 26 years with DS continued to receive primary care with a pediatric provider; in the same study, fewer than 50% of patients had completed a wellness exam in a five-year period and rates for preventive health activities were less than 50%.[3]

In this article, we outline the unique disease risks and screening recommendations for adults with DS. Additionally, we discuss how

routine preventive health practices, such as cancer screenings, cardiovascular risk assessment, and vaccinations, apply to this patient population. Finally, we address some of the more complex healthcare considerations for patients with DS, including transition from pediatric to adult care, medical decision-making, and specific resources to support patients and caregivers.

Specific Disease Risk and Screenings

The GDSF Medical Care Guidelines for Adults with Down Syndrome Workgroup identified 10 high-priority areas of health to address in patients.[1] These are: behavioral and mental health, dementia, diabetes, cardiovascular disease/stroke, obesity, osteoporosis, atlantoaxial instability, hypothyroidism and celiac disease. Due to the increased risk of these conditions, it is recommended that screening for these occurs at an increased frequency compared to the general population.[1] An annual wellness exam is recommended. It allows the clinician to establish a trusting relationship with the patient and their caregivers, establish baseline information regarding behavior, cognition, and general health, and ensure the early detection of illness.[4]

Patients with DS are at increased risk for autoimmune diseases, particularly thyroid disease and celiac disease. They should be screened annually for symptoms of celiac disease, including inquiring about bowel pattern changes, unexplained weight loss, or rash. Laboratory testing is recommended if symptoms are present.[1] Because the prevalence of hypothyroidism in DS patients older than 30 is as high as 50%,[5] patients should be evaluated with a serum thyroid stimulating hormone (TSH) level every one to two years starting at age 21.[1] This screening should be repeated more frequently if new symptoms develop.

Obstructive Sleep Apnea (OSA) is common in patients with DS, and patients can be evaluated by taking a history for typical symptoms, such as snoring and witnessed apnea. The STOP-BANG questionnaire also has a high sensitivity in this patient population.[6] Multiple small studies have shown that when polysomnography is performed for patients with DS based on clinical suspicion for OSA, 100% of those patients were diagnosed with OSA; the mean patient age was 36.[6,7] Therefore, we recommend screening annually, beginning in the early 30s age group. It is important to note that the mean BMI of patients diagnosed in one of these studies was 29, meaning not all patients had the classic risk factor of obesity.[7]

Patients with DS have a 10% prevalence of atlantoaxial instability of the cervical vertebra, yet spinal cord injury in this group is uncommon.[1] Patients should be evaluated annually for symptoms of cervical myelopathy; neither activity restriction nor routine cervical spine imaging are recommended unless indicated based on symptoms or physical exam findings.[1] Families should be educated to monitor for sudden changes in use of extremities, sudden loss of control of bladder or bowel, or change in gait. Immediate medical evaluation should occur for these signs of cervical myelopathy.

There is an increased risk of early Alzheimer's-type dementia in patients with DS. Beginning at age 40, annual screening for dementia should include patient assessment and caregiver interview focused on detecting changes from baseline function.[1] Specific domains that may be impaired with early dementia are memory, personality, communication, adaptive functioning, and mobility. If a patient is showing signs of memory impairment prior to age 40, other underlying diagnoses, such as depression, hypothyroidism, OSA, unrecognized pain, hearing loss, or Down Syndrome Regression Disorder (DSRD) should be considered, as the prevalence of dementia is low prior to this age.[1] DRSD is a rare but serious condition with poorly-understood etiology that occurs in patients less than 40-years old and is characterized by sudden loss of language, social, and/or motor skills, with the occurrence of personality changes.

Cardiovascular disease prevalence is between 40 and 63.5%, primarily due to congenital heart disease.[4] Although it is now common practice to obtain a neonatal echocardiogram in patients with DS to assess for congenital heart disease (CHD), this practice was not introduced until the mid-1980s. For older patients, undiagnosed CHD is a possibility and there is evidence to suggest that they may benefit from adult screening.[4] Therefore, we recommend consideration of an echocardiogram in

older patients. Patients with known CHD should be followed by a cardiologist. Assessment for cardiac disease risk as recommended by the American College of Cardiology and the US Preventative Services Task Force (USPSTF) should occur. This includes lipid screening every five years starting at age 40 and an annual examination.[1]

DS is a risk factor for obesity, and patients should have weight and body mass index (BMI) measurement at their annual exam.[1] Behavioral counseling on weight loss interventions, as recommended by the USPSTF for all adults with obesity, should be shared with the patient and caregivers.[1] Exercise should be encouraged[1,8] for physical, social, and emotional health benefits. Screening for diabetes with hemoglobin A1c or fasting glucose level should occur every two to three years starting at age 21 for patients with DS and obesity, and at age 30 for all patients with DS.[1]

Osteoporosis risk was recognized by the GDSF Medical Care Guidelines for Adults with Down Syndrome Workgroup, however there was insufficient information to make recommendations for testing other than USPSTF screening recommendations. If a fragility fracture should occur, secondary causes of osteoporosis, including hyperparathyroidism, thyroid disease, vitamin D deficiency, celiac disease and medication-related occurrence should be assessed.[1]

Patients with DS are at a higher risk for leukemia and testicular cancers. Leukemia typically occurs in the pediatric age range and is uncommon in adults with DS. In the uncommon adult occurrence, patients are typically symptomatic with signs of anemia, bleeding and bruising; therefore, regular laboratory screening for adult hematologic disorders is not recommended. Testicular cancer occurs 5-50 times more commonly; therefore, annual testicular exam should be performed from age 15-45.[9] Breast and colon cancer rates are lower in patients with DS, so USPTF recommended routine screening is appropriate. Mammography should be discussed and decided with the patient, as some recommend no need for it based on the low rates of breast cancer and the potential to be upsetting to patients.[9] Office breast exams could suffice in certain patients who decide to forgo mammography. Cervical cancer screening is without clear guidelines in this patient population, thus should be determined based on the patient's individual risk and ability to tolerate testing.[9] Any DS patient with a family history of cancer should have routine screening similarly to a patient without an intellectual disability.[9]

Vaccination of patients with DS is important, as respiratory tract infections are a major cause of death.[10] Reduced immunity is known to occur and DS patients can have comorbidities (heart disease, obesity) that increase risks of infection, thus attention to vaccination is important. Vaccination should adhere to 2025 Center for Disease Control guidelines for adults, including newer vaccines such as respiratory syncytial virus.[11] HPV and meningococcal vaccines, in addition to other standard adult vaccines, are also recommended.[12] A Hepatitis B vaccine booster should be considered, as immunity wanes in DS patients.[13]

Transition, Support, and Resources

The same general principles of transition from pediatric to adult health care apply to special needs populations, including individuals with Down Syndrome, and follow recommendations from Got Transition.[14] Individual assessment for financial, medical, and legal decision-making support should start at the time of transition conversations during pediatric visits. These discussions include physicians, the patient, and family members. Families will consider if guardianship or supported decision-making is right for them. Legal filing often happens after the eighteenth birthday. Legal counsel is helpful to consider the unique implications for each individual and situation.

Employment is recognized as a key progression into adulthood. Many adults with DS enjoy the financial, emotional, and social benefits of employment. State and local organizations offer vocational training programs, such as Down Syndrome Innovations (DSI) ACE Academy,[15] and university-based certification programs, such as University of Kansas Transition to Postsecondary Education (KU-TPE)[16] or University of Missouri Preparing Adults for Work and Society (UM-PAWS)[17] programs. An estimated 3% of adults with DS are employed full time, so most do not have access to employer-sponsored health insurance; adults with DS

automatically qualify for Social Security Insurance (SSI) and nearly all are also eligible for Medicaid enrollment.[18]

At the time of health care transition, clinical documentation should include a health care summary of current diagnoses, medications, relevant medical and surgical histories, and ongoing care plans. Clinic visits should also include identification of subspecialty care needs and referral timing. Respite care plans and plans for successor guardianship should be discussed.

Clinicians are not alone in supporting patients with DS during the transition process into adult health care. The Center for Transition to Adult Health Care for Youth with Disabilities[19] is a national health care transition resource center that provides guides for both families and physicians. In Missouri, the University of Missouri-Kansas City (UMKC) Institute for Human Development[20] provides additional supports for patients with developmental disabilities. In the Kansas City area, Down Syndrome Innovations[15] is a helpful resource for families of DS patients of all ages in both Missouri and Kansas.

Summary

As the number of adult DS patients is growing and life expectancy has reached nearly 60 years, adult healthcare professionals are instrumental in providing care to this patient population. This article addresses the specific needs of DS patients, recognizing that routine healthcare needs are also necessary. Transition from a pediatric to adult healthcare setting should include detailed communication about medical needs, as well as the social and familial support for the patient. There are federal, state, and local programs to support the pediatric-to-adult transition and ongoing care of Missourians with DS.

References

1. Tsou AY, Bulova P, Capone G, et al. Medical Care of Adults With Down Syndrome: A Clinical Guideline. JAMA. 2020;324(15):1543–1556. doi:10.1001/jama.2020.17024
2. de Graaf G, Buckley F, Skotko BG. Estimation of the number of people with Down syndrome in the United States. Genet Med. 2017;19(4):439-447. doi:10.1038/gim.2016.127
3. Jensen KM, Campagna EJ, Juarez-Colunga E, Prochazka AV, Runyan DK. Low Rates of Preventive Healthcare Service Utilization Among Adolescents and Adults With Down Syndrome. Am J Prev Med. 2021;60(1):1-12. doi:10.1016/j.amepre.2020.06.009
4. Tishad A, Vadakal S, Talati J, Louis M, Jacob R. Comprehensive Care for Adults with Down Syndrome in Primary Care Settings. Southern Medical Journal. 2024;117(6):296-301. doi:https://doi.org/10.14423/smj.0000000000001693
5. Alexander M, Petri H, Ding Y, Wandel C, Khwaja O, Foskett N. Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. Developmental Medicine & Child Neurology. 2015;58(3):246-254. doi:https://doi.org/10.1111/dmcn.12868
6. Carvalho AA de, Amorim FF, Santana LA, de Almeida KJQ, Santana ANC, Neves F de AR. STOP-Bang questionnaire should be used in all adults with Down Syndrome to screen for moderate to severe obstructive sleep apnea. Romigi A, ed. PLOS ONE. 2020;15(5):e0232596. doi:https://doi.org/10.1371/journal.pone.0232596
7. Landete P, Soriano JB, Aldave B, et al. Obstructive sleep apnea in adults with Down syndrome. Am J Med Genet A. 2020;182(12):2832-2840. doi:10.1002/ajmg.a.61853
8. MEIRA LB, BARRETO LO, FERNANDES JV, NETO OB, OLIVEIRA AS. Impact of physical exercise on health outcomes in people with Down Syndrome: a systematic review and meta-analysis of randomized controlled trials. The Journal of Sports Medicine and Physical Fitness. 2025;66(1):130-142. doi:https://doi.org/10.23736/s0022-4707.25.16935-1
9. Rethoré MO, Rouëssé J, Satgé D. Cancer screening in adults with down syndrome, a proposal. European Journal of Medical Genetics. 2020;63(4):103783. doi:https://doi.org/10.1016/j.ejmg.2019.103783
10. Joshi AY, Abraham RS, Snyder MR, Boyce TG. Immune evaluation and vaccine responses in Down syndrome: Evidence of immunodeficiency? Vaccine. 2011;29(31):5040-5046. doi:https://doi.org/10.1016/j.vaccine.2011.04.060
11. CDC. Adult immunization schedule by age. Vaccines & Immunizations. Published June 27, 2024. https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html.
12. Alrahili M, Binyamen A, Otaibi FA, et al. Importance of vaccines in children with Down syndrome. International Journal of Contemporary Pediatrics. 2018;5(5):1710-1714. doi:https://doi.org/10.18203/2349-3291.ijcp20183503
13. Eijsvoogel NB, Hollegien MI, Bok, et al. Declining antibody levels after hepatitis B vaccination in Down syndrome: A need for booster vaccination? Journal of Medical Virology. 2017;89(9):1682-1685. doi:https://doi.org/10.1002/jmv.24813
14. White, P and McManus M, "Got Transition", Got Transiton.org, accessed 1/16/2026, https://www.gottransition.org/
15. "Down Syndrome Innovations", Down Syndrome Innovations, accessed 1/16/26, https://kcdsi.org/
16. University of Kansas, "University of Kansas Transition to Postsecondary Education (TPE)", University of Kansas, accessed 1/16/2026, https://tpe.ku.edu/,
17. University of Missouri, College of Education & Human Development, "(PAWS) Preparing Adults for Work and Society", University of Missouri, accessed 1/16/2026, https://cehd.missouri.edu/special-education/projects-centers/paws/,
18. Rubenstein E, Michals A, Wang N, et al. Medicaid Enrollment and Service Use Among Adults With Down Syndrome. JAMA Health Forum. 2023;4(8):e232320. doi:10.1001/jamahealthforum.2023.2320
19. "Center for Transition to Adult Health Care for Youth with Disabilities.", Center for Transition to Adult Health Care for Youth with Disabilities, accessed 1/16/2025, https://movingtoadulthealthcare.org/
20. "UMKC Institute for Human Development", University of Missouri Kansas City, accessed 1/16/2026, https://ihd.umkc.edu/

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The Forgotten Few: Pediatric-to-Adult Healthcare Transitions

by Joanne Loethen, MD & Amanda Sommerville, MD

The successful transition of youth from pediatric to adult care has longstanding implications for health outcomes and healthcare utilization.



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Abstract

Healthcare transition is the period when an adolescent or young adult transitions from pediatric, family-centered care to an adult-oriented health care system. Effective transition processes are essential for all youth to promote continuity of care, health literacy, and long-term engagement with the healthcare system. Inadequate transition planning in clinical care can result in poor health outcomes and a young adult's disengagement from medical care. This article reviews the current evidence on healthcare transitions from pediatric to adult care, summarizes the core principles of effective transition, and identifies common barriers faced by those caring for adolescent and young adult populations.

Key Words

Pediatric to adult healthcare transitions, adolescent healthcare, six core elements.

Introduction

Approximately 13% of Missouri's population, more than 800,000 individuals, are between the ages of 10 and 17 years.[1] Over the next decade, these adolescents will transition from dependent minors to independent adults. How this population engages with the healthcare system during this time will influence their perception of medical care for years to come. Despite the long-term impact this period can have, healthcare transitions remain an underdeveloped area of medical practice. Healthcare transition, or transition of care, is the purposeful, planned process by which adolescents shift from pediatric, family-based care to patient-centered, adult-based healthcare.

Historically, healthcare transitions have been focused on adolescents and young adults (AYAs) with chronic medical conditions. Up to 20% of adolescents in North America live with a chronic condition, including but not limited to conditions like sickle cell disease, diabetes, chronic kidney disease, and cystic fibrosis.[2]. Generations ago, many children with severe disabilities and chronic childhood conditions did not survive to adulthood. Advances in medical care have enabled many of these children to survive and thrive with these conditions into adulthood.[3] Because of this, coordinated healthcare transitions are important for youth with existing chronic conditions. However, healthcare transitions are

also central to disease prevention. Risk factors that predict adult cardiovascular disease—such as dietary patterns, sedentary lifestyle, and tobacco exposure—often start with seeds planted in childhood.[4] The same is true for metabolic syndrome and adult-onset diabetes. Healthcare transitions are essential for all adolescents, regardless of whether an underlying condition is present. AYAs who fail to understand how to navigate their own healthcare become adults with the same lack of understanding. An inadequately transitioned AYA represents a missed opportunity for disease prevention, health literacy, and health equity, leading to poorer clinical outcomes, fragmented care, and increased healthcare utilization. Meanwhile, for those with chronic conditions, an under-planned transition of care can mean decreased treatment adherence and progression of disease.[5]

This article reviews the current evidence on healthcare transitions from pediatric to adult care, summarizes the core principles of successful transitions, explores the consequences of poor transitions, identifies common barriers, and provides resources to support AYAs during a transition to adult care.

Definitions and Current State

For those with chronic conditions, the Society for Adolescent Health and Medicine refers to healthcare transitions as the "purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented healthcare systems."[6] The American Academy of Pediatrics (AAP) broadens this definition, stating that healthcare transition is the "process of moving from a child to an adult model of healthcare with or without a transfer to a new clinician".[7] The latter definition emphasizes that healthcare transition applies to all youth (not only to those with chronic medical needs), and also clarifies that not all youth will change clinicians during this process.

The use of the term "transition" rather than "transfer" of care in these definitions is important to note. Transfer of care is the movement from one setting to another at a single point in time, without forethought or planning. To date, a transfer of care is how most youth-to-young-adult healthcare is experienced in the U.S. In contrast, the word "transition" is deliberate and implies an intentional process that occurs over time.

Despite the clear rationale for providing healthcare transitions for AYAs, less than 20% of youth, including those with special health care needs, report receiving guidance or planning for a transition to adult care.[8] Surveys have helped quantify whether youth are receiving a proper transition by asking AYAs (and their caregivers) questions in a few general areas: 1) Did you have time alone to speak with your doctor or other health care clinician during your last preventive visit? 2) Did your doctor talk about transitioning to another doctor who treats adults? 3) Did your clinician work with you to gain self-care skills or understand changes in health care as an adult? Though most AYAs report working with their clinician to develop self-care skills and understand changes in care delivery at age 18, only 17% of youth with special health care needs and 14% without special health care needs reported receiving care coordination and transition planning.[6]

The current state of inadequate transitions has consequences. Lack of transition support for AYAs with or without special health care needs can result in adverse outcomes, including discontinuity of care, non-adherence to treatment plans, excess morbidity, dissatisfaction with healthcare, and preventable emergency room visits. Healthcare transitions present a significant opportunity for both patients and the healthcare system.

Elements of Transition and Evidence of Success

The goals of healthcare transitions for AYAs are the following: 1) Improve the ability of youth and young adults with and without special health care needs to manage their own health care, 2) Help youth effectively use health services, and 3) Ensure an organized process in pediatric and adult health care practices to facilitate transition preparation, transfer of care, and integration into adult-centered healthcare.[9]

In 2011, the AAP, in collaboration with the American Academy of Family Physicians and the American College of Physicians (ACP), published a joint clinical report on healthcare transition. The report, updated in 2018, outlined the Six Core



Figure 1. Steps of the Six Core Elements of Health Care Transition™. ©2020 Got Transition® (www.GotTransition.org).
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Elements of healthcare transitions, from developing a transition policy to ongoing adult-centered care.[5] The Six Core Elements served as the impetus for gottransitions.org, a national resource center for healthcare transitions, and have been updated to provide guidance for physicians in pediatrics, family medicine, internal medicine, and pediatric and adult subspecialties (Figure 1).

Since the development of the Six Core Elements, various systems have implemented healthcare transition processes and demonstrated effectiveness. Reviewing a transition policy and conducting readiness assessments among adolescents aged 12-17 years in a primary care practice improved rates of healthcare transitions among AYAs,[10] suggesting that integrating a structured transition process is feasible in a busy primary care practice. Using a social worker-centered transition model in a pediatric rheumatology clinic doubled the percentage of AYAs who successfully transitioned to an adult rheumatology practice,[11] thereby reducing the likelihood of care gaps and disease progression. Adolescents with a history of renal transplant had reduced transplant failure rates as young adults upon initiation of an integrated pediatric-young adult transition clinic.[12] Using a hospital-based approach to transition patients with type 1 diabetes to adult endocrinology, a structured transfer plan resulted in a lower hemoglobin A1C one year after the transition compared with those not receiving a structured transition.[13] Among children with special healthcare needs within a managed Medicaid program, implementing a structured transition program may help reduce reliance on the emergency department as a usual source of care and better educate AYAs on a more effective use of health services.[14] A systematic review of recent transition literature showed improved outcomes for individual patients, population health, and care utilization. Healthcare transitions planning also resulted in improved patient-reported quality of life and perceived health status.[15] Collectively, these findings suggest that a thoughtful, multidisciplinary transition process can improve clinical outcomes and healthcare utilization among youth with and without underlying chronic conditions.

Challenges of AYAs Entering Adult Care

Many remember that television episode of Friends, "The One With the Pediatrician." As Ross and Rachel look for a new pediatrician for their daughter, it's revealed that 30-year-old Ross still sees his pediatrician for ongoing care. This scene is an extreme example, but it illustrates an inadequate transition and raises the question: What barriers may have prevented a successful transition in this case?

First and foremost, long-standing, trusted relationships with a pediatrician and reluctance to change are among the most significant challenges in transitioning AYAs out of pediatric healthcare. In many cases, children have known one doctor as their primary care physician for their entire lives, and families often use the same pediatrician for all children. It's understandable why one might be reluctant to move to another physician or medical practice.

Furthermore, adolescents are faced with social, developmental, and personal challenges as they mature, often leaving healthcare as a low priority. The

developing adolescent is characterized by physical, cognitive, and psychosocial change. Teens seek autonomy from parents and other authority figures while valuing approval and validation from peers. Moreover, cognitive development continues well into the mid-20s, which encompasses executive function ing, problem-solving, planning, and decision-making. Altogether, taking personal responsibility for one's health—even for AYAs with established medical conditions—often takes a back seat in the adolescent brain, presenting a major barrier to healthcare in this population.

From the clinician and health system standpoint, payment models often do not adequately address the physician time and effort required to transition an adolescent, given the psychosocial challenges mentioned, as well as the coordination that may be required for an AYA with complex medical conditions. For this reason, health systems and clinicians may not see a healthcare transition program as a priority among the complex challenges already facing primary care and specialty practices. Unless the patient is remaining in the same clinic with the same physician—for example, a family medicine or internal medicine-pediatrics clinic—there are inherent silos between pediatric and adult medicine, which makes coordination of care problematic.

There must also be an acknowledgement that family-based pediatric care functions very differently from adult-based care. The latter is a culture that tends to be more patient-centric, with no caregiver involvement unless a patient's cognitive disability requires it. This seemingly small difference in practice style can create anxiety and uncertainty for an AYA who may not be accustomed to making such decisions. Without intentional focus, understanding, and expectation setting by the new, adult-centered physician, the AYA's anxiety and uncertainty can lead to future avoidance of care.

Lastly, communication preferences are changing in society and across generations. Clinical care models designed for face-to-face visits and phone calls for inter-visit communication may not align with the communication preferences of younger generations, who tend to prefer brief text exchanges and online scheduling. The AYA population is also more transient, with more frequent changes in phone number or address, making traditional communication more difficult.[16] Failing to adapt to technological and communication preferences creates barriers that prevent younger generations from reporting positive experiences and, in turn, lead to disengagement from healthcare.

What Physicians Need to Know When Preparing or Receiving a Transitioning Patient

Implementation of a healthcare transitions process is relevant to nearly every specialty and practice model. A process could be as simple as a standardized questionnaire for adult-oriented practices to assess understanding, literacy, and self-efficacy for any new patient aged 18-25 years. Or, the process could be more comprehensive, such as a care coordinator embedded within a pediatric practice who helps counsel, prepare, and coordinate the transition process while ensuring appropriate records are shared with the receiving adult-care practice. Regardless of the process your practice chooses, the most important aspect is that a transition process has been considered, and efforts have been made to improve it.

As mentioned, Got Transition®[7] is a national resource center on healthcare transition. It is a program of the National Alliance to Advance Adolescent Health and provides resources for clinicians, AYAs, parents, and caregivers. A few standard questions as part of pre-visit planning or a clinic intake can help assess a patient's readiness for transition and awareness of how to navigate the healthcare system. Sample questions and forms for a practice to use can be found at GotTransition.org.

Transitioning Special Populations

As practices seek to improve healthcare transitions, certain patient populations may require more specialized support. As mentioned, approximately 20% of AYAs have one or more chronic health conditions.[2] A detailed review of how to transition AYAs with specific medical conditions is beyond the scope of this article, but several general takeaways can be drawn from the literature when transitioning youth with additional needs.

For many conditions, youth will be under the care of a pediatric specialist. Examples include a pediatric

rheumatologist for autoimmune conditions, a pediatric cardiologist for congenital heart conditions, and a pediatric immunologist for congenital immunodeficiencies. Youth with complex syndromic conditions may require care from several pediatric specialties. A patient with DiGeorge syndrome may require care from a pediatric cardiologist, immunologist, and endocrinologist. In these cases, it is essential for the receiving primary care physician to identify which of these specialties will require a transition to an adult specialist and which will remain under the care of the pediatric specialist. In many cases, a pediatric specialist may continue providing care beyond age 18, while others prefer that the youth transition care to an adult specialist.

Similarly, when care for a transitioning youth is more complex, such as when care requires multiple medications, durable medical equipment, ongoing therapies, and engagement in special care programs, enrolling the patient in a care management program may be beneficial. Team-based care models that include nurse care management, care management, and social workers can help improve communication, organize the transition process, and overcome barriers to care. Practices involved in healthcare transitions should also recognize the importance of non-clinical needs during this period. Examples include understanding a patient's needs for educational support, vocational services, and social determinants of health. Recognizing these support needs reflects an understanding of the broader developmental needs of AYAs, including the ability to gain independence or to continue progress through vocational rehabilitation programs.

For example, during the implementation of a transition-of-care program within a managed care organization, patients reported needing education and vocational support services in addition to assistance with their health care.[15] As part of the transition process, nurse care managers and social workers provided support alongside the clinician. Social work support is also critical for addressing guardianship needs and advanced care planning (e.g. durable power of attorney) for certain patient populations. Overall, adult care practices should consider team-based transition models that incorporate licensed professionals to deliver unique services for AYAs, especially those with chronic care needs.

Practical Steps and Resources to Implement a Transition Process

Practical implementation of healthcare transitions for AYAs can be supported through structured, practice-based tools and system-level interventions. The GotTransition® framework offers implementation guides tailored to specific practice types, providing stepwise approaches for integrating transition processes into routine care. The GotTransition® Implementation Guide,[17] for example, breaks down each component needed to successfully integrate an effective, sustainable transitions process from establishing leadership support, forming a quality improvement team, developing a transitions plan, and making efforts scalable. However, if such a process seems daunting, pediatric and adult care practices can start at a small scale by first simply identifying patients who are getting ready for or making a transition to another practice and providing education to these patients. Samples of patient education can be found in the GotTransition® Implementation Guide.[9]

Once the identification of AYAs has been standardized, practices could implement the next step of conducting an assessment of transition readiness. Assessment of transition readiness can be operationalized using validated instruments such as the Transition Readiness Assessment Questionnaire (TRAQ),[18] which is designed for AYAs without special health care needs. Additional questionnaires for specific patients or practices can be found at ACP's Pediatric to Adult Care Transitions Initiative.[19] These tools could be incorporated into pre-visit planning or check-in workflow, with results reviewed by clinical staff or physicians during visits. However, barriers, including question fatigue and time constraints, have been reported.[20]

The Role of Health Systems and Payers

The burden of improved transitions cannot fall solely on healthcare clinicians. Healthcare systems and payers are essential players in the development and sustainability of a transition process. A widely cited article found that primary care physicians need more than 26 hours per day to deliver recommended care.[21] Team-based care models can help distribute components of a transition process, but such efforts require additional personnel whose services may not

be reimbursed in a fee-for-service payment model. Now more than ever, practices are challenged to improve efficiency, handle more volume, and minimize costs. Healthcare transitions are one of many areas of medicine that require time, patience, and a deep trust between the healthcare team and patient. Though the benefits of a successful transition program may not be recognized immediately, investing in such programs is essential to the future of the healthcare system . Physician advocacy will be essential to implementing sustainable payment models that prioritize preventive care and incentivize clinicians for improving health outcomes.

Conclusion

The successful transition of youth from pediatric to adult care has longstanding implications for health outcomes and healthcare utilization. Several studies have demonstrated the positive impact of a team-based, planned transition process. Despite this, widespread investment in healthcare transitions is lacking. It is essential that physicians who care for AYAs in any part of their practice learn the components of a successful healthcare transition and consider implementation within their practice as able.

References

1. Census Reporter. Accessed January 19, 2026. https://censusreporter.org/profiles/04000US29-missouri/
2. Jin M, An Q, Wang L. Chronic Conditions in Adolescents. Exp Ther Med. 2017;14(1):478-482. doi:10.3892/etm.2017.4526
3. Schraeder K, Nettel-Aguirre A, Mackie A, et al. Identifying a retrospective cohort of adolescents with chronic health conditions from a paediatric hospital prior to transfer to adult care: the Calgary Transition Cohort. BMJ Open. 2019;9(5):e027045. Published 2019 May 5. doi:10.1136/bmjopen-2018-027045
4. Abrignani MG, Lucà F, Favilli S, et al. Lifestyles and Cardiovascular Prevention in Childhood and Adolescence. Pediatr Cardiol. 2019;40(6):1113-1125. doi:10.1007/s00246-019-02152-w
5. Meyers MJ, Irwin CE. Health Care Transitions for Adolescents. Pediatrics. 2023;151(Suppl 1):e2022057267L. doi:10.1542/peds.2022-057267L
6. Society for Adolescent Health and Medicine. Transition to Adulthood for Youth With Chronic Conditions and Special Health Care Needs. J Adolesc Health. 2020;66(5):631-634. doi:10.1016/j.jadohealth.2020.02.006
7. White PH, Cooley WC; TRANSITIONS CLINICAL REPORT AUTHORING GROUP; AMERICAN ACADEMY OF PEDIATRICS; AMERICAN ACADEMY OF FAMILY PHYSICIANS; AMERICAN COLLEGE OF PHYSICIANS. Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home. Pediatrics. 2018;142(5):e20182587. doi:10.1542/peds.2018-2587
8. Lebrun-Harris LA, McManus MA, Ilango SM, et al. Transition Planning Among US Youth With and Without Special Health Care Needs. Pediatrics. 2018;142(4):e20180194. doi:10.1542/peds.2018-0194
9. Got Transition®. Six Core Elements of Health Care Transition™. Got Transition. Published online. https://www.gottransition.org/six-core-elements/. Accessed January 16, 2026
10. Arons A, R Tsevat, et al. A Quality Improvement Initiative to Improve Health Care Transition Planning at Adolescent Well Visits. Acad Pediatr. 24(6):973-981.
11. Jensen PT, Karnes J, Jones K, et al. Quantitative evaluation of a pediatric rheumatology transition program. Pediatr Rheumatol Online J. 2015;13:17. Published 2015 May 24. doi:10.1186/s12969-015-0013-0
12. Harden PN, Walsh G, Bandler N, et al. Bridging the gap: an integrated paediatric to adult clinical service for young adults with kidney failure. BMJ. 2012;344:e3718. Published 2012 Jun 1. doi:10.1136/bmj.e3718
13. Cadario F, Prodam F, Bellone S, et al. Transition process of patients with type 1 diabetes (T1DM) from paediatric to the adult health care service: a hospital-based approach. Clin Endocrinol (Oxf). 2009;71(3):346-350. doi:10.1111/j.1365-2265.2008.03467.x
14. McManus M, White P, Pirtle R, Hancock C, Ablan M, Corona-Parra R. Incorporating the Six Core Elements of Health Care Transition Into a Medicaid Managed Care Plan: Lessons Learned From a Pilot Project. J Pediatr Nurs. 2015;30(5):700-713. doi:10.1016/j.pedn.2015.05.029
15. Gabriel P, McManus M, Rogers K, White P. Outcome Evidence for Structured Pediatric to Adult Health Care Transition Interventions: A Systematic Review. J Pediatr. 2017;188:263-269.e15. doi:10.1016/j.jpeds.2017.05.066
16. McManus M, White P, Barbour A, et al. Pediatric to adult transition: a quality improvement model for primary care. J Adolesc Health. 2015;56(1):73-78. doi:10.1016/j.jadohealth.2014.08.006
17. Got Transition®. How to Implement the Six Core Elements of Health Care Transition™ 3.0. Published online. https://www.gottransition.org/6ce/?how-to-implement. Accessed March 4, 2026.
18. Wood D, G Sawicki, et al. The Transition Readiness Assessment Questionnaire (TRAQ): Its Factor Structure, reliability, and validity. Acad Pediatr. 2014;14(4):415-422.
19. American College of Physicians. Pediatric to adult care transitions initiative. American College of Physicians. Accessed January 24, 2026. https://www.acponline.org/clinical-information/high-value-care/resources-for-clinicians/pediatric-to-adult-care-transitions-initiative
20. Arons A, Tsevat RK, Hotez E, et al. A Quality Improvement Initiative to Improve Health Care Transition Planning at Adolescent Well Visits. Acad Pediatr. 2024;24(6):973-981. doi:10.1016/j.acap.2024.03.013
21. Porter J, Boyd C, Skandari MR, Laiteerapong N. Revisiting the Time Needed to Provide Adult Primary Care. J Gen Intern Med. 2023;38(1):147-155. doi:10.1007/s11606-022-07707-x

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Dangers of Injectable Peptides and Other Unregulated "Biohacking" Drugs

by Areeba Moiz, MD, Evan L. O'Keefe, MD & James H. O'Keefe, MD

An important distinction exists between peptides that have undergone rigorous clinical testing and experimental compounds that are largely untested in humans, marketed primarily online, and used without medical supervision.





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Abstract

Injectable peptides are increasingly used without prescriptions for cosmetic and athletic enhancement, driven by digital marketing and social media. While evidence-based, FDA-approved peptides like semaglutide and tirzepatide offer significant clinical benefits under medical supervision, an expanding illicit market provides easy access without a prescription to many unapproved experimental drugs. These unregulated substances—including the veterinary anabolic steroid trenbolone, investigational triple-agonists like retatrutide, and unapproved peptides such as BPC-157, TB-500, and melanotan-II—lack established human safety profiles. Their use introduces severe potential risks, including product contamination, manufacturing impurities, inaccurate dosing, pathological angiogenesis, carcinogenesis, cardiovascular stress, and supraphysiological hormonal signaling. This review differentiates evidence-based therapeutics from unproven, high-risk compounds and outlines the molecular mechanisms of toxicity associated with popular "looksmaxxing" injectables. Clinicians must recognize these trends, and counsel patients on potential long-term health hazards of these potent agents.

Keywords

Injectable peptides, biohacking, drug safety, compounding pharmacies, anabolic agents, looksmaxxing.

Introduction

There is a growing fascination with injectable peptides for use in the pursuit of rapid physical transformation. The intense interest and large-scale rapid adoption have been fueled by social media, podcasts, fitness forums, and wellness clinics. Peptides are increasingly promoted as tools to accelerate fat loss, build muscle, rejuvenate appearance, optimize overall health, boost libido, and improve life expectancy.

Enthusiastic testimonials from influencers and longevity gurus often portray these "looksmaxxing" compounds as the next frontier in personal wellness. Looksmaxxing is a slang term, popularized in online subcultures, that refers to the practice of maximizing one's physical attractiveness through various self-improvement techniques, including injectable peptides and steroids. Yet amid the excitement lies an important question: Are peptide users embracing legitimate medical innovations, or adopting potent therapies before the science has cleared them to be safe and effective?

Peptides are short chains of amino acids that function

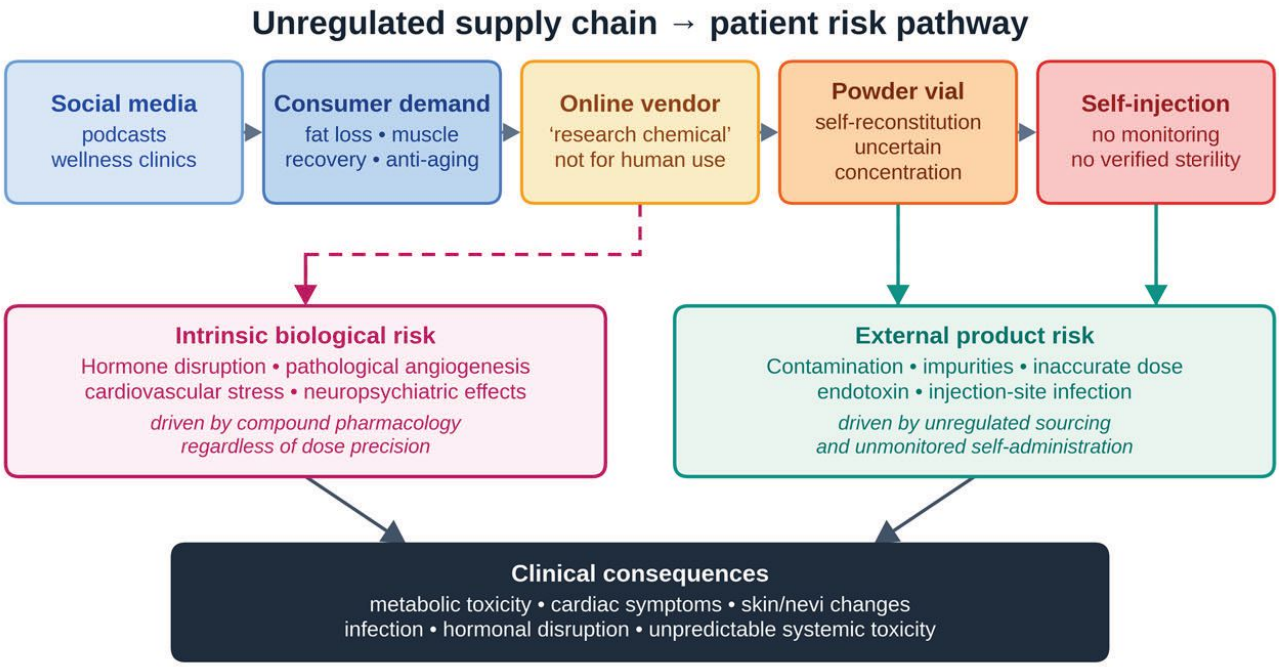


Figure 1. How marketing and unregulated access convert consumer demand into clinical risk

as signaling molecules throughout the body. Many hormones, growth factors, and neurotransmitters are peptides that regulate essential physiological processes, including metabolism, appetite, inflammation, and tissue growth and repair. Because disruptions in peptide signaling contribute to numerous diseases, researchers have increasingly targeted peptide pathways in the development of novel therapeutics.[1] Peptide-based medications represent a rapidly growing area of modern drug development, accounting for more than 11% of all new pharmaceutical entities approved by the US Food and Drug Administration (FDA) between 2016 and 2024.[2]

An important distinction exists between peptides that have undergone rigorous clinical testing and experimental compounds that are largely untested in humans, marketed primarily online, and used without medical supervision. Clinically-validated peptides have transformed the treatment of conditions such as type 1 diabetes, type 2 diabetes, and obesity. For example, semaglutide and tirzepatide are simple peptides composed of 31 and 39 amino acids, respectively, whereas insulin has 51 amino acids.[3,4] Semaglutide and tirzepatide benefits are supported by large randomized clinical trials involving tens of thousands of participants, years of safety monitoring, and regulatory oversight.[3,4] The substantial effectiveness and success of GLP-1 receptor agonists are a testimony to the transformative potential of evidence-based peptide technology.[5]

Unlike many compounds marketed through wellness clinics and online vendors, legitimate peptide therapies must undergo years of rigorous evaluation before being FDA-approved and reaching patients. This process includes extensive laboratory testing, carefully designed clinical trials, manufacturing quality control, stability testing, regulatory review, and ongoing post-marketing surveillance to ensure both safety and efficacy.[6]

Many peptides now popular online were originally abandoned by pharmaceutical companies due to safety concerns, lack of efficacy, or business decisions. Without proper oversight, their use poses significant risks. As demand for these compounds continues to rise, distinguishing evidence-based medicine from marketing-driven claims has become increasingly important. (Figure 1)

Commonly Used Injectable Unapproved Peptides and Compounds

A growing market of unregulated wellness injectables has emerged. Social media influencers,

anti-aging clinics, podcasts, online forums, and direct-to-consumer wellness companies have popularized injectable compounds that are marketed as tools to accelerate recovery, build muscle, promote fat loss, improve cognition and physical appearance, and extend longevity. As interest in biohacking and performance optimization has grown, so has consumer demand for these products.

Unlike approved peptide medications, many of these compounds have not undergone large-scale human clinical trials and lack credible long-term safety data.[7] Some are sold online as "research chemicals" and labeled "for research purposes only" or "not for human consumption," yet are still purchased, usually without a prescription, and injected by consumers. Because they are not FDA-approved medications, they generally cannot be dispensed through traditional pharmacies and are often obtained through online vendors or other unregulated sources.[7]

Several of the most widely promoted injectables illustrate the vast gap that often exists between biological plausibility and demonstrated clinical benefit.

CJC-1295, Ipamorelin, and Growth Hormone Secretagogues

CJC-1295, a synthetic growth hormone-releasing hormone (GHRH) analog, and ipamorelin, a selective ghrelin receptor agonist, have well-defined biological mechanisms that reliably increase endogenous growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels.[8] Growth hormone secretagogues have long been widely prescribed and used in anti-aging and longevity clinics. However, evidence demonstrating meaningful clinical improvements in muscle mass, athletic performance, body composition, or healthy aging remains limited.

Long-term safety concerns of growth hormone stimulators include glucose intolerance, fluid retention, peripheral edema, potential growth promotion of occult malignancy, and reduced life expectancy.[8,9]

Growth hormone and growth hormone-releasing hormone (GHRH) are potent anabolic hormones that upregulate levels of mammalian Target of Rapamycin (mTOR), which promotes cellular growth and muscle development. Paradoxically, these same biological pathways involving growth hormone and mTOR that stimulate growth may also accelerate aging and reduce life expectancy. Animal studies consistently show that reduced growth hormone signaling extends lifespan, while excessive growth hormone shortens lifespan.

In humans, growth hormone replacement is appropriate exclusively for true, documented deficiency. There is no evidence that using growth hormone or its secretagogues as an anti-aging therapy improves longevity, and it may increase the risks of type 2 diabetes, cardiovascular disease, cancer, and premature death.

MK-677 (Ibutamoren)

Commonly used alongside injectable peptides, MK-677 is an orally active, non-peptide ghrelin receptor agonist that potently mimics the growth hormone-stimulating action of endogenous ghrelin. Like CJC-1295, it drives substantial increases in GH and IGF-1. It is widely used in fitness communities to increase appetite, lean mass, and bone density. However, because it bypasses normal hormonal feedback loop controls, its chronic usage results in severe metabolic risks. Clinical monitoring reveals a high incidence of rapid-onset insulin resistance, severe fasting hyperglycemia, and marked fluid retention. Furthermore, its continuous activation of the ghrelin receptor alters hypothalamic signaling, causing persistent, intense hyperphagia that can undermine long-term metabolic health.

Body Protective Compound 157 (BPC-157)

BPC-157 is an experimental synthetic pentadecapeptide (a chain of 15 amino acids) derived from human gastric juice. While promoted informally for musculoskeletal repair, tendon healing, and gastrointestinal health, no peer-reviewed randomized controlled trials have demonstrated clinical benefits in humans.[10] Most supporting evidence originates from preclinical animal models conducted by a highly isolated group of investigators.[11] Its proposed intracellular pathways present considerable systemic and oncogenic safety concerns:

Pathological Angiogenesis: BPC-157 accelerates blood vessel growth by upregulating vascular endothelial growth factor receptor 2 (VEGFR2) and activating the downstream Akt-eNOS signaling cascade.[10] In healthy tissue, this drives healing; however, in the presence of occult malignancies, hyper-activated VEGFR2 signaling prompts uninhibited tumor neovascularization, directly fueling tumor progression and metastasis.

Early Growth Response-1 (Egr-1) Up-regulation: The peptide strongly stimulates the transcription factor Egr-1.[12] While Egr-1 plays a complex regulatory role, its sustained, unmonitored overactivation is tightly linked to cellular proliferation and the progression of certain solid tumors.

Neurotransmitter Distortion: Peripheral administration alters central serotonergic and dopaminergic systems, causing unpredictable behavioral fluctuations and lowering the threshold for central nervous system toxicities when combined with other stimulants.

TB-500 (Thymosin Beta-4 Fragment)

TB-500 is a synthetic peptide fragment replicating the active, acetylated region of the naturally occurring protein thymosin beta-4, which is involved in cell migration, actin polymerization, and tissue remodeling. It is frequently co-administered with BPC-157 in unregulated fitness regimens to accelerate wound healing and muscular recovery. However, no human safety or efficacy trials exist for elective cosmetic or athletic use.

Because thymosin beta-4 naturally upregulates matrix metalloproteinases and promotes endothelial cell motility, its unmonitored systemic use introduces significant concerns regarding the proliferation and migration of occult tumor cells. The World Anti-Doping Agency (WADA) classifies TB-500 as a prohibited substance at all times due to its lack of human approval and potential for athletic abuse.[13]

Melanotan-II (MT-II)

Melanotan-II is a cyclic, synthetic analog of alpha-melanocyte-stimulating hormone (α-MSH). It is marketed as a drug to: stimulate melanogensis and cause skin darkening without UV exposure, increase libido and erectile function, and suppress appetite. Unlike native hormones, MT-II acts as a potent, non-selective agonist across multiple melanocortin receptors (MC_1R, MC_3R, MC_4R, and MC_5R), manifesting severe systemic side effects:

Melanocytic proliferation and nevi changes: MT-II binds directly to MC_1R on melanocytes, hyper-activating the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) cascade. This upregulates tyrosinase, forcing intense eumelanin synthesis. Uncontrolled, chronic MC_1R overstimulation has been clinically documented to cause rapid darkening of existing moles, development of atypical melanocytic nevi, and acute presentation of cutaneous melanoma.[14]

Cardiovascular sympathetic overstimulation: By agonizing MC_4R in the hypothalamus and central nervous system, MT-II stimulates the sympathetic nervous system.[15] This drives sudden, acute elevations in blood pressure and heart rate, predisposing users to hypertensive crises and cardiac arrhythmias.

Systemic toxicity and rhabdomyolysis: Severe systemic responses to non-selective receptor cross-reactivity include acute rhabdomyolysis, where rapid muscle breakdown triggers systemic myoglobin release, directly precipitating acute kidney injury (AKI).

GHK-Cu (Copper Tripeptide-1)

GHK-Cu is a naturally occurring copper-complexed tripeptide found in human plasma that declines with age. Marketed heavily as an injectable and topical anti-aging treatment for collagen synthesis, skin remodeling, and tissue repair, its systemic administration poses distinct biochemical risks. Copper is a tightly regulated micronutrient in the human body; excessive systemic delivery of copper-binding peptides can disturb systemic copper homeostasis, leading to cellular oxidative stress via Fenton-like chemistry and potential hepatotoxicity. Despite widespread adoption in wellness clinics, robust, double-blind, placebo-controlled human trials validating the safety and systemic efficacy of injectable GHK-Cu are entirely absent.

Retatrutide (Investigational Triple-G Agonist)

An essential distinction must be made regarding retatrutide, a novel peptide being developed and rigorously tested by Eli Lilly. Unlike unapproved research chemicals, retatrutide is a highly structured, investigational triple-G hormone receptor agonist targeting the glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors.

Retatrutide has successfully completed landmark, large-scale Phase 3 clinical trials—including the TRIUMPH-1 and TRANSCEND-T2D-1 clinical trial programs.[16,17] Data from the TRIUMPH-1 obesity trial demonstrated bariatric-level weight loss, with patients on the 12 mg maximum weekly dose achieving an unprecedented average body weight reduction of up to 28.3% at 80 weeks and 30.3% at 104 weeks.[17] Data from the TRANSCEND-T2D-1 trial demonstrated phenomenal glycemic efficacy, with Hemoglobin A1c reductions of up to 2.0% in type 2 diabetes patients.[18]

However, retatrutide remains an unapproved investigational drug awaiting formal regulatory review. Its current availability on the illicit market via online research suppliers represents a significant hazard. Unauthorized formulations lack standard commercial stability controls and require proactive clinical warning, as its triple-agonist profile carries unique tolerability risks, including a dose-dependent incidence of transient dysesthesia/hyperesthesia and gastrointestinal adverse events that require precise, monitored titration.[16-19]

Trenbolone (Synthetic Anabolic Steroid)

Frequently discussed and used alongside peptides in fitness and "biohacking" subcultures, trenbolone is not a peptide, but rather a powerful anabolic steroid developed for cattle to accelerate growth and increase lean muscle mass. Although never tested in humans or FDA-approved, it has become popular in bodybuilding circles because of its dramatic muscle-building, physique-optimizing effects. Unfortunately, it is also among the most hazardous performance-enhancing drugs, carrying substantial risks for cardiovascular disease, hormonal dysfunction, psychiatric side effects, and premature death.

It is an extremely potent synthetic 19-nortestosterone derivative and anabolic-androgenic steroid originally developed and approved solely for veterinary use to stimulate hyper-accelerated lean muscle growth, weight gain, and feed efficiency (an organism's biological efficiency at converting dietary calories into skeletal muscle) for cattle before slaughter.[20-22]

Human users often report rapid gains in lean muscle mass, reduced body fat, increased training intensity, and enhanced physical performance. However, these benefits come at a substantial physiological cost. Its administration in humans often induces severe and profound systemic toxicity. At the molecular level, trenbolone acts as a high-affinity agonist of the androgen receptor while exerting powerful anti-glucocorticoid actions. Its adverse effect profile vastly exceeds standard anabolic steroids, driving severe cardiovascular stress, rapid endothelial dysfunction, profound dyslipidemia (characterized by a drastic suppression of high-density lipoprotein and marked elevation of low-density lipoprotein), acute left ventricular myocardial hypertrophy, and accelerated coronary atherosclerosis.[20-22]

Furthermore, trenbolone exhibits profound neurotoxicity and psychiatric side effects, including acute sleep disturbances, severe paranoia, and unprovoked aggression ("tren-rage"). Like other anabolic steroids, trenbolone also suppresses the hypothalamic-pituitary-gonadal axis, reducing endogenous testosterone production and potentially leading to infertility, testicular atrophy, sexual dysfunction, and prolonged hormonal disturbances after discontinuation.[21]

Trenbolone is typically administered by intramuscular injection, most commonly as trenbolone acetate or trenbolone enanthate. Because no FDA-approved human formulations exist, virtually all human use involves products obtained through underground laboratories, veterinary sources, or illicit supply chains, creating additional concerns regarding product purity, sterility, and dose accuracy.

Manufacturing, Contamination, and Regulatory Risks

Beyond intrinsic biological hazards, the procurement mechanism of unapproved peptides introduces severe external risks. Products sourced through online research chemical suppliers operate entirely outside of Current Good Manufacturing Practice (cGMP) guidelines required for pharmaceutical entities. Chemical analyses of direct-to-consumer peptide products have revealed severe manufacturing variability, including significant deviations from stated dosages, truncated peptide impurities, and the presence of heavy metals or organic solvent residues.[7]

Furthermore, because these products are typically distributed as lyophilized powders requiring manual reconstitution by the consumer, the risks of introduction of bacterial endotoxins, inaccurate localized dosing, and localized injection-site infections are profoundly elevated.

Regulatory landscapes have shifted to address these public health hazards. The FDA has identified safety concerns for several nominated peptide bulk drug substances, including BPC-157 and TB-500; their compounding status remains under review, and these compounds are not FDA-approved therapies.[23] This regulatory designation indicates that these substances may present significant safety risks and, according to legal compliance guidance, may limit or preclude their routine use in 503A pharmacy compounding unless they meet applicable federal compounding requirements (Table 1).[24]

Clinical Recommendations and Conclusion

The premature integration of experimental peptides into elective wellness and longevity regimens represents a profound gap between marketing claims and clinical science. While legitimate, evidence-based peptide design has yielded groundbreaking therapeutics like semaglutide and tirzepatide, the unmonitored adoption of unapproved growth hormone secretagogues, angiogenesis promoters, and non-selective receptor agonists carries profound and unpredictable dangers to long-term health and wellbeing, and even life expectancy.

Clinicians must actively screen patients for lifestyle peptide injections, counsel them on the oncogenic,

Table 1. Summary of Peptides

Compound	Classification / Target	Clinical Status	Primary Documented Intracellular Mechanism / Action	Main Medical & Toxicological Risks
Semaglutide	Peptide/GLP-1 Receptor Agonist	FDA Approved (Type 2 Diabetes & Obesity)	Upregulates cAMP pathway to increase glucose-dependent insulin secretion, slow gastric emptying.	Mild-to-moderate GI distress, low risk of pancreatitis, cholelithiasis.
Tirzepatide	Peptide/Dual GIP & GLP-1 Receptor Agonist	FDA Approved (Type 2 Diabetes & Obesity)	Synergistic activation of GIP and GLP-1 receptors; optimizes insulin sensitivity and metabolic efficiency.	Mild-to-moderate GI effects, nausea, dose-dependent gastrointestinal events.
Retatrutide	Peptide/Triple GIP, GLP-1, & Glucagon Receptor Agonist	Investigational Only (Phase 3 complete; Pending FDA review)	Concomitant activation of GIP, GLP-1, and Glucagon pathways; drives bariatric-level lipolysis.	GI distress, dose-dependent transient dysesthesia/hyperesthesia, increased heart rate.
CJC-1295 / Ipamorelin	Peptide/GHRH Analog & Ghrelin Agonist	Unapproved/FDA Category 2 Bulk Drug Substance	Stimulates secretion of endogenous Growth Hormone (GH) and production of hepatic IGF-1.	Glucose intolerance, fluid retention, potential growth acceleration of occult malignancies, reduced lifespan.
MK-677 (Ibutamoren)	Non-Peptide Small Molecule/Ghrelin Agonist	Unapproved (Research Chemical)	Mimics ghrelin receptor activation orally; forces continuous GH and IGF-1 elevation.	Rapid insulin resistance, marked fasting hyperglycemia, hyperphagia, severe edema.
BPC-157	Peptide/ Pentadecapeptide fragment	Unapproved/FDA Category 2 Bulk Drug Substance	Hyper-activates VEGFR2 signaling cascade; forces angiogenesis and upregulates Egr-1 transcription.	Theoretical tumor neovascularization/metastasis, central neurotransmitter distortion.
TB-500	Peptide/Thymosin β-4 active fragment	Unapproved/FDA Category 2 Bulk Drug Substance	Promotes actin polymerization, metalloproteinase expression, and cell migration.	Pro-oncogenic tissue proliferation, cell migration; WADA prohibited at all times.
Melanotan-II	Peptide/Cyclic a-MSH Analog	Unapproved (Illicit Market / Tanning Injection)	Non-selective agonist across multiple melanocortin receptors (MC_1R, MC_3R, MC_4R, MC_5R).	Melanocytic proliferation, atypical nevi/melanoma, hypertensive crisis, rhabdomyolysis.
GHK-Cu	Peptide/Copper-complexed tripeptide	Unapproved (Cosmetic Research Chemical)	Chelation of systemic copper ions; activates intracellular tissue remodeling pathways.	Disturbed copper homeostasis, intracellular oxidative stress via Fenton reactions, lack of safety data.
Trenbolone	Non-Peptide/ Synthetic Anabolic-Androgenic Steroid	Veterinary Use Only (Prohibited in humans)	High-affinity androgen receptor agonist; severe anti-glucocorticoid activity.	Severe cardiotoxicity, profound dyslipidemia, reproductive atrophy, neurobehavioral toxicity.

cardiovascular, and purity risks of research chemicals, and emphasize that long-term safety profiles cannot be bypassed for cosmetic or performance outcomes. (Figure 2).

References

1. Muttenthaler M, King GF, Adams DJ, Alewood PF. Trends in peptide drug discovery. Nat Rev Drug Discov. 2021;20(4):309-325.
2. de la Torre BG, Albericio F. The Pharmaceutical Industry in 2023: An Analysis of FDA Drug Approvals from the Perspective of Molecules. Molecules. 2024 Jan 25;29(3):585. doi: 10.3390/molecules29030585. PMID: 38338330; PMCID: PMC10856271.
3. Wilding JPH, Batterham RL, Calanna S, et al. Safety and Efficacy of Semaglutide 2.4 mg Once Weekly in Adults with Overweight or Obesity (STEP 1). N Engl J Med. 2021;384(11):989-1002.
4. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A; SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022 Jul 21;387(3):205-216. doi: 10.1056/NEJMoa2206038. Epub 2022 Jun 4. PMID: 35658024.
5. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: what comes next? Nat Rev Drug Discov. 2022;21(3):201-223.
6. U.S. Food and Drug Administration. The Drug Development Process: From Concept to Regulatory Approval. U.S. Department of Health and Human Services; 2024.
7. Cohen PA, Travis JC, Keizers PHJ. Analysis of unregulated direct-to-

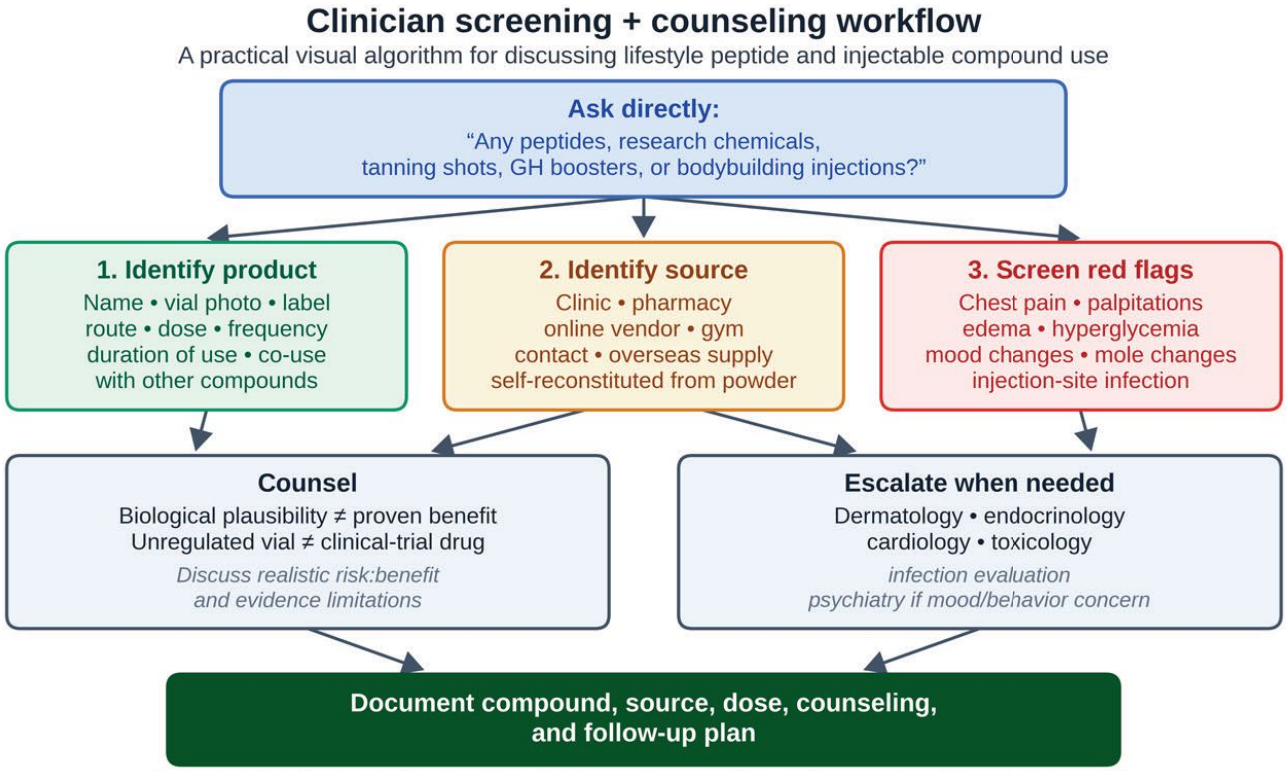


Figure 2. Clinician workflow for identifying and counseling patients using lifestyle injectables

consumer peptide products: Manufacturing variability, chemical impurities, and labeling inaccuracies among online research chemical suppliers. JAMA Netw Open. 2025;8(2):e250124.
8. Sigalos JT, Pastuszak AW. The safety and efficacy of growth hormone secretagogues. Sex Med Rev. 2018;6(1):45–53.
9. Bartke A. Growth hormone, not IGF-1, is the key longevity regulator in mammals. J Gerontol A Biol Sci Med Sci. 2022;77(9):1719–1721.
10. Deek F, Al-Hasan R, Gharaibeh M. Regeneration or Risk? A Narrative Review of BPC-157 for Musculoskeletal and Beyond. Biomed Pharmacother. 2025;178:117240.
11. Sikiric P, Seiwerth S. Brain-gut Axis and Pentadecapeptide BPC 157. Curr Neuropharmacol. 2017;15(1):22-39.
12. Multifuncionality and Possible Medical Application of the BPC 157 Pentadecapeptide. Pharmaceuticals. 2025;18(2):185. Józwiak M, Bauer M, Kamysz W, Kleczkowska P. Multifunctionality and Possible Medical Application of the BPC 157 Peptide-Literature and Patent Review. Pharmaceuticals (Basel). 2025 Jan 30;18(2):185.
13. World Anti-Doping Agency. The Prohibited List: Substances and Methods Prohibited at All Times (Category S0: Unapproved Substances - Thymosin Beta-4 / TB-500). WADA; 2026.
14. Hjuler KF, Lorentzen HF. Melanoma associated with the use of melanotan-II. Dermatology. 2014;228(1):34-6. doi: 10.1159/000356389. Epub 2013 Dec 18. PMID: 24355990.
15. University of New South Wales Medicine & Health. What is Melanotan-II - the drug that regulatory bodies urge consumers to avoid. UNSW Newsroom; 2023.
16. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. N Engl J Med. 2023;389(6):514-526.
17. Eli Lilly and Company. Lilly's triple agonist, retatrutide, delivered powerful weight loss in pivotal Phase 3 obesity trial (TRIUMPH-1). Lilly Investor News. Published May 21, 2026.
18. Bajaj H, Welch M, Shah P, et al. Efficacy and safety of retatrutide, a GIP, GLP-1, and glucagon receptor agonist, in people with type 2 diabetes and inadequate glycaemic control with diet and exercise (TRANSCEND-T2D-1): a double-blind, randomised, phase 3 trial. Lancet. 2026;407(10542):211-223.
19. Goldman J. What Pharmacists Need to Know About Retatrutide's TRIUMPH-1 Phase 3 Results. Pharmacy Times. Published June 3, 2026.
20. National Center for Biotechnology Information. PubChem Compound Summary for CID 25015, Trenbolone. National Library of Medicine; 2026.
21. Kowalski M. Impact of synthetic anabolic-androgenic steroid trenbolone on selected biological systems: A review of nervous and reproductive tissue toxicity. Endokrynol Pol. 2024;75(3):312-322.
22. Bonenti B, Ahmadinejad B, Puljević C, et al. The Trenbolo(g)ne Sandwich: An International Study Comparing Health Harms Among Men Who Use Anabolic-Androgenic Steroids With and Without Trenbolone. Drug Alcohol Rev. 2026 May;45(4):e70162.
23. U.S. Food and Drug Administration. Substances in Compounding that May Present Significant Safety Risks (Bulk Drug Substances Category 2). FDA Bulletin. Updated April 2026.
24. Holt Law LLC. FDA Category 2 Peptide Legal Compliance for Compounding Pharmacies. Legal Insights. Published January 14, 2026.

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A Review of Direct-to-Consumer Home Antibiotic Kits: A Threat to Antimicrobial Stewardship and Patient Safety

by Hilal Abdessamad, MD, Hadie Islam, DO & Brian K. White, DO

Direct-to-consumer prescription antibiotic kits are marketed to exploit patient fear by describing catastrophic scenarios.



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Abstract

Driven by the global wellness industry, pandemic anxiety, and increasing demand for telehealth, a direct-to-consumer (DTC) market for prescription antibiotic emergency kits has emerged. This review examines the clinical, ethical, and public health risks of stockpiling broad-spectrum antimicrobials for self-administration without guidance from a clinician. This model is a health risk to the individual consumers (adverse effects, drug interactions) and to the entire population (propagating antimicrobial resistance). While these kits are marketed as tools of safety and peace of mind, they represent an unmonitored public health threat. This article concludes with a call to action for regulatory bodies and medical societies to investigate misleading marketing and enforce stricter rules on prescribing antibiotics for future hypothetical illnesses, except in high-risk travel medicine contexts.

Keywords

Antibiotics, home kits, antimicrobial stewardship, physician relationship, DTC.

Introduction

The changing healthcare landscape is driven by several converging factors. Disaster preparedness after the COVID-19 pandemic changed how people think about system resilience and geopolitical instability.[1] With the ongoing physician shortage in the United States (US), especially after the pandemic, the Association of American Medical Colleges projects a shortage of up to 40,400 primary care providers (PCPs) in 2036, with an increased demand for healthcare services.[2] Thus, people are concerned that they may not have access to care when they need it. Additionally, the growth of DTC healthcare services during the pandemic has evolved into distribution channels for prescription medications that bypass traditional doctor-patient relationships.[3]

Companies now market and sell "Medical Emergency Kits" and "Emergency Antibiotic Kits" directly to consumers.[4] These are not first-aid supplies, but rather pre-packaged caches of prescription medications. Unfortunately, these kits often have antibiotics that are self-prescribed.[4] Antibiotic misuse is common(even among healthcare providers), and these kits enable

further misuse.[5] This can fuel one of our most urgent global health crises: antimicrobial resistance.[6]

Antimicrobial resistance (AMR) is already responsible for at least 1.27 million annual deaths globally.[7] In the US alone, there are over 2.8 million antibiotic-resistant infections annually, causing more than 35,000 deaths.[7] With antimicrobial exposure, bacteria undergo selective pressure resulting in the preservation of resistant organisms.[8] A 2023 study found that up to 90% of antibiotics are prescribed in the primary care setting, with up to 36.5% of those being inappropriate.

Proper antimicrobial stewardship has four pillars, called the 4 Rights (Figure 1).[9] DTC homecare practices risk incorrect dosing, duration or choice of antibiotic, which are modifiable risk factors for AMR. Antimicrobials also increase the risk of adverse effects, such as infections with *Clostridioides difficile*.[4]

In this analysis, we discuss the contents of these kits with commentary regarding self-directed use of each antimicrobial. We will also evaluate this practice against established standards of medical care and antimicrobial stewardship.

Market and Product Analysis

A new sector of telehealth companies has emerged to serve the "preparedness" market. The major players are well-funded, highly visible companies. The kits typically sell for $300 to $400, which represents a large investment for most families.[10] These companies advertise themselves heavily, with some appearing on television shows and with celebrity physician endorsements.[11]

These companies exploit fears of pandemics, bioterror threats, supply chain shortages, and natural disasters that could render healthcare systems overwhelmed or inaccessible, which drives sales.[28] Because these are prescription medications, companies need to create a legal pathway for dispensing them. They do this through a telehealth process, but it bears little semblance of medical practice.[29]

Consumers select a kit and complete an evaluation form. Rather than a diagnostic encounter, this process functions as a liability screening to check for reported allergies, after which a board-certified physician approves the shipment.[29]

Companies claim to offer "ongoing care" or physician access via messaging after receiving the kit.[30] It is advertised that the patient, after a possible initial video call visit, will have access to a dedicated message portal, where they can message the prescriber or request an appointment.[31] Though ultimately, the untrained consumer is making the medical decision.

Figure 1. 4 RIGHTS of Antimicrobial Prescribing

- Right Diagnosis
- Right Antimicrobial
- Right Dosing/Administration
- Right Duration

Traditional medicine starts with symptoms, followed by a differential diagnosis, diagnostic studies, and resultant prescription; this model inverts that process.[32] It starts with a pre-defined product, the antimicrobial prescription. This marketing strategy mixes real public health advice with concerning medical practices. Organizations like the American Red Cross advocate for disaster preparedness.[33] However, their recommendation is to maintain a seven- to 14-day supply of personal, already-prescribed maintenance medications.[33] On the other hand, DTC companies advocate for a similar stockpiling of drugs such as antibiotics, which is not recommended by any major professional medical or public health organizations.

Included Prescription Medications

The contents of the kits vary by vendor, but there are generally five broad-spectrum antibiotics that appear across most kits (Table 1).[10] Most of these antimicrobials are common, with names familiar to the lay population. This familiarity gives the illusion of safety and efficacy. However, the general populace may not be familiar with the specific indications and adverse effects.. The consumers may not consider the risks of drug-drug interactions, allergies, adverse effects, or the development of antimicrobial resistance.

Amoxicillin-Clavulanate carries a risk of misuse for viral symptoms. Azithromycin is a recognizable antibiotic to the general public in its brand name, which is why it's likely to be misused.[20]

Patients who develop rash after hiking may self-diagnose as Lyme disease based on internet research, and use doxycycline without consideration for local epidemiology, vector, or transmission dynamics. Ciprofloxacin is another antibiotic used with distinct side effects.[21]

Metronidazole, another popular antibiotic in these kits, is ineffective if someone takes it for traveler's

Table 1. Most Common Antimicrobials in DTC Kits. N/A: Not available.

Antimicrobial	DTC Marked Indications	Most Common Adverse Events	Risk of Developing *C. difficile*[12]	Risk of Inducing AMR[13–17]
Amoxicillin-Clavulanate[18,19]	Sinusitis Pneumonia Bite wounds.	Hepatotoxicity, diarrhea, anaphylaxis in penicillin-allergic patients, severe cutaneous adverse reactions (SCAR).	+++	++
Azithromycin[20]	Respiratory infections Traveler's diarrhea	QT prolongation (risk of Torsades de Pointes).	+	++ (to macrolides)
Ciprofloxacin[21]	UTIs Bioterrorism Traveler's diarrhea.	FDA Black Box Warnings: Tendinitis/tendon rupture, peripheral neuropathy, seizures, confusion, aortic dissection risk.	++	+++
Doxycycline[22]	Tick-borne illnesses Skin infections Bioterrorism	Photosensitivity, esophageal ulceration (pill esophagitis), intracranial hypertension, teratogenicity, tooth discoloration (children).	+	+++
Metronidazole[23]	Parasitic infections	Disulfiram-like reactions, peripheral neuropathy, metallic taste.	N/A	+
TMP/SMX[24,25]	Skin infections (MRSA) UTIs	Hyperkalemia, renal failure, severe hypersensitivity, bone marrow suppression, severe cutaneous adverse reaction	+	++
Ivermectin[26,27]	Parasitic infections	Seizures, confusion, coma, hypotension, GI distress.	N/A	N/A

diarrhea.[23] Trimethoprim-Sulfamethoxazole (TMP-SMX) is also widely available.[24] Up to 24% of people who take TMP/SMX will have some form of rash that can be dangerous.[25]

Other drugs included in these kits reveal that marketing considerations are driving product design, such as ivermectin, enforcing unproven treatment for COVID-19 and general well-being.[26] This inclusion utilizes medical misinformation to build a customer base.

The Dangers of Unsupervised Self-Diagnosis and Treatment

While shared decision making is an important way to include the patients in their medical care, the foundation is one of informed consent, whereby the patient is aware of risks, benefits, and alternatives. Removing a trained clinician from the diagnostic process creates a plethora of patient safety risks. The main problem with this model is that it asks an untrained person to make a diagnosis. Health professionals are trained to evaluate symptoms, recognize signs, and distinguish between infectious syndromes. Critical thinking and clinical reasoning helps astute clinicians balance probabilities of various etiologies.

One of the most common diagnostic error of an untrained consumer is to get the diagnosis wrong, resulting in them treating viral infections with antibiotics. This exposes patients to unnecessary harms and side effects without any benefit. This can also delay the diagnosis of life-threatening conditions that may have similar presentation.[34] For example, a pulmonary embolism can present as a cough and fever, if a patient opts to treat themself with azithromycin, the outcome could be fatal.[35]

Adverse drug events are a leading cause of emergency department visits and hospitalizations,

even when medications are prescribed appropriately and monitored by clinicians.[36,37] The Food and Drug Administration (FDA) necessitates post-marketing surveillance to ensure safety reports and labelling are current with necessary warnings.[38] Consumers would not be expected to recognize or report such adverse reactions.

In addition, these kits are designed for long-term storage, which may increase the risk of using expired medications. While many drugs retain potency, tetracyclines can degrade into toxic compounds that cause kidney injury.[39] Expired drugs also have reduced effectiveness, leading to sub-therapeutic dosing that fails to cure infections while promoting resistance.

Each patient is unique. These kits do not account for vulnerable populations with specific contraindications. Elderly patients, for example, face higher risks for ciprofloxacin-induced tendon rupture and are more likely to have underlying cardiac conditions that make the QT-prolonging effects of azithromycin dangerous.[20,21] In addition, they are often prescribed multiple medications, which increases the risk of drug-drug interactions.[40] Pregnant women cannot take doxycycline due to its teratogenic effects. In children, doxycycline is contraindicated until age eight, and there is special weight-based dosing.[22] Patients with kidney disease, liver disease, or heart pathologies require dose adjustments or may need to avoid certain drugs.

Companies attempt to overcome liability by including a guidebook that links drugs to certain conditions.[10] This is dangerous as it encourages the patients to self-diagnose. When patients misdiagnose themselves and suffer harm, the company can argue the patient misused the kit by not following the guide correctly.

Antimicrobial Stewardship

While the risks to individual consumers are serious, population-level dangers are even more pronounced. These kits are in direct opposition to antimicrobial stewardship efforts to reduce the impact of AMR. AMR is a significant public health concern, as it limits treatment options for infections, raising infection mortality, hospitalization and length of hospital stays.[41] The modifiable cause of AMR is antibiotic mismanagement, which contradicts stewardship efforts and threatens the rise of extensive and pan-drug resistant, making common infections deadly.[41]

DTC accelerates AMR through three main mechanisms. First, they encourage unnecessary use of antibiotics, which is a driver of AMR. When a consumer spends $400 on a kit and they get sick, they'll feel pressure to use what they've paid for. They also promote ineffective dosing and the four wrongs: wrong diagnosis, wrong drug, wrong dose, and wrong duration.[37,42] Lastly, they cause microbiome disruption and *C.difficile* infections, as broad-spectrum antibiotics kill healthy bacteria along with the pathogens. This imbalances the gut microbiota, allowing resistant pathogens to take over.[43] *C.difficile* is a common consequence of antibiotic overuse and is itself an urgent public health threat.[43]

This business model directly contradicts antimicrobial stewardship principles endorsed by national guidelines by the Centers for Disease Control (CDC) and Infectious Diseases Society of America, which prioritize establishing the right diagnosis before prescribing the right antimicrobial at the right dose for the right duration. While the CDC's 'Be Antibiotics Aware' campaign discourages viral prescribing, DTC kits facilitate it. [44]

The DTC preparedness kit model fails every element. It bypasses diagnostic guidelines, is untraceable, and its guidebook encourages misuse. This is a socioeconomic concept where individuals acting in their own self-interest will deplete a shared resource, even when it's not in their long-term best interest.[45]

Each individual consumer acts in their own self-interest, creating a population-level pressure for AMR. These companies are selling a product that increases risk for a catastrophe while claiming to prevent another. The healthcare crisis of a shortage of clinicians will not be improved by increasing development of AMR.

Prescribing for a Hypothetical Future

This business model exploits legal and ethical uncertainty, relying on an interpretation of telehealth regulations conflicting with established medical standards.

Both the American Medical Association (AMA) and the Federation of State Medical Boards have published policies on appropriate telemedicine use. They mandate establishing a patient-physician relationship, ensuring prescribed treatment is appropriate for that specific diagnosis.[46–48]

Prescribing a bundle of five antibiotics based on a questionnaire for a future, hypothetical, undiagnosed condition does not comply with established standards.

This violates the principal *primum non nocere* (first, do no harm).[49] The physician who "signs off" on these kits knows they're placing high-risk drugs, including ciprofloxacin with its black box warning and azithromycin with its cardiac risks, into the hands of untrained people. Misdiagnosis, adverse events, and promotion of AMR will be almost guaranteed.

The AMA's rationale is that DTC ads "inflate demand for drugs, even when these drugs may not be appropriate," "promote false expectations," and "encourage consumer self-diagnosis and treatment."[50,51] These DTC antibiotic kits embody the AMA's concerns. Marketing is creating consumer demand for medically inappropriate products for at-home, unsupervised stockpiling.

These companies exploit a regulatory loophole by misusing the term "Emergency Kit." State-level laws regarding emergency medical kits shows that they were designed to allow healthcare professionals and paramedics to maintain limited supplies of life-saving drugs.[52] These drugs can only be removed and administered after a valid prescription order.

The DTC provides the kit to laypeople before diagnosis or a prescription order, bypassing the legal concept of an emergency kit.

The Counter-Argument

These companies often market based on catastrophic scenarios without medical access. For example, in a scenario where a collapsing infrastructure and inadequate supply chains, fail to provide medication in time amidst an emerging pandemic, these kits could be life-saving.[53] On a large scale, the Strategic National Stockpile, which is an all-time ready emergency vaccine and medication stockpile managed by the Departments of Homeland Security and Health and Human Services, is a resource that the US government has available in the event of public health emergencies.[54]

The Wilderness Medical Society (WMS) publishes practice guidelines for medical kits. Regarding antibiotics, WMS recommendations are directed at trained clinicians to "work with a travel medicine doctor to select the most appropriate antibiotic coverage per local resistance patterns."[55] A similar approach is adopted by CDC, which recommends some prescription drugs in travel health kits for high-risk destinations.[56] Traveler's diarrhea provides an example of success of physician-guided self-directed antimicrobial therapy, after careful analysis of the threat of illness, and counseling the patient on indications, administration, and cautions.[57] Another example of the success of self-guided antimicrobial therapy is when taking the 'pill in the pocket' approach to early antimicrobial therapy for high risk, asplenic patients.[58] There, again, though, this approach is only successful when combined with face to face education with a knowledgeable clinician.

Individual home antibiotic stockpiling is discouraged by public health and disaster preparedness experts, where risk outweighs benefit. The correct population-level solution for disasters or pandemics is the US Strategic National Stockpile, designed to rapidly deploy antibiotics and medical supplies to affected areas within 12 hours.[59]

Conclusion

DTC prescription antibiotic kits are marketed to exploit patient fear by describing catastrophic scenarios. The general population is vulnerable to these fears in the setting of the recent global COVID-19 pandemic. These companies are enabled by using telehealth regulatory loopholes that challenge the standard of medical care. These kits pose a threat to patient safety and community public health. The known, high-probability risks outweigh the marketed benefits in hypothetical catastrophic scenarios. They ignore principles of antimicrobial stewardship and physicians' ethical mandate to do no harm. These kits are a risk, not a safeguard. They are designed to combat a hypothetical scenario, yet they contribute to the very real public health crisis of antimicrobial resistance.

True medical preparedness consists of three safe steps: assembling a standard first-aid kit (bandages, antiseptics, and over-the-counter medications like acetaminophen, ibuprofen, diphenhydramine, and loperamide), maintaining a seven- to 30-day supply of maintenance medications that are already prescribed, and consulting a physician for suspected infections.[33]

Professional medical organizations and physicians should have a formal position statement condemning the practice of prescribing preparedness kits of broad-spectrum antibiotics. This practice is not standard of care for telehealth, which requires establishing a valid patient-physician relationship and a valid diagnosis before prescribing. They should inform their patients about the dangers associated with these kits and antibiotic self-medication and redirect their

preparedness concerns toward safe and appropriate measures.

Regulatory bodies have the authority and the responsibility to act on this public health threat. State medical boards exist to protect the public, and they are encouraged to investigate and implement disciplinary measures against signing off these prescriptions via static questionnaires, as this does not meet the standard of care for establishing a patient-physician relationship or valid diagnosis. The Federal Trade Commission should investigate the marketing claims of these companies. Claims that these kits provide safety, when they represent a public health risk, are misleading advertising. In addition, The FDA should issue a public safety communication warning about the specific dangers of at-home antibiotic kits.

A harm-reduction model would invert the current business structure. Instead of pre-prescribed kits, emphasis should be placed on on-demand telehealth access to clinicians with established patient relationships. Pre-filled prescriptions should remain restricted to specific, high-risk scenarios (traveler's diarrhea) rather than general preparedness.[60]

Any such prescription must be tied to antimicrobial stewardship principles. This would allow a trained clinician to confirm the diagnosis and indication in real-time, before the antibiotic is initiated. Such a model would align with CDC recommendations for telehealth and antimicrobial stewardship. It would preserve the physician's role as a diagnostic expert and steward of our shared antibiotic resource, while providing help in exceptional circumstances.

Wellness culture, preparedness anxiety, and telehealth convenience have created an environment that allows the DTC business model to flourish. However, no convenience is without cost. The cost of DTC antimicrobials to be self-prescribed without clinician guidance is paid not only by the individual consumer (via adverse effects and drug interactions), but also by the population as antimicrobial resistance escalates. The healthcare community must act now to reduce the threats to the people we serve.

References

1. Kornreich KRP Edward S. Lessons from the COVID-19 Pandemic: Planning for Disaster Preparedness and Emergency Management in Hospitals. Health Care Law Brief. October 27, 2021. Accessed November 30, 2025. https://www.healthcarelawbrief.com/2021/10/lessons-from-the-covid-19-pandemic-planning-for-disaster-preparedness-and-emergency-management-in-hospitals/
2. The Complexities of Physician Supply and Demand: Projections From 2021 to 2036. Published online 2021.
3. Halpern S. What Clinicians Need to Know About DTC Compounding Pharmacies. Infectious Disease Advisor. November 21, 2025. Accessed November 30, 2025. https://www.infectiousdiseaseadvisor.com/features/dtc-telehealth-companies/
4. Peace of mind or risk? Weighing in on at-home antibiotic kits. The DO. October 20, 2025. Accessed November 30, 2025. https://thedo.osteopathic.org/columns/peace-of-mind-or-prescription-risk-a-do-weighs-in-on-at-home-antibiotic-kits/
5. Sijbom M, Büchner FL, Saadah NH, Numans ME, de Boer MGJ. Determinants of inappropriate antibiotic prescription in primary care in developed countries with general practitioners as gatekeepers: a systematic review and construction of a framework. BMJ Open. 2023;13(5):e065006. doi:10.1136/bmjopen-2022-065006
6. Invisible frontlines: tackling antimicrobial resistance amid conflict and fragility. Accessed November 30, 2025. https://www.who.int/news-room/commentaries/detail/invisible-frontlines--tackling-antimicrobial-resistance-amid-conflict-and-fragility
7. CDC. About Antimicrobial Resistance. Antimicrobial Resistance. January 31, 2025. Accessed November 30, 2025. https://www.cdc.gov/antimicrobial-resistance/about/index.html
8. CDC. Antibiotic Use and Antimicrobial Resistance Facts. Antibiotic Prescribing and Use. January 15, 2025. Accessed December 6, 2025. https://www.cdc.gov/antibiotic-use/data-research/facts-stats/index.html
9. Page S, Prescott J, Weese S. The 5Rs approach to antimicrobial stewardship. Veterinary Record. 2014;175(8):207-208. doi:10.1136/vr.g5327
10. Gold S. Best Emergency Antibiotics Kits for Medical Preparedness. TruePrepper. April 11, 2024. Accessed November 30, 2025. https://trueprepper.com/antibiotics-preppers-emergency-supply/
11. The Cult of Top Direct-to-Consumer (DTC) Brands and How They Use Organic Social Media. June 22, 2023. Accessed November 30, 2025. https://polamarketing.com/our-lab/dtc/the-cult-of-top-direct-to-consumer-dtc-brands-and-how-they-use-organic-social-media
12. Miller AC, Arakkal AT, Sewell DK, et al. Comparison of Different Antibiotics and the Risk for Community-Associated Clostridioides difficile Infection: A Case–Control Study. Open Forum Infect Dis. 2023;10(8):ofad413. doi:10.1093/ofid/ofad413
13. Muteeb G. Network meta-analysis of antibiotic resistance patterns in gram-negative bacterial infections: a comparative study of carbapenems, fluoroquinolones, and aminoglycosides. Front Microbiol. 2023;14:1304011. doi:10.3389/fmicb.2023.1304011
14. Hemeda MS, Elsayed HA, Mohamad AlmME, et al. Investigation of metronidazole resistance-associated mutations and virulence genotypes in helicobacter pylori isolates from the Egyptian population: A cross-sectional study. Journal of Infection and Chemotherapy. 2025;31(2):102533. doi:10.1016/j.jiac.2024.10.001
15. Horner P, Ingle S, Garrett F, Blee K, Kong FYS, Moi H. P09.03 Treatment of mycoplasma genitalium with azithromycin 1 g is less efficacious and associated with induction of macrolide resistance compared to a 5-day regimen. Sex Transm Infect. 2015;91(Suppl 2):A148-A148. doi:10.1136/sextrans-2015-052270.387
16. BCIDP LH PharmD. The Consequences of Doxycycline Postexposure Prophylaxis | Contagion Live. January 26, 2026. Accessed January 26, 2026. https://www.contagionlive.com/view/the-consequences-of-doxycycline-postexposure-prophylaxis
17. Tacão M, Moura A, Correia A, Henriques I. Co-resistance to different classes of antibiotics among ESBL-producers from aquatic systems. Water Research. 2014;48:100-107. doi:10.1016/j.watres.2013.09.021
18. Amoxicillin Clavulanate: Uses, Dosage & Side Effects - Drugs.com. Accessed November 30, 2025. https://www.drugs.com/amoxicillin_clavulanate.html
19. Evans J, Hanoodi M, Wittler M. Amoxicillin Clavulanate. In: StatPearls. StatPearls Publishing; 2025. Accessed November 30, 2025. http://www.ncbi.nlm.nih.gov/books/NBK538164/

20. Sanford Guide AMT: Azithromycin. Accessed November 30, 2025. https://web.sanfordguide.com/en/drug-information/antibacterial-agents/macrolides/azithromycin
21. Ciprofloxacin Uses, Dosage, Side Effects, Warnings. Drugs.com. Accessed November 30, 2025. https://www.drugs.com/ciprofloxacin.html
22. Doxycycline: Uses, Dosage, Side Effects, Warnings - Drugs.com. Accessed November 30, 2025. https://www.drugs.com/doxycycline.html
23. Weir CB, Le JK. Metronidazole. In: StatPearls. StatPearls Publishing; 2025. Accessed November 30, 2025. http://www.ncbi.nlm.nih.gov/books/NBK539728/
24. Kemnic TR, Coleman M. Trimethoprim Sulfamethoxazole. In: StatPearls. StatPearls Publishing; 2025. Accessed November 30, 2025. http://www.ncbi.nlm.nih.gov/books/NBK513232/
25. Cao Y, Bairam A, Jee A, Liu M, Uetrecht J. Investigating the Mechanism of Trimethoprim-Induced Skin Rash and Liver Injury. Toxicol Sci. 2021;180(1):17-25. doi:10.1093/toxsci/kfaa182
26. Effect of Early Treatment with Ivermectin among Patients with Covid-19 | New England Journal of Medicine. Accessed November 30, 2025. https://www.nejm.org/doi/full/10.1056/NEJMoa2115869
27. Ivermectin and COVID-19 | FDA. Accessed November 30, 2025. https://www.fda.gov/consumers/consumer-updates/ivermectin-and-covid-19
28. Staff GB. FDA Scrutinizes Home Anthrax Antibiotic Kits. Global Biodefense. April 3, 2012. Accessed November 30, 2025. https://globalbiodefense.com/2012/04/03/fda-scrutinizes-home-anthrax-kits/
29. Halpern S. What Clinicians Need to Know About DTC Compounding Pharmacies. Infectious Disease Advisor. November 21, 2025. Accessed November 30, 2025. https://www.infectiousdiseaseadvisor.com/features/dtc-telehealth-companies/
30. "Pharm-to-Table": The Impact of Direct-to-Consumer Pharmaceutical Sales on Patient Access, Market Dynamics and Investor Strategy. Debevoise. Accessed November 30, 2025. https://www.debevoise.com/insights/publications/2025/09/pharm-to-table-the-impact-of-direct-to-consumer
31. Halpern S. What Clinicians Need to Know About DTC Compounding Pharmacies. The Cardiology Advisor. November 7, 2025. Accessed December 6, 2025. https://www.thecardiologyadvisor.com/features/dtc-telehealth-companies/
32. Telehealth: Technology meets health care - Mayo Clinic. Accessed November 30, 2025. https://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/telehealth/art-20044878
33. Survival Kit Supplies. Accessed November 30, 2025. https://www.redcross.org/get-help/how-to-prepare-for-emergencies/survival-kit-supplies.html
34. Unnecessary antibiotics: Dangers and more. October 10, 2023. Accessed November 30, 2025. https://www.medicalnewstoday.com/articles/unnecessary-antibiotics
35. Mansella G, Keil C, Nickel CH, et al. Delayed Diagnosis in Pulmonary Embolism: Frequency, Patient Characteristics, and Outcome. Respiration. 2020;99(7):589-597. doi:10.1159/000508396
36. Rather IA, Kim BC, Bajpai VK, Park YH. Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. Saudi J Biol Sci. 2017;24(4):808-812. doi:10.1016/j.sjbs.2017.01.004
37. Inappropriate Antibiotic Prescribing for Adults Comes With Increased Risks. Accessed November 30, 2025. https://pew.org/3iKmiIF
38. Research C for DE and. Postmarketing Surveillance Programs. FDA. Published online April 1, 2020. Accessed December 6, 2025. https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs
39. Fanconi Syndrome. Accessed November 30, 2025. https://www.uspharmacist.com/article/fanconi-syndrome
40. Polypharmacy in Adults 60 and Older. August 29, 2025. Accessed December 6, 2025. https://www.hopkinsmedicine.org/health/wellness-and-prevention/polypharmacy-in-adults-60-and-older
41. Antimicrobial resistance. Accessed November 30, 2025. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
42. Kumar S, Agrawal S, Yasmin T, Sinha S. Exploring knowledge and consequences of parental misuse of antibiotics for children. Porto Biomed J. 2025;10(2):e286. doi:10.1097/j.pbj.0000000000000286
43. Antibiotic Overuse and Misuse — 4 Risks You Should Know | Live Healthy | MU Health Care. Accessed November 30, 2025. https://livehealthy.muhealth.org/stories/antibiotic-overuse-and-misuse-4-risks-you-should-know
44. CDC. Be Antibiotics Aware Partner Toolkit. Antibiotic Prescribing and Use. September 17, 2025. Accessed November 30, 2025. https://www.cdc.gov/antibiotic-use/php/usaaw-partner-toolkit/index.html
45. Tragedy of the Commons: Examples & Solutions | HBS Online. Business Insights Blog. February 6, 2019. Accessed November 30, 2025. https://online.hbs.edu/blog/post/tragedy-of-the-commons-impact-on-sustainability-issues
46. Ethical Practice in Telemedicine | AMA-Code. Accessed November 30, 2025. https://code-medical-ethics.ama-assn.org/ethics-opinions/ethical-practice-telemedicine
47. CDC. Research Anthology: Telehealth and Telemedicine. Public Health Law. July 3, 2024. Accessed November 30, 2025. https://www.cdc.gov/phlp/php/publications/research-anthology-telehealth-and-telemedicine.html
48. FSMB | FSMB Policies on Telemedicine / License Portability. Accessed November 30, 2025. https://www.fsmb.org/advocacy/telemedicine-policies/
49. Gifford RW Jr. Primum Non Nocere. JAMA. 1977;238(7):589-590. doi:10.1001/jama.1977.03280070029018
50. H-105.988 Direct-to-Consumer Advertising (DTCA) of Prescription | AMA. Accessed November 30, 2025. https://policysearch.ama-assn.org/policyfinder/detail/H-105.988?uri=%2FAMADoc%2FHOD.xml-0-89.xml
51. AMA calls for ban on DTC ads of prescription drugs and medical devices. American Medical Association. November 17, 2015. Accessed November 30, 2025. https://www.ama-assn.org/press-center/ama-press-releases/ama-calls-ban-dtc-ads-prescription-drugs-and-medical-devices
52. Registering Emergency Medical Services Agencies Under the Protecting Patient Access to Emergency Medications Act of 2017. Federal Register. October 5, 2020. Accessed November 30, 2025. https://www.federalregister.gov/documents/2020/10/05/2020-21675/registering-emergency-medical-services-agencies-under-the-protecting-patient-access-to-emergency
53. CDC. About Rocky Mountain Spotted Fever. Rocky Mountain Spotted Fever (RMSF). May 22, 2025. Accessed November 30, 2025. https://www.cdc.gov/rocky-mountain-spotted-fever/about/index.html
54. Strategic National Stockpile (SNS) - Radiation Emergency Medical Management. Accessed December 6, 2025. https://remm.hhs.gov/sns.htm
55. An Evidence-Based First Aid Kit. Accessed November 30, 2025. https://wms.org/magazine/magazine/1515/An-Evidence-Based-First-Aid-Kit/default.aspx
56. CDC. Travel Health Kits. Yellow Book. August 13, 2025. Accessed November 30, 2025. https://www.cdc.gov/yellow-book/hcp/preparing-international-travelers/travel-health-kits.html
57. Diemert DJ. Prevention and Self-Treatment of Traveler's Diarrhea. Clin Microbiol Rev. 2006;19(3):583-594. doi:10.1128/CMR.00052-05
58. Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. Clinical Microbiology and Infection. 2001;7(12):657-660. doi:10.1046/j.1198-743x.2001.00355.x
59. Stroud C, Viswanathan K, Powell T, Bass RR, Public C on PMC for the, Medicine I of. Current Dispensing Strategies for Medical Countermeasures for Anthrax. In: Prepositioning Antibiotics for Anthrax. National Academies Press (US); 2011. Accessed November 30, 2025. https://www.ncbi.nlm.nih.gov/books/NBK190045/
60. van Beusekom MM, Grootens-Wiegers P, Bos MJW, Guchelaar HJ, van den Broek JM. Low literacy and written drug information: information-seeking, leaflet evaluation and preferences, and roles for images. Int J Clin Pharm. 2016;38(6):1372-1379. doi:10.1007/s11096-016-0376-4

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Pills and Perils: Navigating Polypharmacy in Older Adults

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Medication reviews should be coordinated by a primary care provider and implemented during transitions of care to avoid polypharmacy.



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Abstract

Polypharmacy encompasses inappropriate prescribing, overprescribing, and underprescribing. Polypharmacy in older adults is quite common and contributes to adverse effects, drug interactions, hospital admissions, and functional and cognitive decline. Efforts to reduce polypharmacy include criterion-based management tools, deprescribing protocols, and the use of electronic clinical decision support tools.

Key Words

Polypharmacy, geriatric medicine, drug interactions, criterion-based management, clinical decision support tools, multimorbidity.

Introduction

Polypharmacy is often defined as the daily use of five or more medications, particularly in older adults and those with multimorbidity. Beyond the number of medications, polypharmacy encompasses inappropriate prescribing, overprescribing, and omission of recommended drug therapy, also referred to as underprescribing. Polypharmacy is very common and contributes to adverse effects, drug interactions, hospital admissions and even death. Polypharmacy can lead to functional and cognitive impairment in older adults and thus is considered a geriatric syndrome: a health condition highly prevalent in older adults that is multifactorial in cause and contributes to adverse health outcomes.

Definitions

Inappropriate prescribing refers to the use of a medication or class of medication with a higher risk of potential harm when a safer or equally effective alternative is available.

Overprescribing is defined as prescribing more medications than necessary, particularly when the potential harm may outweigh ongoing or potential benefit. Overprescribing also includes the failure to stop or attempt dose-reduction of a medication when symptoms or clinical indications are no longer present.

Underprescribing is the lack or suboptimal treatment of a condition by failing to prescribe medications that are clinically indicated and likely to provide benefit. It also includes failure to adequately maximize medication dosing. This typically occurs when necessary medications are perceived to have excess risk of adverse effects in the setting of multi-morbidity, frailty, dementia, economic factors, or absence of clinical data in older populations.

Deprescribing involves the intentional discontinuing of medications that are unnecessary or potentially harmful, while maintaining or initiating those that are beneficial and indicated.

Scope of the Polypharmacy Problem

The predominant consumers of prescriptions, over-the-counter medications, and dietary supplements are adults over age 65.[1] More than 40% of older adults take five or more prescription medications daily, a figure that has more than doubled in the past 25 years.[2] More than one-third of older adults take over-the counter medication and nearly two-thirds take dietary supplements.[3] This can complicate medication reconciliation and polypharmacy management as only half of those taking herbal and dietary supplements report discussing this with their primary care provider.[4] A thorough medication review should take place at every opportunity, especially after transitions of care, to ensure each treatment indication is still present and to evaluate for side effects or drug interactions. When multiple providers prescribe medications for a patient—a common occurrence in older adults—a single clinician such as the primary care provider or geriatrician, should coordinate medication management and communicate changes with other providers.

With the concurrent use of prescription and nonprescription products, nearly one in six older adults in the United States (US) is potentially at risk for a major drug-drug interaction.[3] The likelihood of an adverse drug event increases markedly with medication burden from 13% with two medications to 82% with seven or more.[5] The risk of an emergency department visit for medication harm is estimated at 12 per 1,000 population over age 65.[6] As Missouri's aging population distribution mirrors that of the US, over 216,000 of Missourians are at risk of an adverse drug event with a predicted 15,000 emergency department visits annually for medication harms.

When evaluating a potential adverse drug event, clinicians should inquire about dietary supplements, medical cannabis, alcohol, and recreational drug use, as these may contribute to adverse drug–drug or drug–disease events. Clinicians should counsel patients on the interaction between non-prescription and prescription medications and consider these before initiating new therapies. Patients should be advised to report and discuss all supplements and herbal products with their provider to help prevent adverse drug events and identify potential interactions.

Potentially Inappropriate Medication Prescribing

A potentially inappropriate medication (PIM) is one with an unfavorable benefit-to-harm ratio, often misused, overused, or underused, or associated with a high rate adverse patient outcomes. Among older adults, PIM use is quite prevalent with 33-42% taking one or more high risk medications.[7,8] In cases of hyperpolypharmacy, taking ≥10 medications, the prevalence of PIM use has been reported to exceed 80%.

One of the most influential tools in identifying and reducing PIM use in older adults has been the Beers Criteria. First introduced for the nursing home population in 1993 by an expert panel convened by Dr. Mark Beers, the criteria have since expanded to include older adults across all care settings. The American Geriatrics Society (AGS) became the steward of the Beers Criteria in 2011 with the most recent update in 2023.[9] The Beers Criteria provides an evidence-based categorization of PIM and is a mainstay in guiding safer prescribing practices.

The Beers Criteria identifies medications that should be avoided in older adults in most circumstances, and those with high-risk drug-drug and drug-disease interactions. Highly anticholinergic medications have been associated with an elevated risk of adverse outcomes including falls, cognitive decline, and delirium, especially in older adults with dementia. The Beers Criteria recommends avoiding the concurrent use of two or more agents with anticholinergic properties in older adults. Table 1 shows a variety of medications to avoid due to anticholinergic properties.[9]

Table 1. Beers Criteria Medications with High Anticholinergic Risk

Organ System	Indication	Medications	Rationale
Allergy/ENT	Antihistamine	Brompheniramine, Chlorpheniramine Cyproheptadine, Dimenhydrinate Diphenhydramine, Doxylamine Hydroxyzine, Meclizine, Promethazine, Triprolidine	Less risky options available (2nd generation medications)
Central Nervous System	Depression	Amitriptyline, Amoxapine, Clomipramine, Desipramine Doxepin (>6mg/day), Imipramine Nortriptyline, Paroxetine	Sedation, Orthostatic Hypotension
	Psychosis	Chlorpromazine, Clozapine Olanzapine, Perphenazine	Increased risk of stroke and mortality with dementia
	Parkinson's Disease	Benztropine Trihexyphenidyl	Increased risk of stroke and mortality with dementia
Gastrointestinal	Nausea	Prochlorperazine Promethazine	Less risky options available
	Bowel Spasm	Atropine, Clinidium, Dicyclomine Homatropine, Hyocyamine, Scopolamine	Unclear efficacy
Genitourinary	Urinary Incontinence	Darifenacin, Fesoterodine, Flavoxate Oxybutynin, Solifenacin, Tolterodine Tropsium	Less risky options available
Musculoskeletal	Muscle Spasm	Carisoprodol, Chlorzoxazone Cyclobenzaprine, Metaxalone Methocarbamol, Orphenadrine	Sedation, Falls and fractures

Other classes of potentially PIMs include sulfonylureas, benzodiazepines, proton pump inhibitors, and selected cardiovascular drugs. Opioids used for chronic conditions such as back pain or osteoarthritis are also included. The Beers Criteria are best viewed as a guide rather than a strict set of rules as it does not account for individual patient preferences, comorbidities, or goals of care. The Beers Criteria does not address underprescribing or those receiving hospice or end-of-life care.

Deprescribing

Deprescribing is the systematic approach of reviewing and discontinuing medications. This is a way to manage PIM use and prevent polypharmacy while considering each patient's care goals. The overall objective is to review all current medications, assess the reason for medication prescription, discern drugs for discontinuation, and develop a safe tapering or cessation plan. Deprescribing protocols have been associated with reduced PIM use and medication counts without an increase in emergency department visits or hospitalizations.[10,11]

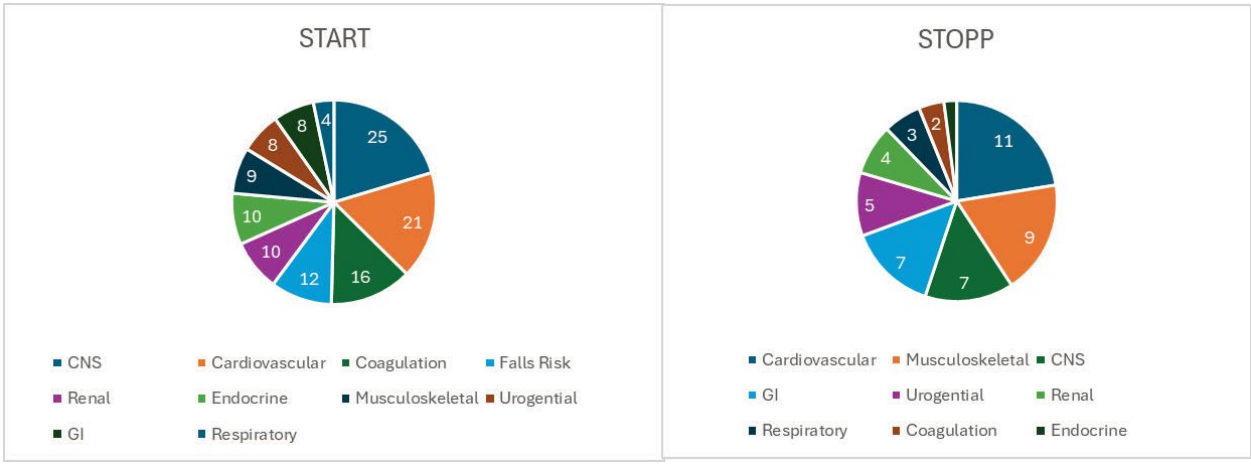
The Agency for Healthcare Research and Quality (AHRQ) SHARE approach to deprescribing provides a clinician-guided shared decision model that incorporates five key steps focusing on treatment benefit, risk, and alignment with individual values and priorities[12] (Table 2). This model has been shown to improve clinician confidence and shared-decision making behaviors in clinical practice.[13] Scott et al. proposed a CEASE framework for deprescribing PIMs in older adults. This process focuses on medication review, assessment of benefits and adverse effects, and prioritization for a stepwise medication reduction[14] (Table 2).

The Post-Acute and Long-Term Care Medical Association (PALTmed) has a national initiative to address polypharmacy in long-term care. Since 2021, Drive to Deprescribe (D2D) has been educating providers and offering resources to optimize medication selection and reduce polypharmacy, especially antipsychotic use. This initiative emphasizes practical strategies to promote shared decision-making and overcome barriers to deprescribing by understanding residents' potential concerns with medication changes.

Table 2. A Deprescribing SHARE-CEASE Framework

S	Seek patient participation	C	Current medication review
H	Help explore & compare treatments	E	Elevated risk evaluation
A	Assess values & preferences	A	Assess medication risk-benefit
R	Reach a decision	S	Sort & prioritize for deprescribing
E	Evaluate the decision	E	Eliminate & monitor in stepwise manner

Figure 1. Most Common Body Systems for START/STOPP Criteria



Screening Tools for Polypharmacy

In addition to the Beers Criteria, there are widely used and validated tools to screen for and manage polypharmacy. These tools are most effective in the setting of a comprehensive medication review performed by pharmacists, physicians, or multidisciplinary teams. The emphasis is on patient-centered, shared decision-making to ensure that recommendations aligned with clinical goals, functional status, personal preferences, and "What Matters Most" from the Age-Friendly 4-Ms (Mentation-Medications-Mobility-Matters Most) model.

STOPP/START

In 2008, the STOPP (Screening Tool of Older People's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) tools were developed to address PIM use and prescribing omissions, thereby offering a more comprehensive framework to manage polypharmacy in older adults. STOPP suggests medications to avoid or discontinue while START refers to prescribing omissions for certain conditions. The criteria for PIM prescribing are categorized by organ system with the cardiovascular and central nervous systems together accounting for about one-third of the total criteria for both START and STOPP. (Figure 1) Last updated in 2023, the tool includes 133 STOPP and 57 START criteria.[15] START/STOPP complements but is more comprehensive than the Beers Criteria.

ARMOR

The ARMOR tool (Assess, Review, Minimize, Optimize, Reassess) provides a structured, stepwise approach to evaluating geriatric patients who are, (1) prescribed nine or more medications, (2) undergoing an initial assessment, (3) presenting with falls and/or behavioral concerns, or (4) admitted for rehabilitation. Designed as a practical and interactive tool, ARMOR integrates the patient's clinical profile and functional status when evaluating each medication for clinical indication[16] (Table 3).

Table 3. ARMOR Evaluation Tool

ARMOR Polypharmacy Evaluation Tool		
A	Assess	Beta blockers Antidepressants Antipsychotics and psychotropics Pain medications Other Beers Criteria Vitamins and supplements
R	Review	Drug-drug interactions Drug-disease interactions Adverse drug reactions Functional impact Body system impact
M	Minimize	Eliminate no-benefit medications Eliminate risk > benefits medications Eliminate high risk for negative functional impact
O	Optimize	Reduce duplication and redundancy Adjust renally cleared medications Adjust hepatically cleared medications Adjust hypoglycemics to clinical target Gradual dose reduction for psychotropics Adjust beta blockers to for pacemaker and physiological heart rate Adjust anticoagulants for bleeding risk Adjust antiepileptics for clinical efficacy
R	Reassess	Vital signs Functional status Cognitive status Clinical exam Medication compliance

MAI

The Medication Appropriateness Index (MAI) is a validated tool to systematically evaluate the appropriateness of individual medications. It assesses each drug against ten criteria: indication, effectiveness, dosage, correct directions, practicality of directions, potential drug–drug interactions, potential drug–disease interactions, therapeutic duplication, duration of therapy, and cost. These criteria are then scored using clinical judgment, and the cumulative score represents overall prescribing appropriateness. As the MAI relies on clinical expertise and individualized patient context it has higher sensitivity in detecting potentially inappropriate prescribing, however, it is time-consuming and may not be suitable as a routine screening tool.

Although, interventions such as START/STOPP, ARMOR, MAI and Beers Criteria have resulted in consistent improvement in medication appropriateness, the effectiveness in reducing adverse drug events, hospitalizations, or emergency department visits is mixed or modest. There is no one intervention that is more effective in improving appropriate medication prescribing and the choice of tool should be guided by clinical context and available resources.

Computerized Clinical Decision Support Systems

Due to the inherent limitations in deprescribing protocols, computerized clinical decision support systems (CDSS) have been designed to identify PIMs, drug-drug and drug-disease interactions, and to support deprescribing

and medication optimization. MedSafer, AdAM, TRIM, SMART, and various AI-supported web applications are some examples of CDSS for polypharmacy management. CDSS offers tremendous opportunity to streamline the future of medication management.

A systematic review shows that CDSS interventions consistently reduce the initiation and continuation of PIMs, improve deprescribing rates, and enhance medication appropriateness. The effect of CDSS on adverse drug events and long-term outcomes is still unclear.[17] CDSS can guide prescribers in safe medication management and deprescribing by embedding explicit elements, such as the Beers Criteria, in an electronic health record prescribing order set.[18] The overreliance on CDSS, however, can produce excessive low-value alerts, contributing to "alert fatigue" and diminishing clinical effectiveness.

Underprescribing

Underdosing of medication is common in older adults due to fewer medication studies in this population and the assumption that frail elders require lower dosing for their aging physiology. In addition, potential prescribing omissions have been documented to be twice as common as PIM prescribing.[19] In this study by Galvin et al, underprescribing was most common in the optimization of hypertension and heart failure, adequate treatment of depression, and management of diabetes associated risk factors.

The prevalence of underprescribing in the older population ranges from 22 to 70%.[20] Although frailty and multimorbidity may be present, medications should be considered based on known diseases, life expectancy, patient preferences, and cautious extrapolation of data from younger populations. A complex analysis may be required to decide whether prescribing a new medication is really the best option for the patient

Commonly underprescribed medications for cardiovascular diseases include beta blockers for heart failure, dual anti-platelet treatment for coronary artery disease, and statins for hyperlipidemia. Recent primary prevention studies in patients older than 75 have demonstrated disease and mortality benefits for statin treatment.[21] Life expectancy as well as the time to response and potential side effects should be considered when starting statin treatment.

Anticoagulation for atrial fibrillation may be withheld in older adults, despite having a high CHADs2-VASc score, due to concern about risk of falls and frailty. Off-label dose reduction of anticoagulants is not recommended due to reduced efficacy and limited reduction in bleeding risk.[22] Falls prevention strategies should be implemented before prescribing anticoagulation, however the risk of bleeding after a fall remains low enough that risk often does not outweigh the benefit of anticoagulation. The anticoagulation decision should be guided by an evaluation of additional risk factors and use of a risk assessment tool like HAS-BLED or ORBIT.[23] As many patients value stroke prevention more highly than bleeding risk, it is more relevant to choose the right agent for the right patient rather than omitting anticoagulation treatment.[24]

In patients on hospice, overprescribing and underprescribing are both common. Depending on life expectancy and the patient's goals, medications that reduce the risk of disability and maintain quality of life should be continued until changes arise in medical conditions. Hospice does not mean stopping all medications or neglecting the treatment of comorbidities. This misunderstanding is one of the main reasons families and patients avoid or delay hospice admission.

Conclusion

Medication prescribing is a complex process in the elderly, and multiple factors need to be considered in the decision to start or stop a medication. Medication reviews should be coordinated by a primary care provider and implemented during transitions of care to avoid polypharmacy. Multiple tools are available to support decision-making and to guide deprescribing according to patient's conditions and care preferences. In all cases, avoiding

adverse drug events, side effects, functional decline, and emergency department visits is a priority. Prescribing should be based on shared decision-making and on what matters most for the patient. When starting a new medication, dosing and selection should be focused on the maximal treatment benefit with fewest adverse risks, not just the patient's age or disabilities.

Use of CDSS, standardized prescribing protocols, and health information technology will shape future efforts to combat polypharmacy among older adults.

References

1. Qato DM et al. Use of Prescription and Over-the-counter Medications and Dietary Supplements Among Older Adults in the United States. JAMA. 2008; 300(24):2867–2878.
2. National Center for Health Statistics. (2019). Health, United States, 2019: Table 039. Hyattsville, MD. Last Reviewed: August 15, 2025. Accessed October 5, 2025. https://www.cdc.gov/nchs/hus/data-finder.htm.
3. Qato DM et al. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. JAMA Intern Med. 2016; 176(4):473-482.
4. AARP and National Center for Complementary and Alternative Medicine. (2011). Complementary and Alternative Medicine: What People Aged 50 and Older Discuss With Their Health Care Providers. Washington, DC: AARP Research, April 2011.
5. Lavan AH et al. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016; 7:11–22.
6. Budnitz DS et al. US Emergency Department Visits Attributed to Medication Harms, 2017-2019. JAMA. 2021;326(13):1299-1309.
7. Clark CM et al. Potentially Inappropriate Medications Are Associated with Increased Healthcare Utilization and Costs. J Am Geriatr Soc. 2020; 68(11):2542-2550.
8. Davidoff AJ et al. Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria. J Am Geriatr Soc. 201563(3):486-500.
9. 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023 Jul;71(7):2052-2081.
10. Lee JW et al. Emergency department visits and hospital readmissions after a deprescribing intervention among hospitalized older adults. J Am Geriatr Soc. 2024; 72(7):2038-2047.
11. Linsky AM et al. Deprescribing in Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2025 May 1;8(5):e259375.
12. The SHARE Approach. (2024). Agency for Healthcare Research and Quality, Rockville, MD. Accessed October 6, 2025. https://www.ahrq.gov/sdm/share-approach/index.html.
13. Scherer LD. Effectiveness of the SHARE Approach for Improving Clinician Shared Decision Making Skills: A Trial in 12 Practices Located in Colorado, USA. J Gen Intern Med. 2025 Sep 10. doi: 10.1007/s11606-025-09465-y.
14. Scott IA et al. Reducing Inappropriate Polypharmacy: The Process of Deprescribing. JAMA Intern Med. 2015; 175(5):827–834.
15. O'Mahony D. et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med. 2023; 14, 625–632.
16. Haque R. ARMOR: A Tool to Evaluate Polypharmacy in Elderly Persons. Ann Long-Term Care. 2009 June; 1-9.
Monteiro L et al. Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review. J Med Internet Res. 2019; 21(11):e15385.
17. Monteiro L et al. Reducing Potentially Inappropriate Prescriptions for Older Patients Using Computerized Decision Support Tools: Systematic Review. J Med Internet Res. 2019; 21(11):e15385.
18. Goldberg EM et al. Enhancing the quality of prescribing practices for older adults discharged from the emergency department in Rhode Island. J Am Geriatr Soc. 2022; 70(10):2905-2914.
19. Galvin R et al. Prevalence of potentially inappropriate prescribing and prescribing omissions in older Irish adults: findings from The Irish LongituDinal Study on Ageing study (TILDA). Eur J Clin Pharmacol. 2014; 70(5):599-606.
20. Lombardi F et al. Underprescription of medications in older adults: causes, consequences and solutions-a narrative review. Eur Geriatr Med. 2021; 12(3):453-462.
21. Nachmias N et al. Statin Treatment for Reducing Mortality Risk in Individuals over 75 Years of Age: A Large-Scale Retrospective Analysis. J Clin Med. 2025; 14(16):5739.
22. Arbel R et al. Effectiveness and safety of off-label dose-reduced direct oral anticoagulants in atrial fibrillation. Am J Med. 2019; 132(7):847–855.
23. Gao X et al. Diagnostic Accuracy of the HAS-BLED Bleeding Score in VKA- or DOAC-Treated Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2021; 8:757087.
24. Mitchell A et al Anticoagulant use in older persons at risk for falls: therapeutic dilemmas-a clinical review. Eur Geriatr Med. 2023; 14(4):683-696.

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10 Years of Youth Sport Concussion Reporting in Missouri

by Katherine R. Newsham, PhD

This is the first study to provide longitudinal analysis of concussion reporting among secondary school sport and activity participants in Missouri.



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Abstract

Concussions in high school athletics are increasingly studied as a public health issue. Little is known about sport-related concussion among Missouri high school student-athletes. This retrospective analysis of data reported through the Missouri State High School Activities Association aimed to describe trends in participation and clinical incidence of concussion and provide comparisons of similar sports. Over 10 years, 39,953 concussions were reported for 2.16 million participants; the number of concussions increased by 48% during this time. Boys reported twice as many concussions as girls, though when adjusted for participation, girls' sports are often higher than matched boys' sports in concussions per 100 player-seasons. This information should increase awareness and may inform policies moving forward.

Key Words

Brain injury, sports medicine, pediatrics.

Introduction

Concussions are a significant public health issue and high school athletes are a well-studied subset of the population, relative to sport-related concussion (SRC).[1-3] The burdens associated with SRC include transient, temporary, and chronic health issues with physical/somatic, emotional, cognitive, vestibular/ocular, and sleep-related symptoms.[4] Additional burdens are associated with lost school and work time, cessation of exercise and recreation activities, and accessing medical treatment.[2,5]

It is estimated that 1.1-1.9 million concussions attributed to sport and recreation occur annually among children and adolescents, with more than 300,000 reported in high school sports.[2,3] High school athletes report a higher rate of lifetime concussion than non-athletes (21% and 7-11% respectively) and 5.8% of athletes report multiple diagnosed concussions compared to 2.2% of non-athletes.[1] Overall, 7-15% of adolescents self-report occurrence of a SRC in the prior 12 months.[2,6] The clinical incidence of SRC has been reported as 1.2-1.8 SRC per 100 athletes.[7,8]

Many studies of SRC in high school athletes utilize a nationwide sampling,[2-4,6,9,10] while others have used state or regional boundaries.[5,7,8] There have been no studies describing concussion reporting in Missouri. The

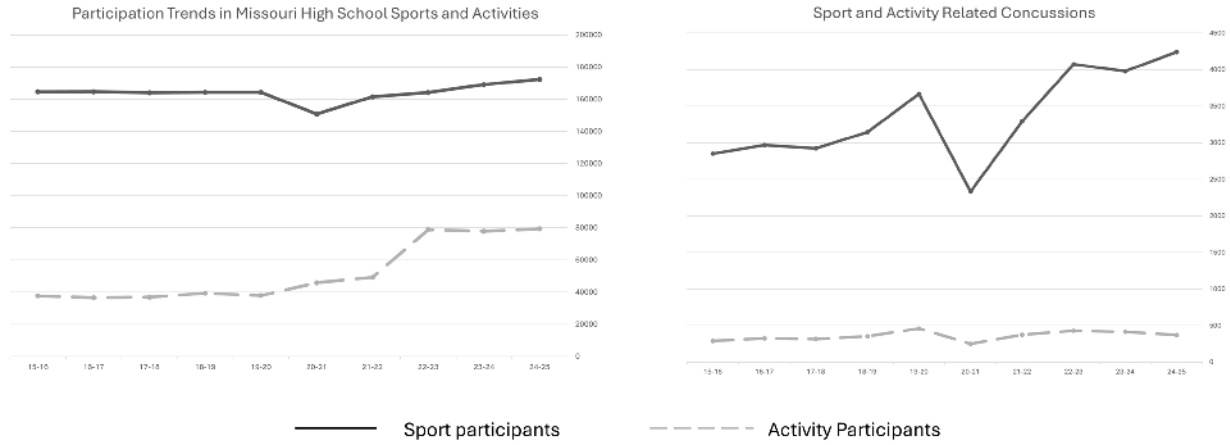


Figure 1. Missouri State High School Activities Association Participation and Concussions 2015-2025

Interscholastic Youth Sports Brain Injury Prevention Act was enacted in Missouri in 2011.[11] This legislation mirrored other states' legislation requiring annual concussion education, removal from play for anyone suspected of sustaining a concussion, and requiring a licensed healthcare provider to approve a return to play. Missouri further required an annual report related to the impact of concussions from the Missouri State High School Activities Association (MSHSAA). The purpose of this study is to examine the trends in concussion among high school athletes over the past 10 years using publicly available data gathered through this mandate.

Methods

The Interscholastic Youth Sports Brain Injury Reports[12] for academic years (AY) 2015-16 through 2024-25 were accessed from the MSHSAA website and processed for analysis (Version 27; SPSS, IBM, Armonk, NY, USA). Descriptive analysis included frequencies, percentages, means, and standard deviations for participants in each sport or activity and for concussions reported for each sport or activity. For the purposes of this analysis, a student who had a head injury and was removed from participation secondary to concussion-like symptoms was considered to have a concussion. Clinical incidence of concussion was calculated by dividing the number of sport- or activity-related concussions by the number of participants, multiplied by 100 player-seasons (presented with 95% confidence intervals).[13] Where boys' and girls' sports share common structure and playing rules, comparisons across gender were made via paired t-tests. The years around the COVID-19 restrictions were analyzed separately, and in combination with, other years.

Results

Participation in Sport and Activities

Participation in MSHSAA sanctioned sports (e.g. football, basketball, volleyball, swim, and dive, etc.) increased 5.5% % (8,915) during this 10-year period, while participation in sanctioned school activities (e.g., sideline cheer, band, dance/pom, bowling, theater, speech, and debate etc.), increased 117% (42,603) (Figure 1). New athletic (sport) opportunities for girls included wrestling (introduced in AY18-19), water polo (AY21-22), and competitive stunt (AY23-24; not included in analysis) (Figure 1). In AY24-25, MSHSAA sponsored 25 sports and 11 activities, with 251,578 participants in total.

Concussions in Sport and Activities

A total of 39,953 concussions were reported for 2,158,157 secondary school students over a 10-year period, with sport participants reporting 90% of all concussions. This includes 33,470 SRC for 1,641,127 athletes (clinical incidence 2.04 (95%CI 2.07, 2.20) /100 player-seasons) and 3,575 SRC for 517,030 activity participants (clinical incidence 0.69 (95%CI 0.69, 0.693) /100 player-seasons). There was a 48% increase in SRC from AY15-16 to AY24-25; activity-related concussions increased 27% (Figure 1). With 4,606 SRC reported in AY24-25, the clinical incidence of SRC was 2.46 (95%CI 2.3, 2.5) /100 player-seasons in sport and 0.47 (95%CI .42, .51) /100 player-seasons

Table 1. Sport- and Activity-Related Concussions in Missouri High Schools 2015-2025

Sport or Activity	Total SRC Reported		SRC/Year Mean (SD)		Pooled Clinical Incidence (95% CI)	
Football -11	13,622		1362 (267.6)		6.6/100 (6.5, 6.7)	
Football – 8	427		43 (22.8)		5.8/100 (5.23, 6.3)	
Sideline Cheer	3,154		315 (59.4)		3.31/100 (3.21, 3.42)	
Lacrosse (G)	436		43.6 (18.8)		2.85/100 (2.59, 3.12)	
Field Hockey (G)	233		23.3 (10.8)		2.08/100 (1.82, 2.35)	
Baseball (B)	874		87.4 (38.2)		0.59/100 (0.56, 0.63)	
Softball (G)	1,233		123.3 (28.9)		1.33/100 (1.26, 1.40)	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Wrestling	1,000	2,805	280.5* (88.5)	127.5 (59.2)	4.13/100 (3.98, 4.27)	7.26/100^ (6.83, 7.69)
Water Polo	99	28	9.9 (4.7)	7.0 (2.5)	1.86/100 (1.5, 2.23)	5.62/100^ (3.6, 7.7)
Soccer	2,406	2,989	240.5 (51.9)	290 (96.9)	2.81/100 (2.7, 2.92)	3.82/100 (3.69, 3.96)
Basketball	1,940	2,716	194 (46.5)	271.5* (43.2)	1.43/100 (1.37, 1.5)	2.91/100^ (2.81, 3.01)
Volleyball	111	1,629	11.1 (8.4)	163 (2.5)	0.78/100 (0.63, 0.92)	1.54/100 (1.46, 1/61)
Swim/Dive	107	191	10.7 (5.4)	9.1 (7.7)	0.58/100 (0.48, 0.70)	0.63/100 (0.55, .073)
Track & Field	167	243	16.7 (5.5)	24.3 (10)	0.11/100 (0.09, 0.13)	0.20/100 (0.17, 0.22)

SRC=Sport-related concussion; 95% CI=95% Confidence Interval; (B)=Boys; (G)=Girls
** Significantly higher annual average compared to opposite gender*
^ Significantly higher clinical incidence compared to opposite gender
Girls Wrestling 7 years of data; Girls Water Polo 4 years of data
Includes only sports and activities with >70 concussions over the 10-year period

Table 2. Sports and Activities with Highest Percentage of Concussions

Sport or Activity	Percentage of SRC in Sports	Percentage of SRC in Sports & Activities
Football - Combined	42	37.9
Sideline Cheer	-----	8.5
Soccer – Girls	8.9	8.1
Wrestling - Boys	8.4	7.6
Basketball - Girls	8.1	7.3
Soccer - Boys	7.2	6.5
Basketball - Boys	5.8	5.2
Volleyball – Girls	4.86	4.4

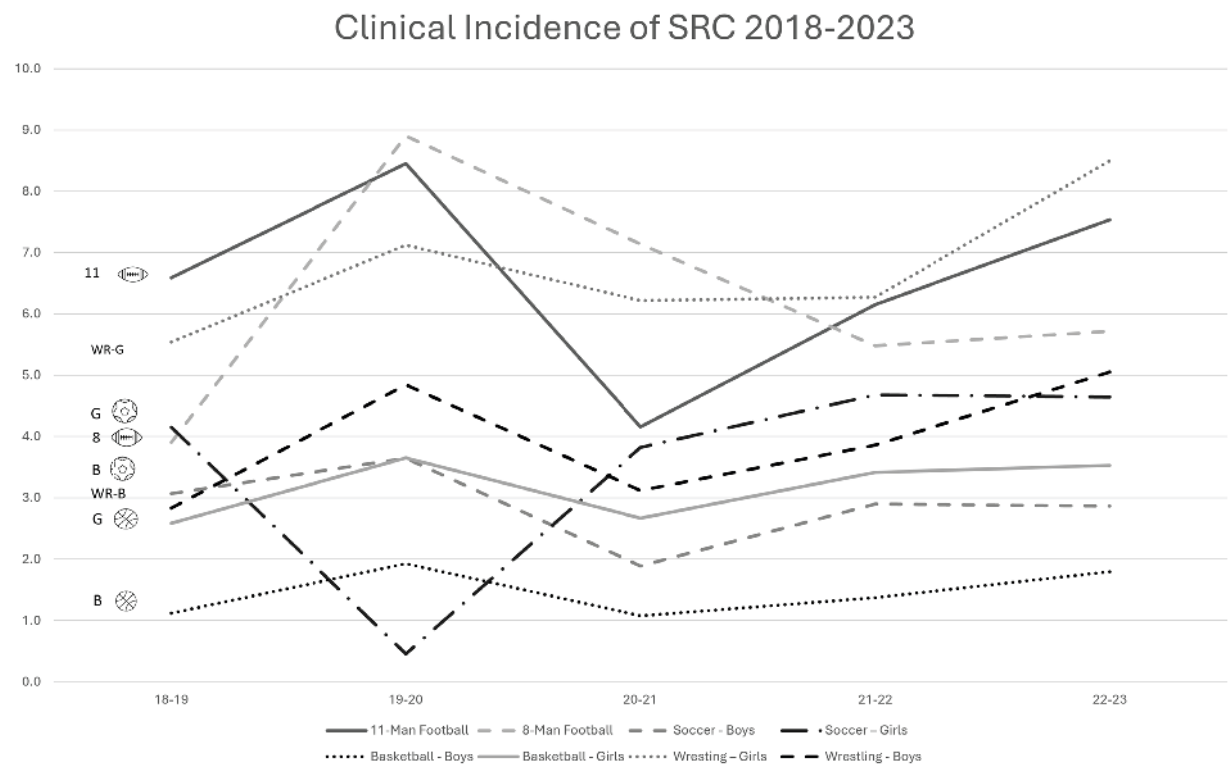


Figure 2. Clinical Incidence of Sport-Related Concussions Pre- and Post-Pandemic Restrictions

in sponsored activities. Concussions occurring outside of sport and activity were also recorded, and these accounted for 7% of all concussions among athletes and 11% of activity participants. While non-sport/activity concussions were not included in analysis of SRC, these increased total concussions reported in AY24-25 to 4934.

Football (11-player and 8-player) accounted for 42% of all reported SRCs, 13,622 SRCs overall, and 6.6 SRCs/100 player-seasons (Tables 1, 2). Boys' sports accounted for 22,674 (68%) of reported SRC (2.32 (95%CI 2.29, 2.35) /100 player-seasons), while girls' sports reported 10,823 SRC (1.63 (95%CI 1.0, 1.66) /100 player-seasons). Contact sports accounted for a majority of SRCs (Tables 1, 2). Sideline cheer (cheer) reported more SRCs (n=3,154; 3.31 (95%CI 3.21,3.42) /100 player-seasons) than any sport other than football, accounting for 8.3% of all sport/activity-related concussions and 88% of SRCs reported for interscholastic activities.

The years around the COVID-19 pandemic demonstrated a sizable increase in SRC from AY18-19 to AY19-20 with 522 (17%) more SRC reported (Figure 1). The change in sport participation between these years was negligible (n=25 fewer). Cheer had 195 (2%) more participants in AY19-20, compared to AY18-19, and reported 110 (37%) more SRCs. In AY20-21, there were 13,537 (8.2%) fewer sport participants and 1,336 (36%) fewer SRCs; cheer had 850 (8.5%) fewer participants and 195 (48%) fewer SRCs. The clinical incidence of SRC from AY18-19 through AY22-24 for selected sports is presented in Figure 2.

Comparable Boys and Girls Sports

The average of reported SRCs and pooled clinical incidence of SRC for boys' and girls' high contact sports were compared (Table 1). Girls' basketball averaged significantly more SRCs annually ($\bar{x}$ =271.5 (43.2)) than boys' ($\bar{x}$ =194 (46.5); p=<.001; 95%CI 56.82, 98.38) and had more SRCs/100 player-seasons (2.91) compared to boys' (1.43; p<.001; 95% I 1.28, 1.72). Girls' soccer participants averaged more SRCs annually ($\bar{x}$ =290 (96.9)), compared to boys' ($\bar{x}$ =240.5 (51.9)); the difference in SRC/100 player-seasons was not statistically significant (3.82 and 2.81,

respectively; p=.06; 95%CI .-2.1, 07). Boys' wrestling reported significantly more SRCs annually ($\bar{x}$ =280.5 (88.5)) than girls' ($\bar{x}$=127.5 (59.2); p=.003; 95%CI 102.4, 276.9) during the 7 years both sexes competed. However, girls' reported more SRC/100 player-seasons (7.26) than boys' (4.13; p<.001; 95%CI -3.15, -2.35). Boys' and girls' water polo had similar annual average of SRCs reported (7.75 (3.8) and 7.00 (2.45), respectively) in the 4 years both sexes competed; yet, girls had significantly higher SRC/100 player-seasons (5.68) compared to boys (1.45; p=.015; 95%CI -6.88, -1.58).

Discussion

This is the first study to provide longitudinal analysis of concussion reporting among secondary school sport and activity participants in Missouri. Participation in interscholastic sports remained relatively consistent during the 10-year period of this study. Participation in sponsored activities increased significantly, though participation was not consistently recorded over this period, making definitive declarations difficult. Nearly 40,000 concussions were reported for 2.16 million sport and activity participants from Fall 2015-Spring 2025; this includes 37,045 SRCs. The number of SRC reported annually increased by 48% in sport and 27% in sponsored activities over the period of this report, culminating with almost 5,000 total concussions reported in AY24-25.

Football (11-player) had the greatest number of participants for sport activities. There had been speculation that participation in football would decrease significantly secondary to safety concerns.[14] This attrition was not realized in Missouri, though, as the number of participants in 11-player football was essentially unchanged (<1% attrition) during this 10-year period. Meanwhile, 45 schools sponsored 8-player football in AY24-25, up 21 from 2015. With 150% increase in participants, 8-player football was the fastest growing sport for boys. Sports introduced during this period experienced significant growth with girls wrestling increasing 212%.

The clinical incidence for SRC reported in Missouri for sports and cheer over this 10-year period (2.11/100) is greater than that reported from Michigan (1.17/100) but lower than two prospective studies (4.9-6.45/100).[7,8,15] Using the earlier estimate of 300,000 SRC in secondary school athletes,[3] and the approximated 7.95 million interscholastic participants,[16] a clinical incidence of SRC at 3.77/100 player-seasons can be calculated. These comparative findings increase confidence that data used in this study is representative of interscholastic sports and activities.

Concussions: 11-Player vs. 8-Player Football

There were 1,260 SRC in 11-player football in AY15-16, or 5.81/100 player-seasons. The clinical incidence of SRC increased to 8.45/100 player-seasons in AY19-20. The following year was affected by COVID-19 restrictions and saw the lowest clinical incidence of SRC at 4.16/100 player-seasons. The numbers have increased steadily since then, with the past three years at 7.5-7.7/100 player-seasons

In contrast, 8-player football averaged 3.55 SRC/100 player-seasons (AY15-16 to AY18-19), before rising to 8.91/100 player-seasons in AY19-20. With resumption of play after COVID-19 (AY20-21), 8-player football demonstrated a higher clinical incidence of SRC than 11-player football did (7.14/100 and 4.16/100, respectively). In these two years, 8-player football SRC clinical incidence exceeded those for 11-player football. The clinical incidence has been similar among these two football classes for the past three years. Participation in 8-player football increased over this period, but that does not explain the increase in clinical incidence.

Two studies utilizing Athletic Trainers (ATs) employed at the schools to collect and report data, have reported SRC clinical incidence as 5.7/100 and 11.2/100 player-seasons for 11-player football.[8,15] In contrast, a study of Michigan high school sports reported the clinical incidence for 11-player football was 3.33/100 player-season.[7] This study also reported on 8-player football with clinical incidence of 2.76/100 player-season, whereas Missouri reported 5.48/100 player-seasons.[7]

In analyzing Missouri data, a student who had a head injury and was removed from participation secondary to demonstrating concussion-like symptoms was considered to have a concussion. The data were reported by athletic directors, ATs, and/or school nurses. In many instances, the data would have been relayed by coaches who were responsible for recognizing the injury and removing students from activity. The standard for non-medical personnel (e.g., coaches) is the Concussion Recognition Tool (CRT) developed in conjunction with the Sport Concussion Assessment Tool (SCAT).[17] Coaches bear

the burden of concussion recognition frequently, as approximately 51% of secondary schools in Missouri (33% in rural settings) have access to AT services and many schools may not have an AT on-site for every practice, game and competition.[18] In Michigan, where 57% of secondary schools have access to AT services, the Michigan High School Athletic Association also requires member institutions to submit annual reports.[7,18] However, Michigan requires suspected concussions to be diagnosed by a primary care provider to be recorded as a concussion.[7] This would almost certainly reduce the number of documented concussions, relative to suspected, as some athletes may decline to seek further care. In two studies utilizing ATs for data collection, a concussion was reported if the evaluating AT's clinical impression of the student, typically using the SCAT or similar criteria, was consistent with the international consensus guidelines for concussions.[8,15,17] Both of these studies also reported higher clinical incidence compared to the Michigan study.

Comparable Boys and Girls Sports

Boys' sports accounted for a majority of SRC during this period. When comparing SRC in sports with similar structure and rules, girls' sports' clinical incidence values were consistently higher than that for boys' sports. Girls' basketball SRC clinical incidence (2.94/100) was roughly double that of boys' (1.44/100). Chun, et al, reported a similar ratio with girls' basketball at 7.06/100 player-seasons and boys' at 3.71/100.[15] As with football, the SRC clinical incidence reported from Michigan was lower, but demonstrated similar disparity between girls' (2.01/100 player-seasons) and boys' basketball (1.01/100).[7]
While the differences in SRC between boys' and girls' soccer were not significant, the ratio of clinical incidence observed in Missouri (2.81/100 and 3.82/100 respectively), compares to Chun's reporting (4.5/100 and 7.2/100, respectively)[15] and Bretzin, et al, (1.22/100 and 1.99/100, respectively).[7] Conversely, Marshall[8] reported higher clinical incidence in boys' soccer (2.9 and 1.9, respectively). The data from that study were collected from 1999-2001 and the competitive seasons for boys and girls varied between fall and spring, thus access to ATs may have been impacted. For example, placing boys' and girls' soccer competitive seasons in the fall, when football was also in their competitive season, increased the athlete-to-AT ratio and may have affected on-campus practice facility access and AT access.

This review noted rapid rises in the number and clinical incidence of SRC in girls' wrestling and girls' water polo. Of note, girls' wrestling demonstrated a higher clinical incidence for SRC than football. While the reasons for this cannot be known, one may speculate on the potential for novice participants lacking requisite skill, inadequate adjustments around coaching techniques, and inappropriate officiating to address style of play or dangerous play. It will be important to monitor these sports going forward. Perhaps, 8-player football deserves similar observation.

Sideline Cheer

Cheer represented the largest number of SRC among activity participants and represents the second largest percentage of SRC when sports and activities are combined with a clinical incidence of 3.31/100 participants. The impact of adding competitive stunt in Missouri remains to be seen. Michigan provided data on competitive cheer, with clinical incidence of 1.8/100 player-seasons; following the pattern of lower clinical incidence in that study compared to the current study.[7] Competitive cheer reported 921 SRC over the 8 years of that study, outpaced only by football, boys' and girls' basketball, boys' and girls' soccer, and boys' wrestling.[7]

Impact of COVID-19

Participation in sport and activities was essentially unchanged between AY18-19 and AY19-20, however, there were 17% more SRC reported in athletics and a 37% increase for cheer. This is despite losing two months of competition secondary to pandemic-related cancellations. Considering the sports most impacted by this included girls' soccer and girls lacrosse, the increase could have been greater. These sports, combined, average 330 SRC annually yet accounted for only 39 SRC in 2019-2020. Most of the sports included in Figure 3 realized an increase in the clinical incidence in SRC in 2019-2020; these are the fall and winter sports which were not impacted by COVID-19 restrictions that year. There is not an obvious explanation for the increase in SRC ahead of the pandemic.

The Fall seasons in 2020 operated under restrictions in most areas, and overall participation decreased in both sports and activities by approximately 8%. However, some sports saw 10-20% participation decreases. The

number of concussions decrease by approximately one-third in sports and by almost one-half in cheer. Girls' soccer demonstrated one of the few increases as they returned to an average season in AY20-21. The Michigan high schools demonstrated lower clinical incidence of SRC for AY19-20, compared to AY18-19, and lower, still, for AY20-21.[7] Interestingly, the clinical incidence for girls sports was remarkably lower than boys in AY19-20, likely influenced by the loss of the girls' spring sports seasons, including soccer, lacrosse, and softball.

Limitations

This report utilized publicly available school-reported data that was aggregated by a third party. There is not a reasonable way to validate the data. Approximately 5-10% of schools did not report data each year and individuals reporting the data may not have complete information regarding concussions at their institutions. The data collected did not allow calculation of rates of SRC as there was not a time/exposure variable; neither mechanism of injury nor practice versus game injury data were reported. These limitations hinder comparisons to existing epidemiologic data regarding SRC. Additionally, increased scrutiny around concussions may have contributed to the increase in reporting**.** The data in these reports may not be robust, yet it represents the best available data for Missouri at this time.

Conclusions

Concussions among interscholastic athletes increased by almost 50% over ten years during a time of stable participation numbers, and the numbers continue to increase. While football was responsible for the most SRCs, the newest sports for girls had clinical incidence per 100 player-seasons comparable to football. In sports with divisions for boys and girls, the clinical incidence was higher for girls' teams. Continued vigilance on education and recognition of concussion among high school student-athletes and activity participants is warranted.

References

1. Veliz P, Eckner JT, Zdroik J, Schulenberg JE. Lifetime Prevalence of Self-Reported Concussion Among Adolescents Involved in Competitive Sports: A National U.S. Study. Journal of Adolescent Health. 2019/02/01/ 2019;64(2):272-275. doi:https://doi.org/10.1016/j.jadohealth.2018.08.023
2. Lowry R, Haarbauer-Krupa JK, Breiding MJ, Thigpen S, Rasberry CN, Lee SM. Concussion and Academic Impairment Among U.S. High School Students. American Journal of Preventive Medicine. 2019/12/01/ 2019;57(6):733-740. doi:https://doi.org/10.1016/j.amepre.2019.08.016
3. Bryan MA, Rowhani-Rahbar A, Comstock RD, Rivara F. Sports- and Recreation-Related Concussions in US Youth. Pediatrics. 2016;138(1) doi:10.1542/peds.2015-4635
4. Didner N, Boltz AJ, Robison HJ, Chandran A, Quinsey C. Concussion Symptomatology by Symptom Resolution Time in US High School Athletes: Findings From the National Athletic Treatment, Injury and Outcomes Network High School Surveillance Program (NATION-SP). Journal of athletic training. Jul 1 2024;59(7):745-750. doi:10.4085/1062-6050-0201.23
5. Yengo-Kahn AM, Kelly PD, Liles DC, et al. The cost of a single concussion in American high school football: a retrospective cohort study. Concussion. Oct 28 2020;5(4):Cnc81. doi:10.2217/cnc-2020-0012
6. Daugherty J, Peterson A, Black L, Waltzman D. Summary of the Centers for Disease Control and Prevention's Self-reported Traumatic Brain Injury Survey Efforts. J Head Trauma Rehabil. Jan-Feb 01 2025;40(1):E1-e12. doi:10.1097/htr.0000000000000975
7. Bretzin AC, Pollard-McGrandy AM, Davis ER, Wiebe DJ, Covassin T. Avenues for prevention using the epidemiology of sport-related concussion from a large high school surveillance study. Neurosurg Focus. Jul 2024;57(1):E3. doi:10.3171/2024.4.Focus24153
8. Marshall SW, Guskiewicz KM, Shankar V, McCrea M, Cantu RC. Epidemiology of sports-related concussion in seven US high school and collegiate sports. Inj Epidemiol. Dec 2015;2(1):13. doi:10.1186/s40621-015-0045-4
9. DePadilla L, Miller GF, Jones SE, Peterson AB, Breiding MJ. Self-Reported Concussions from Playing a Sport or Being Physically Active Among High School Students - United States, 2017. MMWR Morb Mortal Wkly Rep. Jun 22 2018;67(24):682-685. doi:10.15585/mmwr.mm6724a3
10. Waltzman D, Womack LS, Thomas KE, Sarmiento K. Trends in Emergency Department Visits for Contact Sports-Related Traumatic Brain Injuries Among Children - United States, 2001-2018. MMWR Morb Mortal Wkly Rep. Jul 10 2020;69(27):870-874. doi:10.15585/mmwr.mm6927a4
11. Interscholastic Youth Sports Brain Injury Prevention Act, (2011). Accessed March 1, 2026. https://revisor.mo.gov/main/OneSection.aspx?section=167.765
12. Ruckstad J. Interscholastic Youth Sports Brain Injury Report. Accessed March 1, 2026. https://www.mshsaa.org/cmspages/BrainInjuryReports.aspx
13. Knowles SB, Marshall SW, Guskiewicz KM. Issues in estimating risks and rates in sports injury research. Journal of athletic training. Apr-Jun 2006;41(2):207-15.
14. Jeckell AS, Fontana RS, Gonzalez R. Review of Media Representation of Sport Concussion and Implications for Youth Sports. Clinics in sports medicine. Jan 2024;43(1):159-172. doi:10.1016/j.csm.2023.06.012
15. Chun BJ, Furutani T, Oshiro R, Young C, Prentiss G, Murata N. Concussion Epidemiology in Youth Sports: Sports Study of a Statewide High School Sports Program. Sports Health. 2021;13(1):18-24. doi:10.1177/1941738120932570
16. 2024-2025 High School Athletics Participation Survey. National Federation of State High School Associations Accessed March 15, 2026. https://www.nfhs.org/resources/sports/high-school-participation-survey-archive
17. Patricios JS, Schneider KJ, Dvorak J, et al. Consensus statement on concussion in sport: the 6th International Conference on Concussion in Sport-Amsterdam, October 2022. Br J Sports Med. Jun 2023;57(11):695-711. doi:10.1136/bjsports-2023-106898
18. Suzuki-Yamanaka M, Huggins RA, Armstrong KJ, Coleman KA, Casa DJ, Kaneoka K. Athletic Training Employment in US Secondary Schools by Geographic Setting and School Size. Journal of athletic training. Sep 1 2021;56(9):1010-1017. doi:10.4085/109-20

Disclosure

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Concept Study: Small Group Strength and Conditioning Training for Physician Burn-Out

by Amer Avdagic, MD, Stephanie Clookey, MD & Komal Hargovind Ashraf, DO

This concept study suggests a benefit for small-group, coached strength training for the treatment, perhaps even the prevention of physician burnout.



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Abstract

This single-armed pilot study evaluated the feasibility and potential benefit for small-group, coach-led strength training for the treatment of physician burnout. The findings suggest a benefit for the treatment, perhaps even the prevention of physician burnout.

Keywords

Physician burnout, strength training,

Introduction

Burnout is a work-related syndrome involving emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment.[1] Physician burnout has been reported at a prevalence rate of about 50% in studies involving physicians-in-training as well as practicing physicians across the United States.[2] It negatively impacts the health of the physician and is deleterious to the patient care and health care system. In addition, burnout can be a financially burdensome problem for an institution. Various approaches to manage burnout have been proposed. Small group programs to promote community and build a sense of connection and mindfulness stress reduction are some of the approaches shown to reduce burnout.[3-4] There are limited studies on reducing physician burnout. Here we plan to study the impact of small group strength and conditioning on physician burn out. Engaging in small group activities promote a sense of connectivity and can have a positive impact on individual behavior. Strength and conditioning promote optimal well-being of the physician which could help cope with the daily stressors at work which may impact physician burnout.[5–7] We conducted a pilot study to assess the effect of coach-led small group strength training on physician burnout.

Methods

This pilot study was single-armed and participants were physicians from a university-based hospital. Participants were recruited by email and

were asked to complete a single-item burnout scale on how they feel about work. These participants were then asked to complete the Mini-Z and professional fulfillment index questionnaires. After completing the questionnaires, these physicians completed consent and baseline measurements surveying heart rate, blood pressure, hours of sleep, percent body fat, and functional mobility. All of these metrics were completed again at the conclusion of the study.

The participants were asked to complete three coach-led small group training sessions a week that were each 60 minutes in length. This study lasted for three months. These sessions were held in a local fitness center where the professional trainers' qualifications were American Council of Exercise certification, Functional Movement System evaluation, and Master of Health Education and Promotion. All programming and workouts were modified based on each participant's abilities as determined by the functional mobility assessment. After three months of this exercise regimen the participants completed the same questionnaires and measurements at the beginning of the study.

Inclusion Criteria

- Adults over the age of 18
- Participant must be clinical faculty, residents, and/or fellows in any departments within the same academic hospital.
- On the initial burnout scale participants that answered with either: "I am definitely burning out and have one or more symptoms of burn out, such as physical and emotional exhaustion." or "The symptoms of burn out that I'm experiencing won't go away. I think about work frustrations a lot."
- Healthy volunteers with BMI in range 18.5-30
- Those who agree to the consistency/scheduling requirements of the study.
- Those who complete Mini-Z and fall between score of 15-30 range.
- Those who complete Stanford PFI.

Table 1. Demographics of Participants in Study

Characteristic	Value
Age Range (years)	28–53
Mean Age (years)	35.67
Gender	Male = 2; Female = 4
Race	6 Caucasian
Average Height	Male: 182 cm; Female: 170 cm

Table 2. Mini Z & Functional Movement Scale

Measure	Pre-Training	Post-Training
Mini Z	31.5	34.67
FMS	14.33	16

Exclusion Criteria

- Non-physicians.
- Those who answer "Yes" to the questions: "Have you done strength/conditioning exercise in the last three months?" and "Have you been advised by a health care provider not to participate in exercise?"
- Participants who have physical restrictions as advised by their healthcare providers, and BMIs <18.5 or >30.
- Those who complete Mini-Z and fall out of 15-30 score range.
- Those who complete Stanford PFI and fall out of 15-30 score range.

A total of six physicians (2 males and 4 females) were included in this study (Table 1). The average age of the participants was 36 years with range from 28 years to 53 years. Given the small sample size and study duration, statistics were not performed to evaluate for significance.

The Mini Z Burnout Scale is a validated survey that assesses clinician burnout, job satisfaction, and stressors such as control, leadership, and electronic health record burden. The scoring ranges from 10-50 with the higher score signifying a more joyful workplace (Table 2). The functional movement screening tool was conducted by the certified trainers looking at fundamental movement patterns such as squats and active straight-leg raises. Scoring is 0-21 and having a score of less than 14 signifies increased risk of injury secondary to poor body mechanics (Table 2).

During the pre- and post-training evaluation participants would have vital signs and body measurements collected as outlined above (Tables 3 and 4). Even though participants felt subjectively better in terms of physical health and wellness, we were unable to assess for any significant benefit due to the small sample size of this study.

Conclusion

Over the three-month course of this study, there were no adverse events or injuries noted. This implies the low risk of injury when training under a coach-led course. The study showed that the physicians that participated in this study were able to consistently complete two to three sessions per week during the three-month trial.

The major limitation of this study is the small sample size due to lack of funding and exclusion criteria. This concept study suggests a benefit for small-group, coached strength training for the treatment, perhaps even the prevention of physician burnout.

Table 3. Vital Sign Measurements

Measure	Pre-Training	Post-Training
Weight (kg)	87.26	85.25
BMI	28.44	27.85
Heart Rate	81.5	75
SBP	127	109
DBP	77.5	72.67

Table 4. Body Mass Measurements

Measurement	Pre-Training	Post-Training
Waist (cm)	97.46	94.6
Hip Circumference (cm)	101.92	105.22
Right Arm (cm)	31.27	33.57
Right Thigh (cm)	54.72	62.97
Body Fat (%)	36	36

References

1. L. M. Naczenski, J. D. de Vries, M. L. M. van Hooff, and M. A. J. Kompier, "Systematic review of the association between physical activity and burnout," J Occup Health, vol. 59, no. 6, pp. 477–494, Nov. 2017.2. S. Ofei-Dodoo, P. Callaway, and K. Engels, "Prevalence and Etiology of Burnout in a Community-Based Graduate Medical Education System: A Mixed-Methods Study," Family Medicine, 2019. /familymedicine/2019/october/ofei-dodoo-2018-0359/ (accessed Feb. 21, 2021).
3. West CP, Dyrbye LN, Rabatin JT, et al. Intervention to Promote Physician Well-being, Job Satisfaction, and Professionalism: A Randomized Clinical Trial. JAMA Intern Med. 2014;174(4):527–533. doi:10.1001/jamainternmed.2013.14387
4. West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis. Lancet. 2016 Nov 5;388(10057):2272-2281. doi: 10.1016/S0140-6736(16)31279-X. Epub 2016 Sep 28. PMID: 27692469.
5. K. M. Fargen, A. M. Spiotta, R. D. Turner, and S. Patel, "The Importance of Exercise in the Well-Rounded Physician: Dialogue for the Inclusion of a Physical Fitness Program in Neurosurgery Resident Training," World Neurosurgery, vol. 90, pp. 380–384, Jun. 2016, doi: 10.1016/j.wneu.2016.03.024.
6. C. J. Weight, J. L. Sellon, C. R. Lessard-Anderson, T. D. Shanafelt, K. D. Olsen, and E. R. Laskowski, "Physical Activity, Quality of Life, and Burnout Among Physician Trainees: The Effect of a Team-Based, Incentivized Exercise Program," Mayo Clinic Proceedings, vol. 88, no. 12, pp. 1435–1442, Dec. 2013, doi: 10.1016/j.mayocp.2013.09.010.
7. "Incorporation of a Physical Education and Nutrition Program Into Neurosurgery | Neurosurgery | Oxford Academic." https://academic.oup.com/neurosurgery/article-abstract/79/4/613/2837437 (accessed Feb. 21, 2021).
8. "wlcMiniZ.pdf." Accessed: Feb. 21, 2021. [Online]. Available: https://www.vumc.org/health-wellness/sites/vumc.org.health-wellness/files/public_files/PDFs/wlc/wlcMiniZ.pdf.
9. Trockel, Mickey, "A Brief Instrument to Assess Both Burnout and Professional Fulfillment in Physicians: Reliability and Validity, Including Correlation with Self-Reported Medical Errors, in a Sample of Resident and Practicing Physicians."
10. Knox M, Willard-Grace R, Huang B, Grumbach K. Maslach Burnout Inventory and a Self-Defined, Single-Item Burnout Measure Produce Different Clinician and Staff Burnout Estimates. J Gen Intern Med. 2018;33(8):1344-1351. doi:10.1007/s11606-018-4507-6

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Myeloablative Matched Sibling Donor Hematopoietic Stem Cell Transplantation as a Curative Treatment for Congenital Erythropoietic Porphyria: A Cohort Study from Low-Middle Income Country

by Aamir Aslam Awan, FCPS, Tariq Azam Khattak, FCPS, Muhammad Shah Miran, MD, Tariq Ghafoor, FRCP, Raheel Iftikhar, FRCP, Ammara Iftikhar, FCPS & Haider Nisar, FCPS

This study presents the first cohort of CEP patients successfully treated with MSD HSCT in a low middle income country. Early recognition and prompt curative therapy are essential to prevent irreversible tissue mutilation, reduce disease associated morbidity and optimize long term quality of life.



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Abstract

Congenital Erythropoeitic Porphyria is extremely rare autosomal recessive disorder caused by deficiency of uroporphyrin synthase III deficiency, leading to accumulation of toxic precursors of Heme biosynthesis. Severe Phenotypes present in neonatal period with reddish brown colored urine followed by photosensitivity and erythrodontia. Allogenic hematopoietic stem cell transplant is the only curative option.

We retrospectively analyzed 4 patients (2 males , 2 females) with clinically and biochemically confirmed Congenital Erythropoeitic Porphyria who underwent fully matched sibling donor hematopoietic stem cell transplant with myeloablative conditioning Busulphan (Bu) and Cyclophosphamide (Cy) at the Armed Forces Bone Marrow Transplant Centre Pakistan from 2020 to 2025. These four transplants were performed at a centre with over 550 transplants during this period, highlighting the extreme rarity of disease even within a high volume transplant centre.

Median Age of onset of symptoms was five days (range 2-15), median age of diagnosis was 27 months (range12-72) and median age of hematopoietic transplant was 100.5 months (range 54-126). All patients received myeloablative conditioning ($Bu^{16mg/kg}$, $Cy^{160-200mg/kg}$). Peri-transplant period was complicated by febrile neutropenia and mucositis. Neutrophil engraftment was achieved at a median of Day+16 (range 14-18) and platelet engraftment at median of Day+21 (range 18-21). At a median follow up of 240 days (range 116-2555), all patients were alive, transfusion independent with complete resolution of photosensitivity. Additionally, serum and urine porphyrin levels became normal in all patients.

This cohort, though very small supports the efficacy of early myeloablative Hematopoietic stem cell transplant with matched sibling

donors to prevent irreversible tissue damage and significantly improve clinical outcomes.

Key Words

Hematopoietic stem cell transplant, Congenital erythropoietic porphyria, Low Middle Income Country

Introduction

Congenital Erythropoeitic porphyria (CEP) is a rare autosomal recessive cutaneous porphyria caused by deficient activity of uroporphyrinogen III synthase (UROS), a key enzyme in the heme biosynthetic pathway.[1] The enzymatic block results in accumulation of photo reactive type I porphyrin isomers, primarily uroporphyrin I and coporphyrin I in erythrocytes, plasma, urine and tissues.[2]

CEP typically presents in early infancy with reddish discoloration of urine followed by severe cutaneous photosensitivity, blistering and progressive scarring of sun exposed skin. Additional features include erythrodontia, hypertrichosis, hemolytic anemia, and splenomegaly. Severe phenotypes are transfusion dependent and the disease substantially impairs quality of life. The diagnosis is confirmed by measuring levels of porphyrins in blood and urine, enzymatic assays and molecular testing of UROS gene.[3]

Despite its curative potential, HSCT remains underutilized in CEP largely due to its rarity, diagnostic delays and the perceived risks of transplant related complications. Most published reports are limited to individual case studies or case reports from high income countries, often with short follow up periods and variable transplant protocols. There is lack of consolidated data from low middle income countries where delayed diagnosis, limited access to specialized care and resource constraints further complicate management. This gap in literature highlights the need for real world data from diverse healthcare settings to better define the role and timing of HSCT in CEP.

At our centre, which has performed 1,870 HSCT procedures to date, only four were for CEP underscoring this exceptionally rare indication. Nevertheless, successful outcomes in these patients suggest that early HSCT may offer transformative benefit when a matched donor is available.

This study aims to report the safety and efficacy of allogenic HSCT in children with severe CEP. By presenting detailed outcomes from a single center, we seek to bridge gap between symptomatic management and definitive cure.

Materials and Methods

This was a retrospective observational study conducted at the Armed Forces Bone Marrow Transplant Center from 2020 to 2025. The study was approved by the hospital ethical review board.

Data from four pediatric patients diagnosed with CEP who underwent allogenic hematopoietic stem cell transplantation (HSCT) were evaluated. A detailed medical history was taken and relevant clinical examination was conducted. The diagnosis of CEP was confirmed based on both characteristic clinical features and elevated urine and serum porphyrin levels.

Human leukocyte antigen typing I and II was performed to identify a fully matched sibling donor. Pre-transplant evaluation was carried out in accordance with the Center for International Blood and Marrow Transplant Research (CIBMTR) guidelines and patients were enrolled in emergency HSCT list.

Patients (Table 1) were admitted to the transplant ward. Central Venous Line (CVL) insertion was performed on Day -11. Conditioning therapy included intravenous busulfan administered in once daily dose from Day -10 to Day -7 followed by dyclophosphamide once daily dose from Day -5 to Day -2. Donors were admitted on Day -1. Bone marrow harvest was used as stem cell source. The final volume of stem cells was adjusted according to targeted TNC, CD34+ and CD3+ doses (Table 2).

Graft versus host disease (GVHD) prophylaxis included cyclosporine starting from Day -2 and methotrexate administered on Day +1, Day+3 and Day +6. CMV quantitative PCR was performed on Day+7 and then weekly till Day+100. Valganciclovir was given until one week after two consecutive CMV PCRs became negative.

Patients were discharged following hematopoietic engraftment and were monitored with twice weekly follow up visits until Day +90. Short tandem repeat (STR) chimerism analysis was conducted on Days+30, +60 and +90. Immunosuppression was continued for nine months post-transplant and then gradually tapered until discontinuation.

All Transplants were reported to CIBMTR registry.

Results

Data from four pediatric patients diagnosed with CEP who reported to AFBMTC were analyzed. The cohort included two males and two females. The median age of onset of symptoms was five days

Table 1. Demographics

S/ No	Sex	Age at onset of symptoms	Age at diagnosis	Age at HSCT	Clinical features at Diagnosis	Examination findings at the time of HSCT	Pre HSCT-Comorbid	Pre HSCT-Transfusions
1	F	1st week	3.5 years	4.5 yrs	Red Urine, brown teeth, blistering, scarring, transfusion dependence	Liver 3 cm, Spleen 2 cm	None	3
2	M	1st month	6 years	6.3 yrs	Red Urine, brown teeth, blistering, scarring, transfusion dependence	Liver 3 cm	None	7
3	F	2nd month	1 year	13 yrs	Red Urine, brown teeth, blistering, scarring, transfusion dependence	Facial and Hand scarring Nose and fingers deformity Splenectomy scar	Splenectomy at 11 years of age	50
4	M	1st week	1 year	10.6 yrs	Red Urine, brown teeth, blistering, scarring, transfusion dependence	Face, Hand and Feet Scarring Liver 5 cm	Hepatoblastoma and Hepatitis C	20

Table 2. Transplant Characteristics

S/ No	Conditioning Regimen	GvHD Prophylaxis	CD34+ Dose ($x10^6$/kg)	TNC Dose ($x10^8$/kg)	CD3+ Dose ($x10^8$/kg)	Engraftment		Peri-transplant Problems
						Neutrophil	Platelet	
1	Bu 16mg/kg Cy 200mg/kg	CSA, MTX	8.63	5.02	6.11	Day +15	Day+19	Mucositis, Gut toxicity, CMV reactivation
2	Bu 16mg/kg Cy 160mg/kg ATG 10	CSA, MTX	10.6	5.0	6.52	Day +11	Day+12	FN, Mucositis, Epistaxis, Gum bleed, CMV reactivation
3	Flu 120 Bu 16mg/kg Cy 160mg/kg	CSA, MTX	6.9	5.5	8.7	Day +12	Day+15	FN, Mucositis
4	Bu 16mg/kg Cy 160mg/kg	CSA → Tac, MTX	9.9	4.3	7.5	Day +15	Day+34	FN, Epistaxis, Gingivitis, Mucositis

(range 2-15), with a median age of diagnosis of 27 months (range 12-72) and a median age of HSCT was 100.5 months (range 54-126). The median interval from onset of symptoms to consulting a bone marrow transplant physician was 101.25 months (range 54-155).

All patients presented with red-colored urine followed by photosensitivity and red cell transfusion dependence with a median onset of anemia at four months (range two to six months). At the time of HSCT, disease burden was significant: one had undergone splenectomy (patient 3) and one had a history of hepatoblastoma (patient 4), in remission after chemotherapy. The median age at HSCT was 8.7 years (range 4.5-13 years).

Bone marrow was the source of stem cells in all cases. The median volume of stem cell infused was 350 ml. median total nucleated cell (TNC) was 5.01 x 10^8/kg, CD34+ cell dose was 9.4 x 10^6/kg and CD3+ cell dose was 7.85 x 10^7/kg. Neutrophil engraftment was achieved at a median of Day+16 (range 14-18) and platelet engraftment at a median of Day+21 (range 18-21). The last day of red cell transfusion was a median of Day +10 (range 8-11). The median day of discharge was Day +17 (range: Day+15-Day +18). At a median follow up of 240 days (range 116-2555), Overall survival and DFS survival was 100% and no adverse events were observed during follow up visits.

The clinical resolution of photosensitivity was one of the most significant improvements post HSCT. Patients reported a complete cessation of new blister formation and reduction in skin fragility. This allowed for sun exposures and marked improvement in quality of life (Figure 1).

Discussion

We report the outcomes of four patients with congenital erythropoietic porphyria who successfully underwent HSCT from fully matched sibling donors. All patients showed substantial clinical improvement and biochemical response post HSCT, without any transplant related mortality or morbidity.

To our knowledge, this is the first report of successful HSCT for CEP from a low to middle income country (LMIC), demonstrating that excellent outcomes can be achieved in resource-constraint settings.

Although all patients exhibited onset of symptoms within first one to two months of life, the diagnosis was significantly delayed. These delays reflect the rarity of CEP and lack of disease awareness among clinicians. Recent studies report a median age of diagnosis around seven months, with characteristic symptoms such as red urine, skin lesions and anemia appearing in early infancy. In our series, the median age of diagnosis was 27 months and the median time to HSCT consultation exceeded 100 months, underscoring the need for early recognition and referral.

The role of HSCT in CEP was reported for the first time by Kauffman et al. in 1991 in a 10-year-old girl who showed clinical response to HSCT but died of transplant related complication.[4] Since then more than 25 successful cases have been published showing durable remission and improved quality of life.[5] Besnard et al. reported six patients with follow up of up to 25 years, four of whom maintained near normal porphyrin levels and no clinical manifestations of CEP.[6] Our cohort, using fully matched sibling donors and standardized myeloablative conditioning provides additional evidence of the safety and efficacy of HSCT in an optimal donor setting.

While supportive care in CEP can manage symptoms, it requires lifelong compliance which is particularly difficult in children. Poor compliance leads to complications like scarring, deformities, and transfusion dependence, significantly impairing quality of life.[7] In LMIC settings, where access to photo protection, transfusion support and chelation therapy may be limited or inconsistent, curative approaches assume even greater importance. Therefore, HSCT should be prioritized as the only curative option available to date to halt disease progression and prevent irreversible sequelae.

Despite its curative potential, HSCT remains underutilized likely due to disease rarity, diagnostic delays and the perceived risks of transplant related morbidity. Furthermore, the global literature is limited to small case series and individual case reports mostly from high income countries. These often lack long term follow up or organ function data, making it challenging to draw robust generalizations. Our study addresses this gap by providing detailed clinical data from a single center with long term follow up in a LMIC context.

Nonetheless our study has limitations. The small sample size is an inherent challenge in studying extremely rare disease like CEP. Additionally, we lacked genetic confirmation in all cases and single center design may limit external validity. However, the



Figure 1. Before and After Transplant
Photos taken with consent of patient and parents.

uniform success across varying ages and disease burdens may offer reassurance to centers considering HSCT for CEP.

Conclusion

This study represents the largest cohort of CEP patients treated successfully with matched sibling donor and the first reported from low middle-income country. Our findings highlight the importance of early diagnosis and timely referral for curative treatment to prevent irreversible complications.

References

1. Erwin AL, Desnick RJ. Congenital erythropoietic porphyria: Recent advances. Mol Genet Metab. 2019;128(3):288-297. doi:10.1016/j.ymgme.2018.12.008.
2. Di Pierro E, Brancaleoni V, Granata F. Advances in understanding the pathogenesis of congenital erythropoietic porphyria. Br J Haematol. 2016;173(3):365-379. doi:10.1111/bjh.13978
3. Stölzel U, Stauch T, Kubisch I. Porphyria [published online June 29, 2021]. Internist (Berl). 2021;62(9):937-951. doi:10.1007/s00108-021-01066-1.
4. Kauffman L, Evans DI, Stevens RF, Weinkove C. Bone-marrow transplantation for congenital erythropoietic porphyria. Lancet. 1991;337(8756):1510-1511. doi:10.1016/0140-6736(91)93198-i
5. Tezcan I, Xu W, Gurgey A, et al. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. Blood. 1998;92(11):4053-4058
6. Besnard C, Schmitt C, Galmiche-Rolland L, et al. Bone Marrow Transplantation in Congenital Erythropoietic Porphyria: Sustained Efficacy but Unexpected Liver Dysfunction. Biol Blood Marrow Transplant. 2020;26(4):704-711. doi:10.1016/j.bbmt.2019.12.005
7. Fritsch C, Lang K, Bolsen K, Lehmann P, Ruzicka T. Congenital erythropoietic porphyria. Skin Pharmacol Appl Skin Physiol. 1998;11(6):347-357. doi:10.1159/000029857

Disclosure

No financial disclosures reported. Artificial intelligence, language models, machine learning, or similar technologies were not used in the conceptualization, study, research, preparation, or writing of this manuscript. **MM**



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