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QUARTERLY
SPRING 2024 SAFETY

Patient Safety

Creating Systems That Prevent Harm

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Mitigating AI Risks
TO REDUCE HEALTH MISINFORMATION

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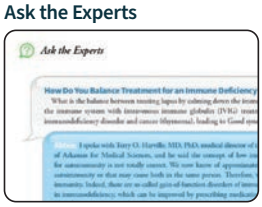

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First Do No Harm: Increasing Patient Safety

PATIENT SAFETY is at the heart of healthcare. The Hippocratic Oath — First, Do No Harm — has been in existence since 400 BC. Yet, while medical professionals undoubtedly have patients' best interests in mind, healthcare systems are run by humans who are not infallible, and today, healthcare diagnostics and content are more frequently being generated with the assistance of artificial intelligence (AI) that has the potential to increase security risks and the spread of health misinformation. As such, it's imperative to put in place systems and regulations to reduce patient harm.

Despite the best intentions, medical errors, adverse events and negligence still happen, all of which result in patient harm. And, according to the World Health Organization, since most mistakes are made by a confluence of factors, it's important to shift the responsibility for these errors from blame to shared responsibility, especially in the primary care setting. In our article "Improving Patient Safety in the Primary Care Setting" (p.20), several roadblocks exist to establishing a systems approach to patient safety in primary care. But, by following eight National Patient Safety Goals and five key tips to improve patient care, it is possible to reduce patient harm.

With the advent of AI, patient safety is taking on a whole new dimension. There is no arguing how AI can positively impact the healthcare industry in terms of diagnostics and administrative functions. However, AI is also being used to generate healthcare content, often leading to the spread of misinformation. And, unfortunately, there are currently only small pieces of AI regulations in place created by various entities. But, as we explain in our article "Mitigating AI Risks for Consumer Health Information" (p.26), these entities are now working together to develop overarching plans to mitigate the risks. These include new strategies for countering the capture and use of erroneous data and flagging AI-generated content. But, perhaps the most effective way misinformation generated by AI can be curtailed is by healthcare professionals engaging with their patients by encouraging them to assess the credibility of content; not engaging misinformation by correcting it online, which can further increase the content's visibility; increasing their social media presence; and importantly, listening to and empathizing with their patients.

An often overlooked part of patient safety in healthcare is clinical trials — not the safety of the trials themselves, necessarily, but the ability to complete trials so drugs can be brought to market to treat and cure patients. It may be surprising, but the primary cause of trial delays is failure to meet the initial enrollment target and timeline. In our article "Solving Clinical Trial Delays by Accelerating Patient Recruitment" (p.30), we discuss how software developers have begun partnering with pharmaceutical manufacturers to help them meet their patient recruitment goals by developing programs, some of which use AI algorithms. We highlight three of these companies that have, to date, achieved remarkable success, with the hope of potentially getting more drugs to patients in a timely manner.

As always, we hope you enjoy the additional articles in this issue of *BioSupply Trends Quarterly*, and find them both relevant and helpful to your practice.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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New Rule Expands Access to Health Information and Improves Prior Authorization Process

The Centers for Medicare and Medicaid Services (CMS) has finalized the CMS Interoperability and Prior Authorization Final Rule that sets requirements for Medicare Advantage (MA) organizations, Medicaid and the Children's Health Insurance Program (CHIP) fee-for-service (FFS) programs, Medicaid managed care plans, CHIP managed care entities and issuers of Qualified Health Plans (QHPs) offered on the Federally-Facilitated Exchanges (FFEs) to improve the electronic exchange of health information and prior authorization processes for medical items and services. Together, these policies are intended to improve prior authorization processes and reduce burden on patients, providers and payers, resulting in approximately $15 billion of estimated savings over 10 years.

This final rule establishes requirements for certain payers to streamline the prior authorization process and complements the MA requirements finalized in the 2024 MA and Part D final rule, which add continuity of care requirements and reduce disruptions for beneficiaries. Beginning primarily in 2026, impacted payers (not including QHP issuers on the FFEs) will be required to send prior authorization decisions within 72 hours for expedited requests and seven calendar days for standard requests for medical items and services. For some payers, this new time frame for standard requests cuts current decision time frames in half. The rule also requires all impacted payers to include a specific reason for denying a prior authorization request, which will help facilitate resubmission of the request or an appeal when needed. Finally, impacted payers will be required to publicly report prior authorization metrics, similar to the metrics Medicare FFS already makes available.

The rule also requires impacted payers to implement a Health Level 7 Fast Healthcare Interoperability Resources Prior Authorization application programming interface (API), which can be used to facilitate a more efficient electronic prior authorization process between providers and payers by automating the end-to-end prior authorization process. Medicare FFS has already implemented an electronic prior authorization API, demonstrating the efficiencies other payers could realize by implementing such an API. Together, these new requirements for the prior authorization process will reduce administrative burden on the healthcare workforce, empower clinicians to spend more time providing direct care to their patients, and prevent avoidable delays in care for patients. ❖

CMS Announces Model to Advance Integration in Behavioral Health. U.S. Department of Health and Human Services news release, Jan. 19, 2024. Accessed at www.hhs.gov/about/news/2024/01/19/cms-announces-model-to-advance-integration-in-behavioral-health.html?utm.

New Guidance Recommends All Federal Facilities Have Access to Naloxone

The U.S. Department of Health and Human Services and the General Services Administration have announced new guidance recommending that all federal facilities across the nation include overdose reversal medications in their safety stations on site. The recommendation will make lifesaving medications like naloxone more readily available in case of an emergency situation.

"Today, we are taking the historic step to recommend that every federal facility across the nation has lifesaving overdose reversal medications like naloxone on site," said White House Office of National Drug Control Director Rahul Gupta, MD. "These lifesaving medications should be as readily available as fire extinguishers or defibrillators in all public spaces, from schools, to housing communities, to restaurants, retail and other businesses. And now, as the nation's largest employer, we are leading by example."

The updated guidelines expand the concept of an automated external defibrillators program by introducing the "safety station," which would enable anyone located within a federal facility to access the necessary tools quickly and easily to respond to an emergency situation. ❖

Biden-Harris Administration Announces New Action to Increase Naloxone Access in Federal Facilities Across the Nation. U.S. Department of Health and Human Services news release, Dec. 21, 2023. Accessed at www.hhs.gov/about/news/2023/12/21/biden-harris-administration-announces-new-action-increase-naloxone-access-federal-facilities-across-nation.html?utm_source=news-releases-email-A&utm.

$13M NIH Grant Funds Research to Rejuvenate Immune System in Older Adults

University of Arizona Health Sciences researchers have received a $13.1 million grant from the National Institute on Aging to continue studies aimed at rejuvenating the immune system of older people to improve health throughout the lifespan. The goal of the National Institutes of Health (NIH)-funded research is to contribute to the fundamental knowledge of T cell aging and create interventions to improve immune defense. The program consists of three research studies and four supporting cores that span multiple sites across the country.

The first project, "Response of Aged Thymus to Injury and Rejuvenation Signals," led by Jarrod Dudakov, PhD, associate professor at Fred Hutchinson Cancer Research Center and affiliate associate professor at the University of Washington, hopes to increase an understanding of how the thymus responds to injury and repairs itself. The project will focus on enhancing thymic regeneration in older individuals, which could result in clinical approaches to enhance the immune system.

The second project, "Role of the Microenvironment in Regulating Early Stages of Thymic Involution and Central Tolerance," led by Lauren Ehrlich, PhD, professor of molecular biosciences and oncology at the University of Texas at Austin, will examine how the cellular composition of the thymus changes with age, which could impact the quantity and quality of developing T cells.

The third project, "Peripheral T Cell Maintenance Defects with Aging," focuses on how aging affects the lymph nodes. It is part of Janko Nikolich's, MD, PhD, principal investigator, professor and head of the department of immunobiology at the University of Arizona College of Medicine in Tucson, continuing studies of how the decline in naive T cells impacts the immune system. Naive T cells are produced in the thymus but need additional support from the lymph nodes to function effectively.

"This program is a great example of integrated and coordinated team science. We exchange our ideas and findings and troubleshoot each other's experiments," said Dr. Nikolich, who leads two University of Arizona Health Sciences strategic initiatives: Personalized Defense and the Aegis Consortium. "Everyone is working on their separate projects, but each project benefits from what we all discover." ❖

Craig, M. $13M NIH Grant Funds Research to Rejuvenate Immune System in Older Adults. News Medical Life Sciences, Nov. 1, 2023. Accessed at www.news-medical.net/news/20231101/2413M-NIH-grant-funds-research-to-rejuvenate-immune-system-in-older-adults.aspx.

CMS Finalizes Rule to Advance Health Equity

The Centers for Medicare and Medicaid Services (CMS) has finalized policies to support primary care, advance health equity, assist family caregivers and expand access to behavioral and certain oral healthcare. These policies are included in the 2024 Medicare Physician Fee Schedule (PFS) final rule, which also provides payment for principal illness navigation services to help patients and their families navigate cancer treatment and treatment for other serious illnesses.

The 2024 PFS final rule includes updates to PFS payments for clinicians as required by law. In accordance with updated factors specified by law, finalized payment amounts under the PFS are reduced by 1.25 percent overall compared to 2023. CMS has also finalized increases in payment for visits for many services such as primary and longitudinal care. Overall, the finalized 2024 PFS conversion factor is $32.74, a decrease of $1.15, or 3.4 percent from 2023.

"The impact of these changes means that people with Medicare will be able to access marriage and family therapists and mental health counselors for behavioral health treatment; access culturally-sensitive care from community health workers, care navigators and peer support workers; access primary care where the provider is invested in a long-term, trusting relationship; and that caregivers for persons with Medicare will have access to appropriate training," said Meena Seshamani, MD, CMS deputy administrator and director of the Centers for Medicare. "Taken holistically, these are some of the largest changes ever toward a Medicare that recognizes people with Medicare as whole persons, with their own families and unique life stories. After all, people are more than the sum of their ailments and diagnoses." ❖

CMS Finalizes Physician Payment Rule That Advances Health Equity. U.S. Department of Health and Human Services news release, Nov. 2, 2023. Accessed at www.hhs.gov/about/news/2023/11/02/cms-finalizes-physician-payment-rule-advances-health-equity.html.

Drug Reimbursement: Working with Payers

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

IN A DIGITAL AGE, drug reimbursement hinges on a variety of issues such as site of care, drug affordability, the addition of newly approved drugs, including biosimilars, and single-dose packaging.

Site-of-Care Considerations

Site-of-care considerations are high on the list when working to meet patient needs and mitigate costs. Patients may have preferences about where they want to receive treatment, but reimbursement challenges, including co-pays and payer mandates, can influence the site-of-care decision because each site has its own payer relationships and requirements.

There are many site-of-care options for infusion drugs such as hospital outpatient infusion centers, pharmacy infusion suites and the home, among others. The cost of using each of these options is dramatically different, with the hospital outpatient infusion center at the top of the list. And, facilities often justify an add-on facility fee to support care for patients with complex medical conditions.

Regardless of a patient's condition, the care received or the facility used, reimbursement requirements are payer-driven, and contracts could be government, commercial, fee-for-service, managed care or value-based. Peculiarities facilities need to consider to manage these differences include compliance and data integrity; clinical documentation; pharmacy and therapeutics (P&T) committee involvement; electronic health record build; charge master build and maintenance; coding and billing with a claims clearinghouse; denials avoidance teams; revenue integrity and underpayment teams; and finance relationships. Site-neutral payment (paying the same amount for a service, medication, treatment, etc., regardless of where a patient is treated) plays a role as well.

Regardless of a patient's condition, the care received or the facility used, reimbursement requirements are payer-driven, and contracts could be government, commercial, fee-for-service, managed care or value-based.

Drug Affordability

Let's not forget the financial impact on patients. Medicare beneficiaries covered under Part B usually are responsible for a 20 percent co-pay. This co-pay may be an out-of-pocket expense for patients, or it may be covered by co-insurance that patients also carry. And, because these co-pay rates are not affected by the site of care, the more expensive the site, the larger co-pay burden patients bear.

In 2024, the physician fee schedule (PFS) payment rates for drug administration services generally decreased across the board. The percentage decrease (relative to 2023) ranges from -2.53 percent to -36.91 percent for physician services performed in the facility setting and from 3.95 percent to -22.94 percent in the non-facility (freestanding office) setting. These decreases are primarily due to the decrease in the conversion factor for 2024.

The Health Care Price Transparency Act of 2023 (H.R. 5378) requires off-campus outpatient hospital departments to use separate and unique provider identifiers for billing Medicare and to be reimbursed for clinician-administered drugs at the same level as the Medicare PFS (site-neutral payments). This will be phased in for health professional shortage areas, rural areas and cancer hospitals. H.R. 5378 also calls for off-campus grandfathered drug administration services (those that are assigned to designated ambulatory payment classification groups as yet undefined) to be cut starting in 2025.

Adding Biosimilar Products in 2024

Patent expirations have led to the approval of an astounding number of biosimilar products for 14 reference branded products. And, many key payers have announced strategies for covering these new drug products, including biosimilars, which can apply to both Medicare Part B products paid under the 2024 OPPS, Medicare Advantage and

private insurance.

But, new biosimilar products present a complicated scenario for facilities concerning payer decisions. These decisions may differ from what facilities believe is the best-case scenario for patients and the practice. Indeed, it can be a tussle between decisions payers are making and the facilities' strategies for implementation. However, remember that payment under OPPS is the biosimilar average sales price (ASP) plus 8 percent of the reference biological's ASP for the first five years.

The U.S. Food and Drug Administration (FDA), through the Center for Drug Evaluation and Research Division of Drug Information, is trying to help by creating educational materials for patients, caregivers and healthcare providers to help share information and improve awareness and understanding of biosimilars, which can be located at www.fda.gov/drugs/biosimilars/multimedia-education-materials-biosimilars.

Action Items for Newly Approved Drugs

When deciding whether a facility's P&T committee should consider any newly FDA-approved drugs, the following steps can help:

1) Work alongside pharmacy purchasing to determine which products to use.

2) Use the quarterly ASP tables crosswalk file to identify the correct billing and payment code for each applicable product: www.cms.gov/medicare/payment/all-fee-service-providers/medicare-part-b-drug-average-sales-price/asp-pricing-files.

3) Consider the complexity and nuanced nature of the differences between each product and limitations of approved indications.

4) Be aware of payer limitations and prior authorization requirements.

5) Use the provider data management (PDM)/charge description master (CDM) systems using the applicable healthcare common procedure coding system (HCPCS) code to add each drug product purchased.

6) Create computerized provider order entries (CPOEs) that reflect these decisions.

7) Remember: The order entry must be for the actual product that is being purchased.

Keep in mind there may be situations in which using the new drugs is warranted while this rather lengthy and laborious process plays out. In such cases, the following steps must be taken in conjunction with the revenue cycle and IT/informatics team, and completed before any new drug is used in the facility:

1) Add the product to the drug dictionary/PDM used be the facility's IT system.

2) Add the product to the CDM with the newly assigned HCPCS code, and link it to the PDM (if a separate step is required).

3) Ensure the assigned billing unit is correct and the crosswalk tables converting dose given into billing units is functional.

4) Create a CPOE entry for the product, including supporting documentation for prior authorizations or other payer requirements.

Assuming all of this is done prior to the use of drugs, the order entry should automatically trigger a chain reaction allowing the drugs to be prepared, administered, charted and passed on to the revenue cycle with the appropriate documentation needed to garner payment. The conversion of dose to billing units will also flag any possible waste that may or may not be submitted for payment with the appropriate modifiers (JW versus JZ) attached.

Reimbursement for Discarded Drugs from Single-Dose Packaging

The Infrastructure Investment and Jobs Act of 2021 requires manufacturers to provide a refund to the Centers for Medicare and Medicaid Services for certain discarded amounts from a refundable single-dose container or single-use package drug. The data to determine this refund comes directly from the claims submitted for wasted/discarded portions of the drug. Rigorously adhering to the Part B JW and JZ modifier policy is essential to effectively identify and monitor billing and payment for discarded/wasted amounts of drugs. ❖

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Is Hybrid Care the Future?

By Ronale Tucker Rhodes, MS

WHILE THE pandemic is credited by many for the hybrid work trend, the truth is hybrid work is not new. In fact, it can be traced back to the 1960s and even earlier, but it really took off in the 2000s when the Internet became reliable enough at home. Since then, hybrid work arrangements have transformed into various modes and models. What the pandemic *should* be most credited for is *convincing* even the more resistant employers that hybrid work can benefit both employees and employers.

Indeed, since restrictions were lifted post-pandemic, 74 percent of U.S. companies have said they are using or plan to implement a permanent hybrid care model.[1] And, while it may seem counterintuitive for medical practices to do so as well since they rely so heavily on physician-patient interaction, healthcare organizations are right in line with this statistic. In fact, most medical practices using a hybrid or remote care model began doing so during the pandemic, and they say they have no plans to stop anytime soon. One reason for this is that one in five medical employees in the United States have quit their jobs since the beginning of the pandemic, mostly due to burnout and stress. But, 86 percent of healthcare organizations that adopted a hybrid care model report their employees got happier since the transition.[2]

What Is Hybrid Care?

Hybrid care "is a set of business strategies that allow a physician practice or hospital to expand its services to reach more patients while still providing quality care at an affordable price," says Martyn Eeles, general partner and director of Europe for Global Health Impact Network. "The goal of hybrid health is flexibility without sacrificing quality care — in other words, it's about being able to provide patients with better access to medical attention without breaking their bank accounts in the process."[3]

Essentially, it works by combining the best of telehealth and in-person visits. Providers are able to deliver care in person, virtually or both. Providers and support staff rely on technology for secure video conferencing, automatic appointment reminders, billing and more, all of which apply to both in-person and virtual visits.[4]

Hybrid care uses tools to connect clinical partners, minimize risks and provide greater insight into individual health through active remote monitoring. It also increases patient engagement with reminders, educational content, chat features and other services.[5]

Benefits and Challenges of Hybrid Care

Surveys of medical practices show a host of benefits from hybrid care, including increased revenues, productivity and employee morale. In a survey of 150 healthcare providers by Software Advice, a company that helps companies find the right software for their needs, they found 56 percent of healthcare practices using hybrid or fully remote work models saw increased productivity, 39 percent saw increased revenue and 61 percent were able to see an increased number of patients. What's more, 89 percent of practices said employees feel positively about working remotely some or all of the time, and 86 percent of practices that offer flexible work hours due to a hybrid or remote work environment saw improved employee morale.[6]

Hybrid care also addresses significant issues that undermine healthcare delivery such as shortages of nurses, clinical specialists and primary care providers.[5] This is because it allows organizations to recruit professionals who live farther away and may only need to come into the office once a week or less frequently.[7]

But, of course, hybrid care also poses some challenges such as maintaining a sense of connection and engagement with employees, as well as difficulty with training and onboarding.[7]

Adopting a Hybrid Care Model

Mountain Mover, a virtual assistant outsourcing company specializing in the healthcare industry, outlines the following essential steps for a successful hybrid care model:[8]

1) *Define a hybrid care strategy.* This involves deciding the proportion of care to be delivered virtually versus in person, which services will be devoted to

virtual care, which patient populations can benefit from hybrid care and what metrics will be used for gauging patient satisfaction, improved health outcomes and cost-effectiveness.

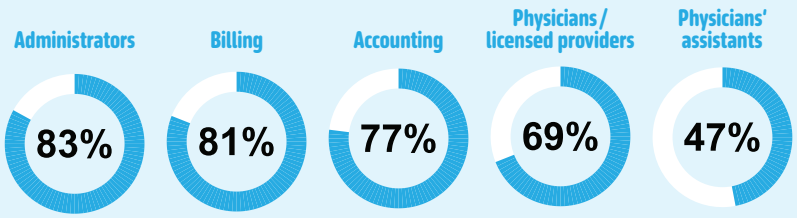
2) *Invest in technology.* Select a secure and user-friendly telehealth platform that meets regulatory requirements for the Health Insurance Portability and Accountability Act, and ensure it integrates seamlessly with the practice's choice of electronic health record system. Consider investing in remote monitoring devices capable of collecting and transmitting patient data such as vital signs or glucose levels in real-time to healthcare providers. Develop or enhance patient portals that allow patients to schedule appointments, access health records and communicate securely with their healthcare team from the comfort of their homes. Explore secure messaging platforms for patient-provider communication, appointment reminders and educational materials. (According to survey results by Software Advice, 51 percent of practices spent less than $5,000 setting up their hybrid or remote practice, with the most common related purchases being telemedicine software (77 percent) and teleconferencing hardware (74 percent).[6])

3) *Train the team.* Train staff, including administrative and support staff, on the utilization of telehealth platforms, digital health tools and new workflows.

4) *Develop clear workflows.* Determine how patients will schedule virtual appointments; the process for conducting virtual consultations, including patient onboarding and consent; how providers will access and update patient records during virtual visits; how prescriptions and follow-up care will be managed in a virtual setting; and what contingency plans need to be in place for emergencies or situations that require in-person evaluation.

Medical Employees Who Can Work Remotely[6]

According to results of a survey of 150 healthcare practices, these were the percent of positions working in hybrid or remote positions:



5) *Pilot the model.* Consider conducting a pilot program among a subset of providers and patients to test workflows, technology and training within a controlled environment.

6) *Communicate with patients.* Make patients aware of the new hybrid care options, the methodology for accessing virtual services and the advantages that come with this approach.

7) *Monitor and evaluate performance.* Establish a system for ongoing monitoring and evaluation by regularly collecting and analyzing data pertaining to patient outcomes, satisfaction, operational efficiency and cost savings.

Adena Health System, which has four hospitals and six regional clinics in Ohio, has come up with a couple of solutions to address the challenges to a hybrid workforce. To maintain a sense of connection among employees, it has adopted technology platforms such as WebEx teams and Workplace from Meta that allow employees to communicate and recognize great work across departments. And, to help train and onboard new employees, it has implemented an Emerging Leader program to pair up new employees with mentors or coaches to share expertise and provide exposure to opportunities they might not otherwise have.[7]

Making Hybrid Healthcare Work

Of course, healthcare services will in many instances require in-person care, and there is a lot to be said for the healing benefits of physical presence. However, by blending technology into the background, hybrid care can be tailored to fit almost any healthcare organizations' circumstances, as long as there are optimal clinical outcomes, staff burden and patient experiences. ❖

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RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

Medicines

Third Humira Biosimilar Is Approved by FDA

Alvotech's Simlandi (adalimumab-ryvk) has been approved by the U.S. Food and Drug Administration (FDA) as the third interchangeable Humira biosimilar, joining Pfizer's Abrilada (adalimumab-afzb) and Boehringer Ingelheim's Cyltezo (adalimumab-adbm). Interchangeability means the biosimilar can be substituted for the reference product or another biosimilar at the pharmacy level, although state-level pharmacy regulations can complicate matters. A total of nine Humira biosimilars are on the market in the U.S., so Alvotech's Simlandi will be the 10th.

"The approval of Simlandi marks the first high-concentration, citrate-free biosimilar to Humira with [interchangeability] status," said Eric Hughes, MD, PhD, executive vice president of global research and development and chief medical officer at Teva. "Biosimilars create opportunities for cost savings across the healthcare system and introduce additional treatment options for patients. This approval marks an important milestone for Teva and Alvotech's partnership to collaborate on seven biosimilars and expand the availability, access and uptake of biosimilars in the U.S." ❖

Wherwein, P. FDA Approves Simlandi, Third Interchangeable Humira Biosimilar. Managed Healthcare Executive, Feb. 24, 2024. Accessed at www.managedhealthcareexecutive.com/view/fda-approves-simlandi-third-interchangeable-humira-biosimilar.

Medicines

FDA Approves First Cell Therapy to Treat Melanoma

The U.S. Food and Drug Administration (FDA) has approved Iovance Biotherapeutics' Amtagvi, the first cellular therapy indicated for the treatment of adult patients with melanoma that is unable to be removed with surgery (unresectable) or has spread to other parts of the body (metastatic) that previously has been treated with other therapies (a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor).

Approval was based on a global, multicenter, multicohort clinical study including adult patients with unresectable or metastatic melanoma that evaluated whether Amtagvi established an objective response rate to treatment and duration of response (measured from the date of confirmed initial objective response to the date of progression, death from any cause, starting a new anti-cancer treatment or discontinuation from follow-up, whichever came first). Among the 73 patients treated with Amtagvi at the recommended dose, the objective response rate was 31.5 percent, including three (4.1 percent) patients with a complete response and 20 (27.4 percent) patients with a partial response. Among patients who were responsive to the treatment, 56.5 percent, 47.8 percent and 43.5 percent continued to maintain responses without tumor progression or death at six, nine and 12 months, respectively.

The most common adverse reactions associated with Amtagvi included chills, fever, fatigue, tachycardia (abnormally fast heart rate), diarrhea, febrile neutropenia (fever associated with a low level of certain white blood cells), edema (swelling due to buildup of fluid in body tissues), rash, hypotension, hair loss, infection, hypoxia (abnormally low oxygen levels in the body) and feeling short of breath.

According to FDA, patients treated with Amtagvi may exhibit prolonged severe low blood count, severe infection, cardiac disorder or develop worsened respiratory or renal function or have fatal treatment-related complications. A boxed warning is included in the label containing information about these risks. Patients receiving this product should be closely monitored before and after infusion for signs and symptoms of adverse reactions. Treatment should be withheld or discontinued in the presence of these symptoms, as indicated.

Amtagvi was approved through the accelerated approval pathway, under which FDA may approve drugs for serious or life-threatening illnesses or conditions where there is an unmet medical need and the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients (improving how patients feel or function, or whether they survive longer). ❖

FDA Approves First Cellular Therapy to Treat Patients with Unresectable or Metastatic Melanoma. U.S. Food and Drug Administration news release, Feb. 16, 2024. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-first-cellular-therapy-treat-patients-unresectable-or-metastatic-melanoma.

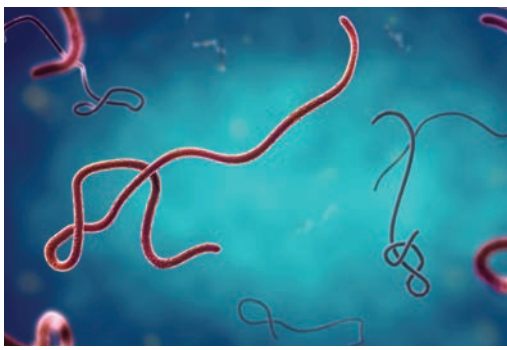
Research

Study Shows Patients Vaccinated Against Ebola Are Half as Likely to Die Than Unvaccinated Patients

Results from a study conducted in the Democratic Republic of the Congo (DRC) showed patients with confirmed Ebola virus disease were half as likely to die if they were vaccinated against the virus than if they were not. Results from an initial trial of the vaccine nearly a decade ago during the West African Ebola epidemic indicated it could be 100 percent effective at preventing Ebola, and a subsequent trial conducted by the DRC's National Institute for Biomedical Research and the World Health Organization during a large outbreak in the DRC determined the vaccine was 97.5 percent effective.

In this new study, researchers analyzed outcomes from 2,279 patients with confirmed Ebola virus disease who were treated in the DRC between July 27, 2018, and April 27, 2020, a study period that coincided with the second largest Ebola outbreak ever recorded, which killed more than 2,200 people. Results showed the fatality rate among 423 participants who had received the vaccine was approximately 25 percent, and among unvaccinated participants, it was 56 percent. What's more, the vaccine's protective effect increased the longer a person had been vaccinated, with the mortality rate falling from 27 percent among participants vaccinated just two days or fewer from the onset of their symptoms to 18 percent among those who received the vaccine 10 days or more before they got sick. Most vaccinated participants were aged 15 to 59 years.

The researchers listed several potential reasons other than primary vaccine failure for the more than 400 breakthrough infections identified during the study, including cold chain failure, inadequate dosing or injection technique and immunosuppression.



"Our results reinforce the importance of vaccinating populations who are at risk of exposure to Ebola virus to reduce the risk of infection and — if infection occurs — the risk of death," the researchers wrote. ❖

Gallagher, G. Ebola Vaccine Halves Mortality Rate, New Data Show. Healio, Feb. 12, 2024. Accessed at www.healio.com/news/infectious-disease/20240212/ebola-vaccine-halves-mortality-rate-new-data-show.

Guidelines

FDA Approves New Safety Labeling for Opioid Medications

The U.S. Food and Drug Administration (FDA) has approved and implemented updated warning labels for all opioid prescriptions, part of a continuing effort to reduce unsafe opioid use and risk for overdose, as well as to urge healthcare professionals to take a more patient-centered approach when prescribing opioid analgesic products. The updated labels include the following information:

- The risk for overdose increases as the dosage increases for all opioid pain medicines.
- Immediate opioids should not be used for an extended period of time unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate.
- Many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine.
- It is recommended to reserve extended release/long-acting opioid pain medicines for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.

The update also includes a new warning about opioid-induced hyperalgesia and how to differentiate between that condition and symptoms of opioid tolerance and withdrawal. Despite these changes, FDA emphasized that pain management requires collaboration between providers and patients.

"While FDA understands the importance of ensuring patients continue to have access to opioid analgesics in their pain management regimens, we believe it is equally important to ensure that patients and prescribers are fully aware of all the benefits and risks of treatment with opioid pain medicines," said Patrizia Cavazzoni, MD, the director of the Center for Drug Evaluation and Research at the FDA. "Approving these class-wide labeling updates facilitates safer use of these medicines and furthers our goal to reduce the risks of nonmedical use and overdose." ❖

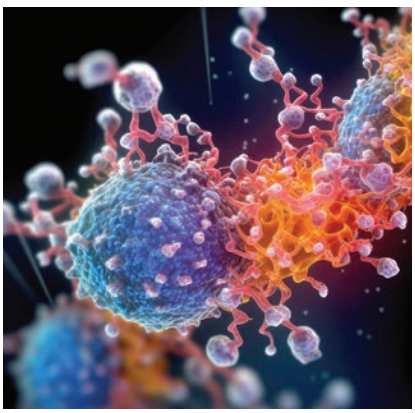
Starr, M. FDA Approves New Safety Labeling Changes for Opioid Medications. Pharmacy Practice News, Feb. 8, 2024. Accessed at www.pharmacypracticenews.com/FDA-Approvals/Article/02-24/FDA-Approves-New-Safety-Labeling-Changes-for-Opioid-Medications/72804.

Research

First Cancer Patients Receive mRNA Therapy in Clinical Trial

Imperial College Healthcare NHS Trust has enrolled the first United Kingdom (UK) patients who have received an experimental messenger RNA (mRNA) therapy — a type of immunotherapy treatment called mRNA-4359 — in its Phase I/II clinical trial. The trial aims to evaluate its safety and potential for treating melanoma, lung cancer and other solid tumor cancers. The treatment is designed using mRNA and works by presenting common markers of tumors to the patients' immune systems. The goal is to help train patients' immune systems to recognize and fight cancer cells expressing these markers, but also to potentially eliminate cells that may suppress the immune response.

Patients in the trial will receive either mRNA-4359 alone, or mRNA-4359 and pembrolizumab (Keytruda), and will be



followed up for a period of up to 34 months. Preclinical testing in both cell and animal models of cancer provided initial evidence that mRNA-4359 had an effect on the immune system, providing a rationale for it to be offered in early-phase clinical trials. The study is a non-randomized trial, so all patients receive the same treatment. It is also an open-label trial, so clinicians and patients know what they are receiving — unlike blinded trials in which patients don't know which treatment they are receiving.

The trial is sponsored by pharmaceutical company Moderna and is set to recruit patients globally over the next three years. It is being undertaken through the Moderna-UK Strategic Partnership, which is bringing mRNA vaccine manufacturing to the UK and building resilience to future health emergencies. Under the 10-year partnership with the government, Moderna has also committed substantial investment to research and development, which includes running a large number of clinical trials such as this one in the UK. ❖

O'Hare, R. First UK Patients Receive Experimental mRNA Therapy for Cancer. Imperial College London, Feb. 4, 2024. Accessed at www.imperial.ac.uk/news/251213/first-uk-patients-receive-experimental-mrna.

Research

Study Shows New Blood Test May Predict Alzheimer's Risk

A recent study has found that a commercially available plasma p-tau217 (phosphorylated tau 217) immunoassay accurately identified biological Alzheimer's disease (AD), comparable with results using cerebrospinal fluid (CSF) biomarkers, with reproducible cut-offs across cohorts. What's more, it detected longitudinal changes, including at the preclinical stage. P-tau is a specific blood biomarker for AD pathology, with p-tau217 considered to have the most utility. However, availability of p-tau217 tests for research and clinical use has been limited.

The study sought to determine the utility of a novel and commercially available immunoassay for plasma p-tau217 to detect AD pathology and evaluate reference ranges for abnormal amyloid β (Aβ) and longitudinal change across three selected cohorts: cross-sectional and longitudinal data from the Translational Biomarkers in Aging and Dementia (TRIAD) cohort (visits October 2017 through August 2021), Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort (visits February 2007 through November 2020) and cross-sectional data from the Sant Pau Initiative on Neurodegeneration (SPIN) cohort (baseline visits March 2009 through November 2021). Participants included individuals with and without cognitive impairment grouped by amyloid and tau (AT) status using PET or CSF biomarkers. Data were analyzed from February to June 2023.

Seven hundred and 86 participants (mean [SD] age, 66.3 [9.7] years; 504 females [64.1 percent] and 282 males [35.9 percent]) were included. High accuracy was observed in identifying elevated Aβ (area under the curve [AUC], 0.92-0.96; 95% CI, 0.89-0.99) and tau pathology (AUC, 0.93-0.97; 95% CI, 0.84-0.99) across all cohorts. These accuracies were comparable with CSF biomarkers in determining abnormal PET signal. The detection of abnormal Aβ pathology using a three-range reference yielded reproducible results and reduced confirmatory testing by approximately 80 percent. Longitudinally, plasma p-tau217 values showed an annual increase only in Aβ-positive individuals, with the highest increase observed in those with tau positivity. ❖

Ashton, NJ, Brum, WS, Di Molfetta, G, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *Journal of the American Medical Association*, Jan. 22, 2024. Accessed at jamanetwork.com/journals/jamaneurology/fullarticle/2813751?guestAccessKey=46653b11-2129-407d-ac0a-1fe7d79e32c6&utm.

Research

Study Will Test Vaccine That Kills Cancer Cells Without Side Effects

A Phase III clinical trial will test a new cancer vaccine that is designed to harness the power of a person's immune system instead of eliminating it. This is in contrast to many traditional cancer treatments such as chemotherapy that work by killing off cancer cells but also killing off non-cancerous cells throughout the body, which can cause a range of side effects, including hair loss, nausea, vomiting or knocking out a person's immune system, putting them at risk of life-threatening infections.

The vaccine is known as a tumor lysate particle only (TLPO) vaccine that uses a person's tumor cells to identify particular parts that are then presented back into the body using the vaccine in a way that can stimulate the immune system to gain the ability to detect these cancer cells like an infection, allowing the immune system to fight the cancer itself.

In Phase II clinical trials, the TLPO cancer vaccine was tested in hundreds of patients with advanced forms of melanoma. Data from those trials showed nearly 95 percent of people given only the vaccine were still alive three years after starting treatment and 64 percent were still disease-free. Among the most advanced forms of melanoma, disease-free survival after three years for people with stage III disease was 60 percent in the vaccine-only group, compared to about 39 percent in the placebo group. Disease-free survival for those with stage IV disease was about 68 percent in the vaccine-only group and zero in the placebo group. The most common side effects were redness or pain at the injection site, fever and fatigue after the injection — similar to other vaccines that stimulate an immune response.

However, Vernon Sondak, MD, cutaneous oncologist at Moffit Cancer Center who was not involved in the clinical trial but has worked with tumor lysate vaccines throughout his career, said that even though these results are promising, the Phase II clinical trials aren't conclusive. The new larger Phase III clinical trial will have to ultimately validate if this cancer vaccine will truly be a game-changer in the field. ❖

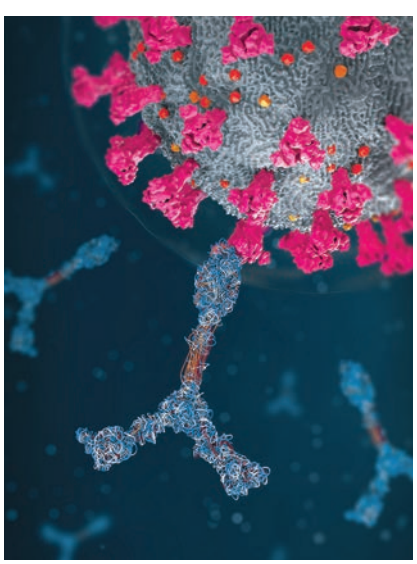
Cancer Vaccine with Minimal Side Effects Nearing Phase 3 Clinical Trials. Deltaplex News, Jan. 20, 2024. Accessed at www.deltaplexnews.com/cancer-vaccine-with-minimal-side-effects-nearing-phase-3-clinical-trials.

Research

Study Uses Flu Virus to Speed Up COVID-19 Antibodies

Researchers at the University of California, Riverside, have developed a vaccine to help speed up the process of making antibodies against SARS-CoV-2 by using preexisting immunity to a separate virus (the influenza virus).

To develop the vaccine, the researchers targeted SARS-CoV-2 as a representative pandemic virus and generated a "fusion protein" vaccine that combines the nucleoprotein from influenza A virus and the receptor-binding domain, or RBD, of the SARS-CoV-2 spike protein. The SARS-CoV-2 virus uses the spike protein to attach to a receptor on the surface of cells — the first step in the infection of the cell by the virus. Antibodies against RBD block the interaction of the spike protein with the receptor, thereby preventing the virus from infecting the cell.



The new vaccine design addresses a long-standing challenge in the field of virology: the delay in developing protective adaptive immunity for emerging viral pathogens. According to the researchers, in any infection, antibodies are made by a type of cell called the B cell. Each B cell produces one antibody against one specific target; only a small subset of B cells, however, can produce antibodies against RBD.

"Any delay in the immune response to SARS-CoV-2 means there is some time when people are left poorly protected against the virus. Our vaccine is designed to get people those protective antibody responses faster, so they are not vulnerable to the coronavirus. This is better protection for everyone. It could be especially valuable for people who still lack immunity to SARS-CoV-2 such as children," explained Rong Hai, PhD, MSc, associate professor of microbiology and plant pathology at the University of California, Riverside. ❖

New Vaccine Turns Preexisting Flu Immunity into COVID-19 Weapon. News Medical Life Sciences, Jan. 17, 2024. Accessed at www.news-medical.net/news/20240117/New-vaccine-turns-preexisting-flu-immunity-into-COVID-19-weapon.aspx.

Research

Researchers Identify an Immune Cell That Can Attack Cancer

Researchers at City of Hope have discovered that a type of immune cell in the human body known to be important for allergy and other immune responses can also attack cancer. In addition, these cells, called human type 2 innate lymphoid cells (ILC2s), can be expanded outside of the body and applied in larger numbers to overpower a tumor's defenses and eliminate malignant cells in mouse models with cancer.

"The City of Hope team has identified human ILC2 cells as a new member of the cell family capable of directly killing all types of cancers, including blood cancers and solid tumors," said Jianhua Yu, PhD, a professor in the Department of Hematology and Hematopoietic Cell Transplantation at City of Hope and the study's senior author. "In the future, these cells could be manufactured, preserved by freezing and then administered to patients. Unlike T cell-based therapies like CAR T cells, which necessitate using the patient's own cells due to their specific characteristics, ILC2s might be sourced from healthy donors, presenting a distinct potential therapeutic approach as an allogeneic and 'off-the-shelf' product."

Previous research focused on mouse ILC2s had not consistently shown promise when tested for their cancer-killing abilities. However, in the highly translational labs at City of Hope, researchers prioritized the examination of human cells and found that human ILC2s do not work the same as mouse ILC2s.

The researchers plan to continue to work with their collaborators to understand and learn more about human ILC2s now that they know the cells are assassins. "We aim to really expand the applications of these findings, potentially beyond cancer treatments," Dr. Yu said, noting that ILC2s may even work against viruses such as COVID-19. "Additionally, we are working toward translating our discovery into tangible clinical benefits." ❖

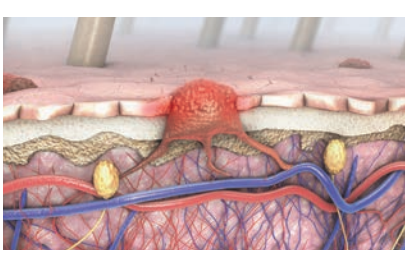
Neith, K. City of Hope Research Reveals an Immune Cell That Can Attack Cancer. City of Hope, Jan. 10, 2024. Accessed at www.cityofhope.org/city-hope-research-reveals-immune-cell-can-attack-cancer-1.

Research

Discovery Could Predict Immunotherapy Response in Melanoma

A team of British researchers from King's College London, Guy's and St Thomas' Hospital Trust and the Francis Crick Institute have discovered a rare type of immune cell that potentially predicts how likely it is certain patients with skin cancer will be responsive to treatment via immunotherapy. Specifically, they found that Vd1-gd T cells had the ability to recognize and kill cancer cells without identifying mutations, and can be found inside tumors where the immune checkpoint protein programmed cell death protein 1 (PD-1) is also present.

"The study findings may help doctors decide which patients are most likely to benefit from current immunotherapies," stated co-first author Shraddha Kamdar, PhD, MSc, a research fellow at King's College London. "These therapies are both costly and importantly can cause severe and lifelong side effects, so it is important to be able to predict when they will actually work."



The findings were based on clinical trial data of 127 patients with melanoma who had been treated with PD-1-targeting immune checkpoint inhibitors, and this data revealed that Vd1-gd T cells' presence could predict positive response to immunotherapy, especially in cancers with a low number of mutations. Researchers then grew cells from human tissue in a laboratory setting to illustrate that immune checkpoint inhibition therapy could reactivate Vd1-gd T cells, and learned that therapies utilizing Vd1-gd T cells could be effective for relatively longer than therapies using other types of T cells.

According to the National Cancer Institute, immune checkpoints, a standard element of a patient's immune system, keep the body from destroying healthy cells and engage when proteins on the surface of T cells identify and bind to immune checkpoint proteins on cells such as tumor cells, and the bond between the checkpoint and the protein deactivates T cells. Immune checkpoint inhibitors block the binding of checkpoint and partner proteins, enabling the T cell to remain active and fight cancer cells.

Given the potential side effects associated with immunotherapy, including inflammation of the skin, intestines and liver, being able to predict which patients are likely to benefit from the treatment could be useful information for patients and their care teams. ❖

Biese, A. Rare Immune Cell May Predict Immunotherapy Response in Melanoma. Cure, Jan. 7, 2024. Accessed at www.curetoday.com/view/rare-immune-cell-may-predict-immunotherapy-response-in-melanoma.

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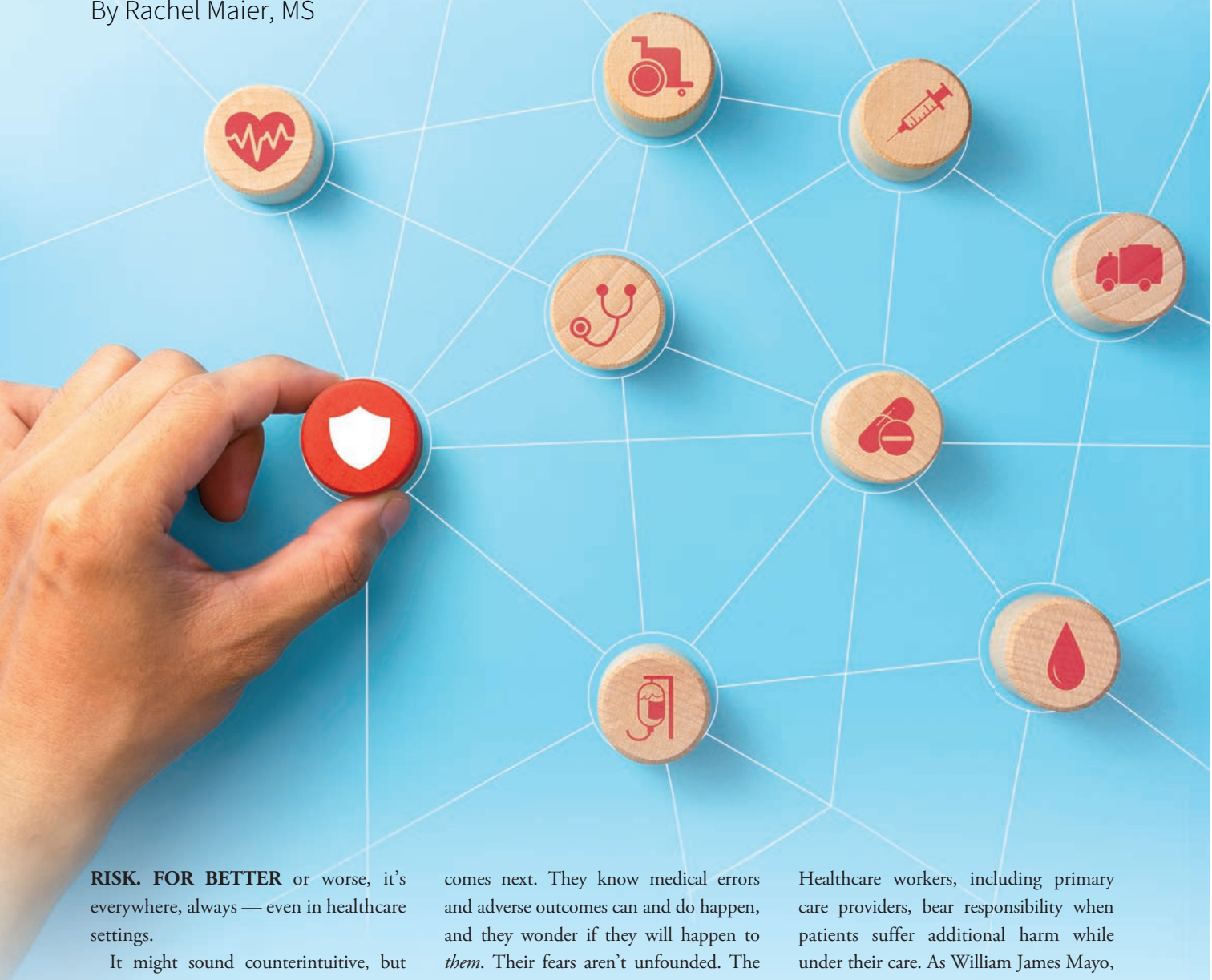
Improving Patient Safety in the Primary Care Setting

First, do no harm. Next, create systems that help prevent harm before it happens.

By Rachel Maier, MS



RISK. FOR BETTER or worse, it's everywhere, always — even in healthcare settings.

It might sound counterintuitive, but for patients seeking medical attention to help them heal, the possibility of hurt, damage or loss is top of mind. They are nervous about what their symptoms might mean, overwhelmed by the pros and cons of a given treatment, and afraid of what comes next. They know medical errors and adverse outcomes can and do happen, and they wonder if they will happen to *them*. Their fears aren't unfounded. The human body, though strong and resilient, is also fragile and finite. Best-case scenarios don't always play out.

Mitigating the risk and building a practice that emphasizes patient safety is important to patients and providers alike. Healthcare workers, including primary care providers, bear responsibility when patients suffer additional harm while under their care. As William James Mayo, MD, famously said, "The best interest of the patient is the only interest to be considered."[1] If it isn't in the patient's best interest, it's a no-go.

But how well do the processes and procedures of primary care practices

support patients' best interests? After all, medical errors, adverse events and negligence can still happen. In many cases, poorly designed processes and procedures lead to human error, which can lead to patient harm. In fact, most medical errors that jeopardize patient safety are out of clinicians' control, and can instead be traced back to the breakdown of systems.[2]

We know this to be true in the hospital setting. Much has been said about improving safety there, but improving patient safety in the primary care setting is equally important for the health and well-being of patients and, by extension, the physician and clinical team. The best way to improve patient safety is to understand what it is and how it is related to medical error, assesses how and why mistakes are made and implement processes and procedures that prevent medical errors from happening in the first place.

Ancient Idea, Modern Mandate

The simplicity of Hippocrates' ancient imperative "First, do no harm" still remains at the heart of the solemn pledge healthcare providers make today.[3] Physicians still practice medicine with the goal of preventing intentional injury, but despite their best intentions, mistakes still happen, and patients can and do get hurt.

In 1999, the United States Institute of Medicine (IOM) published a paper titled "To Err is Human: Building a Safer Health System," a report that echoed Alexander Pope's famous observation that making errors is part of human nature. According to the paper, it's natural that physicians should make mistakes from time to time because physicians are people, and it is human nature for people to make mistakes.[4] When mistakes are made in healthcare, patient safety is in jeopardy. Between the two ideas — actively working to keep the patient from harm and recognizing humans are fallible — is where modern patient safety finds its nexus.

Modern patient safety caught national attention nearly 25 years ago when IOM reported that an estimated 98,000 hospitalized patients die every year because of medical errors.[4] More recently, a 2016 study conducted by Johns Hopkins Medicine found that medical error is responsible for 250,000 deaths in the United States annually, making it the third leading cause of death in the nation.[5] However, the accuracy of this number remains debated, as it remains unclear whether those deaths were directly due to medical error, or whether medical errors coincided with deaths that would have occurred anyway.

Defining Patient Safety

According to the Patient Safety Network (PSNet), a division of the Department of Health and Human Services' Agency for Healthcare Research and Quality, patient safety is the "freedom from accidental or preventable injuries produced by medical care."[6] While helpful, this definition remains broad, and it encompasses safety issues ranging from keeping patients' personal healthcare information confidential to ensuring the right prescription is dispensed to the right patient at the right time (and so much more). Ensuring patient safety is a big task, and despite their best efforts, even the most conscientious practices will encounter a medical error that could jeopardize patient safety. U.S. family physicians report that the top errors in their practices include errors in prescribing and dispensing medication, completing the right lab test(s) for the right patient at the right time, filing system errors and appropriately responding to abnormal lab tests. Further, studies show that most of the errors that occur in primary care are preventable.[7]

Patient safety involves medical errors of both commission (doing something wrong) and omission (failing to do the right thing) that lead to an undesirable outcome or significant potential for such an outcome. Notably, errors of commission are more difficult to recognize, but according to PSNet, they likely represent a larger problem.[6]

Adverse events, or harmful, negative outcomes that happen when patients have been provided with medical care, are often due to preventable medical error, but sometimes, they are not, and it's difficult to tease out whether or not human error caused the event. Determining whether patient harm is due to an error or an adverse event (or some combination of both) is difficult, but proactive processes and protocols that reduce the occurrence of preventable errors and adverse events seem to best provide for patient safety.[6]

What Leads to Patient Harm?

According to the World Health Organization (WHO), most mistakes that hurt patients are a result of system or process failures that lead healthcare workers to make mistakes. A confluence of factors lead to patient harm, and more than one factor is usually involved in a single incident. These factors include:[8]

- system and organizational factors: the complexity of medical interventions, inadequate processes and procedures; disruptions in workflow and care coordination; resource constraints; inadequate staffing; competency development;
- technological factors: issues related to health information systems such as problems with electronic health records or medication administration systems; misuse of technology;
- human factors and behavior: communication breakdown among healthcare workers, within healthcare teams and with patients and their families; ineffective teamwork; fatigue; burnout; cognitive bias;

- Approximately 400,000 hospitalized patients experience some type of preventable harm each year.
- Depending on the study, medical errors account for more than $4 billion per year.
- Medical errors cost approximately $20 billion per year.
- Medical errors in hospitals and clinics result in approximately 100,000 people dying each year.
- Medical errors typically include surgical, diagnostic, medication, devices and equipment, and systems failures, infections, falls, and healthcare technology.
- Missed diagnoses or injuries from medication are common in outpatient settings.
- Most malpractice claims in hospitals are related to surgical errors, whereas most claims for outpatient care are related to missed or late diagnoses.
- Slightly more than half of the paid malpractice claims are related to outpatient care.
- To decrease overhead, hospitals often reduce nursing staff; staffing of registered nurses below target levels is associated with increased mortality.

• patient-related factors: limited health literacy, lack of engagement; non-adherence to treatment; and

• external factors: absence of policies, inconsistent regulations, economic and financial pressures; challenges related to the natural environment.

From Blame to Shared Responsibility

Standardized policies and processes for identifying and reporting errors help give a framework for improving patient safety, but people still bear the weight of responsibility when errors occur. What motivates people to report errors, particularly if they are the ones who are at fault for the incident? When individuals feel guilty or responsible for the misstep, or when they perceive they are betraying the colleague who was involved, they are less inclined to report errors.[2]

True, those who make errors must be held accountable for their mistakes. However, blaming and shaming for medical mistakes does little to improve patient safety and instead has a considerable effect on underreporting mistakes when they inevitably happen. Guilt, shame, fear, anger and the possibility of legal action can cause a slew of psychological problems in the people who caused the mistake, but feelings do not lead to any real or meaningful change. Shifting focus away from *who* made the mistake and toward *what*, *where* and *how* the mistake was made, and then identifying ways to alter and improve the system that yielded the mistake, is a better way to reduce medical error over time.

A culture of safety recognizes patient safety challenges and empowers stakeholders to actively participate in addressing them. Identifying systems that don't work and establishing systems that do work is in the best interest of everyone. And, a system that cares less about the who and more about the what, where and how will help cultivate a culture in which errors are seen as areas of concern to address, not incompetence to punish. As WHO explains, "Understanding the underlying causes of errors in medical care requires shifting from the traditional blaming approach to a more system-based thinking where errors are attributed to poorly designed system structures and processes, and the human nature of all those working in healthcare facilities under a considerable amount of stress in complex and quickly changing environments is recognized."[8] Shifting from a culture of blame to one of shared responsibility can help encourage employees to report errors as "incidents of concern."[2]

Patient Safety Systems in Primary Care

How to best achieve a systems approach to safety in a private practice setting is unclear. While it is well-established that a systems approach improves patient safety in the hospital setting, how efficiently it improves patient safety in primary care has not been extensively studied or well understood. Several roadblocks make implementing and studying a systems approach in primary care difficult, including time, cost and lack of overarching standards for reporting errors. Each facility manages its error reporting system differently, making it more difficult to study. Primary care settings vary in location (urban, suburban, rural), type (academic, private, healthcare system, etc.), resources and patient community, and what works for one practice may not work for another. And, with the advent of artificial intelligence and the growth in telemedicine, remote patient monitoring

and hybrid medical teams, patient safety is taking on new dimentions and raising questions about whether machine learning and computers negatively or positively influence patient safety, too. Investing in a systematic method of reporting errors, analyzing them and implementing new processes in primary care is time-consuming and costly, and questions about the benefits versus the risks of reporting errors remain. Developing a system that provides clarity and ease of reporting and that encourages providers to report errors without shame or fear of punishment is a daunting task.

National Patient Safety Goals

To help point healthcare organizations in the right direction, the Joint Commission established its National Patient Safety Goals (NPSGs) in 2002 to work with practitioners, provider organizations, purchasers, consumer groups and others to establish national safety goals for healthcare. According to the Joint Commission, the goals address specific concerns in patient safety, highlighting areas that are prone to avoidable harm. It encourages healthcare organizations to prioritize these goals as they adopt best practices for reducing patient harm. The first set of goals became effective in January 2003, and they are revisited each year to keep them relevant to the changing healthcare landscape. For 2024, the NPSGs are:[9]

1) Identify patients correctly.
2) Improve staff communication.
3) Use medicines safely.
4) Use alarms safely.
5) Prevent infection.
6) Identify patient safety risks.
7) Improve healthcare equity.
8) Prevent mistakes in surgery.

These strategies include appointing leadership that is committed to creating a culture of safety; establishing safe procedures and clinical processes; building competencies of healthcare workers and improving teamwork and communication; engaging patients and families in policy development, research and shared decision-making; creating and implementing systems for patient safety incident reporting; and being committed to learning and continuous improvement.

Five Key Steps to Improve Patient Safety

Where does a practice start? According to Stephanie Iorio, vice president of operations of products and services at American Data Network, a company that helps healthcare organizations improve patient care, the five most important steps toward improving patient safety include:[9]

1) *Risk assessment and gap analyses.* Regularly review and evaluate your practice's environment, processes and procedures. Identify potential patient safety issues, and proactively implement changes to address them.

2) *Education and training.* Keep your staff up to date with patient safety best practices. Empower them with the knowledge they need to provide the best care possible.

3) *Verification processes.* Enforce strict patient verification processes, paying particularly close attention to dispensing and administering medications. Always double check.

4) *Monitoring and reporting.* Create a cooperative environment in which clinicians and staff work together to report potential errors, both major and minor, to help track, recognize and address error patterns.

5) *Focus on high-risk areas.* Pay particular attention to fall risks, infection risk and other high-risk areas, and implement strategies to improve patient safety.

Look Back to Move Forward

Risk can't be eliminated completely. However, it can be mitigated by cultivating a culture in which safety is a priority. When mistakes happen and patients get hurt, it can be embarrassing to admit fault, tedious to look backward, difficult to dissect what went wrong and slow-going to move forward, but the investment in patient safety is worth the effort. Learning from mistakes — what works for a given practice and what doesn't — takes time and effort, but another piece of Dr. Mayo's insight can help inspire forward movement: "The glory of medicine is that it is constantly moving forward, that there is always more to learn. The ills of today do not cloud the horizon of tomorrow, but act as a spur to greater effort."[1] The rapidly evolving healthcare landscape inevitably (and incessantly) introduces new challenges and, along with them, opportunities to learn. An attitude of all-hands-on-deck creates a collaborative effort to prioritize effective, efficient systems and processes that will reduce patient harm and thus begin to build a safer tomorrow today. ❖

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Mitigating AI Risks for Consumer Health Misinformation

While agencies race to put in place regulations for using artificial intelligence to reduce the spread of health misinformation, healthcare providers can help to correct this by engaging with their patients.

By Amy Scanlin, MS

WHILE ARTIFICIAL intelligence (AI) has the power to positively impact the healthcare industry, it also has the potential to cause harm if left unchecked. While AI is heralded for supporting diagnostics, decision-making and administration, detractors of AI warn of significant risks, chief among them cybersecurity, privacy and ethical and legal considerations surrounding the Health Insurance Portability and Accountability Act (HIPAA). Increasingly, generative AI is also being used to create news-related stories, including stories about healthcare. And this, too, can pose risks due to the inability of AI to discern between factual information and misinformation. When factually inaccurate content based on poorly vetted sources is used to create and publish new content, it leads to consumer confusion, often creating distrust in legitimate scientific evidence.

Whether content is legitimate or not, its spread online reverberates echo chambers of information algorithms and social media shares, creating an increasingly challenging literacy environment. In the healthcare space, for instance, patients are tasked with parsing out sound medical science from fluff to make sense of increasingly complex information. Add to this the compounding risks of social discord caused by competing narratives, and patients may begin to question factual messaging from legitimate public health sources. This poses a threat to health literacy and can create patient-imposed limits on their own access to care.[1]

Regulatory Environment

AI's use in healthcare is a regulatory gray area with no overarching AI-specific regulations currently in place. Instead, oversight is largely piecemealed in the United States between federal agencies such as the Department of Health and Human Services (HHS), Office of Civil Rights (OCR), Food and Drug Administration, Federal Trade Commission and Department of Justice, as well as numerous state and local agencies,[2] all of which are working to develop proactive strategies that protect patients and ensure the integrity of the healthcare system.

Foreign regulatory agencies also have their own rules concerning AI such as the European Union's draft Artificial Intelligence Act that, when finalized, will classify AI systems by risk category, each with their own requirements, and the World Health Organization's (WHO) 2021 guidance document pertaining to ethical and governance considerations when using AI in health.[2]

Even so, misinformation continues to pervade Internet searches as evidenced by anecdotal accounts of people's use of ChatGPT when searching for health information online and accepting and even sharing that information on social media without understanding its validity and truthfulness.[3] In 2023, the HHS Health Sector Cybersecurity Coordination Center warned that nefarious actors are using AI to develop malware, evade security and spread targeted phishing emails.

That being said, numerous entities are working diligently to counter these potentially ill effects by using AI to conduct risk assessments and develop appropriate mitigation plans. Indeed, ensuring appropriate use of AI to support legitimate healthcare needs has great potential, so getting ahead of the risks remains a top priority.

AI Engineering and Large Language Models

Large language models (LLM), a type of generative AI trained to recognize and generate text, are used to create Internet-based content. Whether they're articles, websites and/or emails, use of generative AI can enhance productivity, but its challenge lies in the inability of LLMs to parse out and exclude misinformation from newly generated content. That means as LLMs generate new text, unchecked information can be incorporated and used as source information again and again, lending apparent legitimacy to content regardless of its factual nature.

Likewise, AI can be used to alter text, images, audio and videos, further lending credence to inaccurate information and even falsely attributing the information to legitimate journalists and repurposing copyrighted information without attribution.[4]

Teaching LLMs to unlearn information is complex and currently requires human intervention to identify and exclude erroneous content. However, with the volume of information available, the practicalities of this strategy are limited. Therefore, many legitimate sources use human review and verification tools to fact check information prior to publication. These "reviewed by" and "fact checked by" statements incorporated into blogs and articles are important steps in lending legitimacy regardless of how content was generated.

New strategies for countering the capture and use of erroneous data are in development and include flagging AI-generated content so readers can recognize it and further investigate any claims and statements. Another concept

How to ACT with Misinformation

1 Analyze claims.

Don't passively accept that health claims are true. Investigate and critically examine them to determine credibility: Who made the claim? What are their credentials? What research is cited?

2 Communicate with patients.

Engage with patients by listening to their concerns, responding to their questions, confirming what they know to be true and correcting what is false with compassion. Give them trustworthy information in a way they can understand and apply.

3 Tune it out.

When using social media, ignore false information: Don't engage with the algorithm. Liking and sharing false information – even when doing so to set the record straight – will influence the algorithm and increase the false content's visibility. Only engage with accurate information.

is the development of language models that use smaller data sets in an effort to both create a more impactful AI and to provide healthcare entities an opportunity to participate in its design in an evidence-based way.[3]

Addressing Misinformation

Although the prolific nature of false and misleading health information causes mental and social stress, changing one's interpretation of health information is challenging, particularly when that information is viewed as coming from a trusted source. Social media in particular has shown to be a conduit of spreading poor-quality information, as evidenced during the COVID-19 public health emergency, and has led to a host of problems, including vaccine hesitancy.[1] A Kaiser Family Foundation review found that 24 percent of adults surveyed look to social media at least weekly for health information, and 54 percent said they believed at least one false COVID-19 and vaccine statement to be true.[5]

Increasingly, misinformation incorporates more scientific language and fewer emotional statements in an attempt to lend credibility. Therefore, it is important for providers to proactively identify health misinformation trends to which their patients will be exposed, as well as understand how patients are seeking this information and identify the context and framing of how it is presented. For instance, not only is inaccurate information regarding diabetes prolific on YouTube, these inaccurate videos tend to be more popular than others containing evidence-based information.[6]

The American Medical Association (AMA) formally addressed AI in 2018, touting the potential benefits for supporting clinicians. However, they also warned of the potential for AI's misuse, the introduction of bias and how the dissemination of incorrect information can harm patients, providers and the industry as a whole. AMA urges education be at the forefront of patient conversations, including both the benefits and risks of AI-generated information.[7]

Direct and Lasting Impacts

It can be difficult for laypersons to parse out factual health information and to use that information to develop and sustain appropriate health-promoting behaviors. This is where healthcare providers can have a direct and lasting impact through active engagement with patients to discern how well they understand their own health conditions and available treatments. Providers, as trusted entities, can help to correct misinformation regardless of its source in an empathetic and personalized way. These conversations can happen one on one in the treatment room or can take place more broadly through online and in-person community forums that promote health literacy with sound, publicly available information.[8]

Providers are further tasked with staying ahead of available health information that is both factual and that contains misinformation. This will better enable meeting patients where they are. It is important that providers acknowledge any information presented by patients that is in fact factual as opposed to completely disregarding their beliefs. By asking patients open-ended questions and having valuable information readily available, providers can help patients learn to think critically and evaluate their own health assumptions.

Countering the Narratives of Misinformation

One of the best tools available when countering the narratives of misinformation is a discerning eye. Providers should encourage patients to assess the credibility of content by looking at the "About Us" section of a publisher's website and cross-referencing health-related information through CDC.gov and other public health department websites. Patients should also be encouraged to ask questions of their providers.

American Family Physician (AFP) recommends that physicians not engage with false information, even in an effort to correct it online. Algorithms are an important part of Internet search returns, and engaging with content can influence those algorithms, increasing the content's visibility. Instead, AFP recommends providers only "like" and "share" verified information from reliable sources.[9] Likewise, misinformation can be reported directly to most social media platforms, some of which are additionally working with WHO and other authorities to screen for medical misinformation.[10]

All of this being said, without question, social media can be an incredibly valuable tool to quickly gather and disseminate health information. In fact, some believe that government and health institutions should increase their social media presence because of its power, particularly during pandemics,[6] to get and stay ahead of potentially harmful information that could have negative consequences on public health.

It takes time, active listening and empathy to help patients counter their fears. Providers must arm patients with written information in a language in which they are fluent, and include infographics for particularly complicated topics so they have valuable facts to consider even after they've left the office. They should make sure patients understand what they have heard during their office visit, and

inquire how they feel about it in an effort to address any lasting concerns.[9]

HIPAA, Ethical and Legal Considerations

A final note about use of AI in healthcare information concerns privacy. AI use introduces liability concerns for HIPAA-covered entities. The HHS OCR urges a thorough AI-focused threat analysis and the development and strengthening of comprehensive mitigation plans. Employees and contractors should have appropriate cybersecurity training, and entities can execute incidence response protocols and regularly review regulatory and best practice frameworks that affect AI in healthcare settings. Importantly, the use of AI tools must be disclosed to patients. And, there must be consideration of billing development practices when using AI-assisted tools.[2]

Powerful but Challenging

Although AI is a powerful tool for healthcare entities, it can also introduce serious challenges, including the introduction and proliferation of misinformation. Unchecked, this information can spread, potentially causing widespread harm. While tools are in development to counter these threats, providers can help alleviate patient stress through open communication and empathetic listening so patients can learn to vet information and make sound decisions regarding their health. ❖

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Solving Clinical Trial Delays by Accelerating Patient Recruitment

Enrolling patients in clinical trials is a slow and costly process, but software companies are working to address the problem.

By Diane L.M. Cook

CLINICAL TRIALS are the linchpin for bringing new medications to market, and they depend on patient participation. However, stalled patient recruitment is a significant, ongoing problem that leads to unwanted trial delays. In fact, a recent review and meta-analysis of online patient recruitment for clinical trials revealed that patient recruitment is the primary cause of trial delays. "Around 80 percent of trials fail to meet the initial enrollment target and timeline, and these delays can result in lost revenue of as much as $8 million per day for drug developing companies."[1]

The extent of the problem is no secret. According to Attila A. Seyhan, PhD, director of translational oncology operations at the Cancer Center at Brown University, "The crisis involving the translation of basic scientific findings in a laboratory setting into human applications and potential treatments or biomarkers for a disease is widely recognized both in academic and industry."[2] Harsha Rajasimha, PhD, founding member of the Organization for Rare Diseases in India, concurs. In fact, Dr. Rajasimha revealed that the difficulty of getting candidate drugs approved by the U.S. Food and Drug Administration (FDA) is so well-known that the regulatory review process is colloquially referred to as the "Valley of Death."

"The FDA's process averages about seven years in the clinical development phase, but for a total of 12 to 15 years, with only an average of about one out of every 10 candidate drugs, or 12 percent of the candidate drugs, actually receiving regulatory approval and making it to market," Dr. Rajasimha explained.[3] Further, the process is also very expensive. "It can cost over $2.5 billion to bring one successful candidate drug to market because pharmaceutical companies have to underwrite the cost of the nine drugs that failed to receive FDA approval," he added. "The burden of getting that one successful drug to market means that there are nine potential failures before that happens."[3]

Further, travel and logistical burdens, restricting search to a five-mile radius of selected investigator sites due to expectation of in-person visits each time, high screen failure rates demanding higher number of potential subjects, and effort involved for participants during the active period of the clinical trial all cause costly delays in clinical trials.

To solve the mulitfaceted challenge of addressing clinical trial delays and getting more drugs to market, patient recruitment needs to be accelerated. And, software developers may be part of the answer: They have entered the digital health technology space to address the challenges of online patient recruitment so pharmaceutical companies can efficiently start and successfully complete their clinical trials. Here are three companies that are working to help pharmaceutical companies accelerate clinical trial patient recruitment.

Jeeva Clinical Trials Inc.

Jeeva Clinical Trials Inc. is a clinical trial software company that developed the Jeeva eClinical Cloud, a software as a service (SaaS) platform driven by artificial intelligence (AI), to accelerate clinical trial timelines, electronic data capture efficiencies and remote clinical outcome assessments of participants in therapeutic areas such as oncology, rare diseases and chronic conditions by eliminating the bottlenecks commonly found in the clinical trial process.

According to Dr. Rajasimha, who is also the founder and chief executive officer of Jeeva Clinical Trials Inc., "The Jeeva eClinical Cloud platform effectively tackles the challenges of patient recruitment and retention in clinical trials through a multifaceted approach integrated into a single modern technology platform. It expedites patient recruitment timelines by three times while cutting costs by 50 percent and minimizing user burden by 80 percent. With an integrated calendar scheduling system, Jeeva minimizes the risks of missed participant appointments and the burden of appointment management."

This is achieved with:

- *Streamlined processes.* Restructuring configuration of study databases, enabling rapid remote eligibility screening, and facilitating electronic informed consent, electronic clinical outcomes assessments and electronic patient-reported outcomes all contribute to a more efficient process.

• *Efficient design*. The eClinical Cloud is protocol-fit, disease-neutral, device-agnostic, flexible and modular to support patient-centered, modern clinical trials that are significantly more efficient and accessible to most patients. It was designed for ease of use, efficiency and collaboration among sponsors, and for investigator teams and participants to have real-time access to the same centralized study database.

• *Unified platform*. The eClinical Cloud allows sponsors to conduct efficient trials at single or multiple centers with central institutional review boards (IRBs) or site-specific IRBs on a unified clinical trial management platform to engage, screen and enroll participants remotely from the convenience of their homes from multiple channels such as social media advertising, online ads, email campaigns, SMS campaigns and other connected networks. With one unified platform, the eClinical Cloud configures versatile trial protocol designs and minimizes manual effort with the ability to make remote clinical assessments, televisits and intelligent automation built into the platform. "The platform supports remote and hybrid clinical research models, allowing for greater flexibility and accessibility for participants. Thus, Jeeva has become a crucial solution for enrolling and engaging diverse patients in clinical studies," explained Dr. Rajasimha.

4) *Personalized engagement*. The eClinical Cloud enables personalized patient engagement for minimizing drop-out rates, especially in long-term clinical trials. The platform fosters a strong connection with participants, thereby improving patient retention rates. This emphasis on the patient-centric approach contributes to the success of long-term trials, ultimately enhancing the quality and reliability of the research conducted on the platform.

Results are promising. According to Dr. Rajasimha, "Since the Jeeva eClinical Cloud was commercially launched in the fourth quarter of 2021, 16 clinical studies are successfully running on the platform, including one approved CAR T cell/gene therapy for B-cell lymphomas. All clinical trials are renewing year-on-year and new studies are onboarding with confidence as we achieve significant software quality, validation and compliance. Jeeva is thrilled to note that all clinical studies are achieving their patient enrollment goals and are well-positioned to be completed successfully."

Antidote Technologies Inc.

Antidote Technologies Inc. is a cloud-based patient engagement company that enables faster medical innovation by transforming how sponsors and patients connect. The company uses its clinical trial search tool, Antidote Match, to connect patients with research opportunities in a streamlined manner.

Chief Product Officer Sam Veeck says the company designs their products to be simple and effective, making the user experience positive and productive for patients. "Finding clinical trials can be a daunting experience for many patients, but as we know, patients need to get these drugs approved and to market. Therefore, our user experience is centered on enabling patients to find suitable trials with ease. Ultimately, the more effective our Antidote Match platform is, the more patients we are able to filter into clinical trials, increasing Big Pharma's likelihood of bringing their drugs to market."

Antidote Match:

• Uses structured eligibility criteria and proprietary algorithms to provide a user-friendly alternative to ClinicalTrials.gov. Individuals interested in participating in a clinical trial are able to answer just a few questions and find active research opportunities for which they might be eligible. They are also given the opportunity to sign up for trial alerts to get emails about new studies that align with their search parameters.

• Uses inclusionary/exclusionary logic and proprietary ontology to ask questions most relevant to the clinical trials in which patients are interested. This is done by codifying the text of inclusion/exclusion criteria into machine-readable logic to create a patient-centric list of search results that is easy to navigate and understand.

• Pulls clinical trial listings from ClinicalTrials.gov, and uses structured data and proprietary algorithms to explore patients' eligibility as they answer questions. It collects the complex information and medical jargon included in a trial listing and translates it so it's easy to comprehend. Patients can opt-in to receive alerts when new trials that fit their profiles become "live," allowing them to find out about research opportunities on an ongoing basis.

• Thoroughly verifies patients' potential eligibility before referring them to sites with the use of a study-specific landing page, custom prescreener and subsequent phone validation.

Antidote offers patients the ability to learn more about clinical trial opportunities in this streamlined manner. It also offers sponsors the ability to accelerate their research with its patient recruitment services and helps them fill clinical trials faster. Not only is it able to reach patients others cannot through its extensive network of industry partners and patient advocacy groups, but the company also does extensive condition research to conduct optimized digital marketing campaigns that reach the most qualified patients — and it appears to be working. For example, in a U.S. Alzheimer's study, Antidote Match's

platform achieved a 267 percent patient recruitment goal delivery.

Antidote Match is offered on the Antidote Technology Inc. website, as well as free of charge to hundreds of patient advocacy organizations that advance clinical trial awareness and access for millions of patients. The company also licenses its matching platform with pharmaceutical companies and corporations and configures its product based on their clinical trial specifications and requirements.

Within3

Within3 built the world's first insights management platform (IMP) for life science companies to gather the insights that drive innovation and deliver powerful results for businesses and life-changing results for patients around the world. The company's AI-powered, cloud-based insights management SaaS-based platform helps life science companies make faster, better decisions across the product life cycle.

• *Clinical trial design and operations.* The platform supports many activities related to clinical trial design and operations, including gathering feedback in the preclinical stage, engaging patients and investigators to understand better trial design, and engaging doctors and nurses to get feedback on proposed trial protocols from different perspectives.

• *Strategic insight generation*. According to Kristen Bushka, vice president of the Insights Solutions Group at Within3, "The IMP includes several components that support pharmaceutical teams in strategic insight generation, including advanced network analytics, social media listening, group engagement capabilities and AI-powered analysis and reporting." Sponsors can use Within3's IMP to shorten their clinical trial protocol development timelines, improve patient recruitment and retention, and gather patient feedback.

Pharmaceutical teams can use Within3's IMP throughout the drug commercialization process to identify key external experts; monitor social channels to understand prevailing sentiment about brands, disease states, competitors or scientific information; hold discussions and gather insight via a group engagement application; and shorten analysis and reporting timelines through the application of unique and secure AI. Within3 works with the world's top 20 global pharmaceutical companies.

One example of how Within3's IMP can help pharmaceutical teams is from one client who wanted to recruit 700 patients for a Phase III randomized cancer trial slated to run across multiple countries simultaneously. The client company saw this trial as an opportunity to improve outcomes for patients with the most common form of the disease. The client company wanted to tackle one of the primary reasons for recruitment failure: poor site engagement.

Using the Within3 IMP's group engagement capabilities, the client company quickly trained and onboarded sites across multiple locations. Live and in-platform translation functionality meant all participants could engage in their native language asynchronously at a time and place that worked for them. The result was extraordinarily engaging live meetings with more than 80 percent of training completion on the platform. As a result, the client company met its recruitment targets earlier than expected by ensuring trial sites were well-trained and adequately engaged.

Looking Forward

According to Dr. Seyhan, some progress has been made across the preclinical and clinical divide. Pharmaceutical companies are now using open innovation models to address research and development challenges; a new breed of pharmaceutical companies from emerging economies are using research and development and business models that challenge U.S. and European models; and, perhaps most importantly, using AI in biomedical research and development will affect the future of pharmaceutical research and development.[2] In fact, Rejuve Biotech Chief Executive Officer and senior biologist Kennedy Schaal says that AI in biomedical research is revolutionizing drug development and clinical innovation by predicting clinical trial outcomes. "AI algorithms can analyze data from past trials to predict the outcomes of new clinical trials better. This can help improve trial design and recruitment."[4]

If pharmaceutical companies can solve their clinical trial delays by accelerating patient recruitment and retaining their participant population throughout the trial process, more drugs could potentially be more successful in surviving the Valley of Death and go on to receive FDA approval. This would result in more drugs becoming available to more patients in a timelier manner to treat or cure their illnesses and diseases. ❖

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Caring for Mental Health in a World of Uncertainty

Post-pandemic America is facing a mental health crisis, but collaboration and creativity in healthcare aim to improve the nation's mental wellness.

By Lee Warren

IN THE WAKE of the unprecedented global events of the past few years, our country is grappling with a profound mental health crisis. Recent studies underscore the heightened likelihood of an escalating burden of mental health disorders in the post-pandemic era, reflecting a spectrum of challenges, from anxiety and depression to substance abuse and suicidal tendencies. As we navigate this era of uncertainty, the statistics paint a concerning picture.

Each year, more than 20 percent of U.S. adults experience mental illness (57.8 million in 2021); just over five percent experience serious mental illness; and nearly 17 percent of U.S. youth between the ages of 6 and 17 experienced a mental health disorder in 2016. And, suicide is the second leading cause of death among people between the ages of 10 and 14.[1]

Mental illnesses include varying degrees of severity, ranging from mild to moderate to severe. In a 2021 study, the prevalence of any mental illness (AMI) was higher among females (27.2 percent) than males (18.1 percent). Young adults aged 18 to 25 years had the highest prevalence of AMI (33.7 percent) compared to adults aged 26 to 49 years (28.1 percent) or aged 50 and older (15.0 percent).[2] And, some demographics are more susceptible than others to mental health challenges (Table 1).

The Pandemic Effect

In December 2021, the *New York Times* asked 1,320 mental health professionals how their patients were coping as pandemic restrictions eased. Nine out of 10 therapists said the number of clients seeking care is on the rise, and most are experiencing a significant surge in appointment calls and longer waiting lists.[3]

One Boston University study revealed that depression rates tripled, and symptoms worsened during the pandemic. The statistics reveal an increase in depressive symptoms in Americans from 2021 (32.8 percent) compared to 2020 (27.8 percent), with just 8.5 percent before the pandemic.[4]

During the pandemic, at least four in 10 adults (41 percent) experienced high levels of psychological distress, and more than a third (37 percent) of high school students reported mental health challenges.[5]

But the pandemic isn't the only cause. The list of additional reasons for the mental health crisis is a long one, including but not limited to patients with social and economic inequalities, public health emergencies, traumatic events, economic stressors, the death of a loved one, divorce, political unrest, war, genetic factors, chronic homelessness, loneliness, climate change, childhood sexual abuse, as well as exposure to toxins, alcohol or drugs while in the womb. Further, technology also contributes to feelings of isolation, loneliness and depression among an older demographic that struggles to use it, and students are facing challenges that are unique to their generation in the form of cyberbullying.

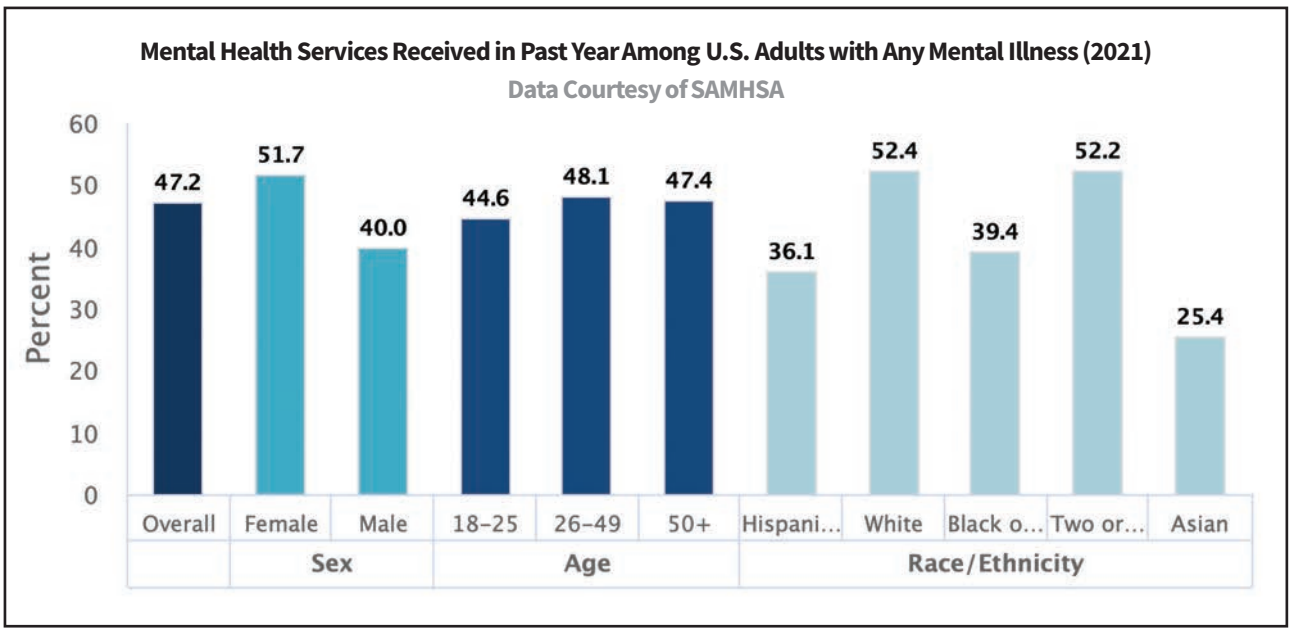
The Medical Crisis

When considering all these modern mental health challenges, it's understandable why mental health services jumped by 38.8 percent among U.S. adults with commercial health insurance between 2019 and 2022.[6] The increase has put a real strain on the healthcare system. Another study paints an even clearer, more disturbing picture: One-third of respondents could not get the mental health services they needed.

Table 1. Annual Prevalence Rates of Any Mental Illness Among All U.S. Adults by Demographic Group

Demographic	Prevalence
All adults	23%
Asian adults	16%
Native Hawaiian or Pacific Islander Adults	18%
Black Adults	21%
Hispanic or Latino Adults	21%
White Adults	24%
American Indian or Alaskan Native Adults	27%
Adults who Report Mixed/Multiracial	35%
Lesbian, Gay or Bisexual Adults	50%

Source: National Alliance on Mental Illness. You Are Not Alone. Accessed at www.nami.org/NAMI/media/NAMI-Media/Infographics/NAMI_YouAreNotAlone_2023.pdf.



Eighty percent cited cost, and more than 60 percent pointed to shame and stigma as the primary obstacles.

Complicating matters further, 60 percent of psychologists do not have openings for new patients.[7] In a study of more than 16,000 psychologists, more than half (56 percent) do not even keep waitlists. Of those who do, 17 percent reported their waitlist had shortened while more than double (38 percent) reported that their waitlist had grown over the previous 12 months. Not only is demand for services up, but psychologists are reporting an increase in the severity of symptoms among patients, and many say an increased length of treatment is necessary for existing patients. Perhaps it's no wonder that in that same study, 36 percent of psychologists said they are burned out.[8]

As a result, in another study, one in five psychologists (21 percent) said that they were planning to reduce their practice hours in the next year. The good news is nearly three-quarters (73 percent) said they were able to practice self-care and nearly two-thirds (63 percent) said they were able to maintain a positive work-life balance.[9]

The Medical Response

For all these reasons, the medical response to the mental health crisis is complicated, multifaceted and, in some cases, broader than one might expect. Here are some approaches:

• *Telehealth*. The idea behind telehealth, which was used extensively during the pandemic, is that it allows patients to be seen faster and, therefore, diagnosed earlier so they can be more efficiently and effectively treated. Telehealth allows in-person therapists to focus on higher acuity patients who truly require them.

• *Digital self-help tools*. Wearable devices, sensors and mental health apps are being used to point patients toward proper diagnosis and care. These tools can provide remote monitoring, as well as real-time data collection and intervention. For example, some of these tools can target trauma (such as post-traumatic stress disorder); some can help women adjust to menopause; and still others can help patients with anxiety. These allow patients to be treated for whichever specific mental or behavioral health issue they are experiencing.[10]

• *Integration of mental health into primary care*. Emphasizing a collaborative approach addresses mental health issues early on and eases the burden on providers. One study said more than four in five psychologists (86 percent) have worked alongside other healthcare providers. Seventy six percent of psychologists said they collaborate with psychiatrists; 45 percent said they collaborate with other physicians (occupational therapists [30 percent], physician assistants [41 percent], community health workers [30 percent] and speech language pathologists [28 percent]).[9] Healthcare workers are also receiving ongoing training to enhance their understanding of many variations of mental health issues that patients face.

• *Crisis intervention programs and hotlines*. These services give distressed patients access to mental health professionals who can provide immediate support. In 2022, the National Suicide Prevention Lifeline's 10-digit phone number changed to 988, making it easier to remember and quicker to dial. It offers crisis care and also links to the Veterans Crisis Line, putting people in crisis in reach of the professional help they need.

• *Community or county mental health center programs.* These facilities provide outpatient services, medication management, case management services and more. They often manage contracts with mental health service providers such as psychiatrists, psychologists, social workers and counselors, and make referrals. The centers often allow for emergency walk-in services and some have mobile crisis units.[11]

• *School-based cognitive behavioral therapy*. This therapy is led by trained school staff or other designated health leaders. One study of such a group of 41 participating schools that taught emotional regulation, anxiety management and problem-solving were randomized into three arms: health-led, school-led and a comparison group of personal, social and health education that was provided by the school staff. The health-led group was more effective in decreasing social anxiety and generalized anxiety.[12]

• *Federal funding*. In 2022, the Department of Health and Human Services, through the Substance Abuse and Mental Health Services Administration and the Office of Minority Health, announced a $35 million plan to fund opportunities to strengthen and expand community mental health services and suicide prevention programs for America's children and young adults through seven types of grants.[13]

• *Mindfulness-based interventions*. These strategies incorporate mindfulness practices such as meditation, yoga and art therapy. This option is especially used among Generation Z, which is said to be one of the most stressed generations of our time.

• *Workplace mental health initiatives*. These programs are good options for helping employees reduce stress and promote a work-life balance, as well as overall health. Certified Angus Beef and TiER1 Performance Solutions are two such companies. Certified Angus Beef provides on-site wellness consultations with a clinical psychologist in addition to holding lunchtime learning sessions regarding mental health stigma, as well as promotion services that are available to employees. TiER1 Performance Solutions has a "Start the Conversation about Mental Illness Awareness" campaign that focuses on depression, anxiety, obsessive-compulsive disorder, schizophrenia, bipolar disorder and addictions.[14]

• *Artificial intelligence (AI)*. AI is allowing doctors to obtain a more comprehensive understanding of patients' mental health by gathering feedback and following trends.[15] It's also being used to analyze medical images to expedite pathology assessments. Further, it's being used to assist with diagnoses faster and more accurately. And, AI can help minimize wait times for patients. Humber River Hospital in Toronto was the first in Canada to track and control patient flow with AI.

Ongoing Challenges, Original Solutions

While formidable challenges exist in our current mental health crisis, collective efforts are being made to address and alleviate the burden on our healthcare system. The array of options available today reflects a departure from the limitations of the past, offering new avenues for individuals to seek and receive support. While the challenges are real, so are the solutions. It is crucial to continue fostering awareness, dismantling the stigma and advocating for improved access to mental health services. As communities consistently prioritize mental well-being, a sense of hope will emerge in the ongoing commitment to care for those genuinely in need. ❖

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Update on **Malaria**

While malaria is no longer endemic in the United States, the mosquito-borne disease can still affect those who live in or travel to tropical areas of the globe.

By Jim Trageser

GIVE THE British foot soldier credit for creativity in medication: When treating patients in their care, 19th century British army doctors in colonial India prescribed quinine — the only available cure for malaria at that time. Young British army soldiers billeted to the region grew to hate the bitter taste of quinine, but after a bit of experimenting with different combinations of spirits, sugar and fruit, they came up with something palatable: the classic gin and tonic cocktail.[1]

While British soldiers developed the gin and tonic cocktail, credit for the discovery of quinine lies with the indigenous peoples of the Andes who taught 17th century European Catholic missionaries called the Jesuits about the healing properties of the native cinchona tree's bark, which is highly effective in treating fevers. The Jesuits went on to share this knowledge with their fellow Europeans.

As trade and conquest brought Europeans into more and more tropical areas where the malaria-causing parasite *Plasmodium* was prevalent, the Europeans brought quinine with them to fight it. The Dutch were soon growing the cinchona tree in tropical Indonesia, while the British planted orchards in the Tamil and West Bengal regions of India. Both options were far less expensive and more reliable than importing the tree bark from the Pacific coast of South America.[2]

However, as delicious as a gin and tonic may be, it is no longer a recommended treatment for malaria. Modern tonic water contains far less quinine than it did in previous decades, making it medicinally ineffective. And, although there are five different *Plasmodium* species known to affect humans, it turns out that quinine is effective only against one of them: *Plasmodium falciparum* (*P. falciparum*).[3,4]

Fortunately, during World War II, research into developing synthetic alternatives to quinine was ramped up, resulting in primaquine. In the decades since then, modern medicine has developed numerous treatments for malaria that are not only able to work against all variants of the causative parasite, but that also spare patients the bitter taste of quinine and the not-insignificant side effects of gin. While capsule-form quinine is still prescribed for treating *P. falciparum* in locations where more modern prescriptions are unavailable, it is now only one option in the contemporary physician's arsenal.

Plasmodium cannot survive outside of a host, and the five *Plasmodium* species that can infect humans are all spread by mosquitoes. *Plasmodium* rely on both human and mosquito hosts for different parts of its life cycle, and need to move from human to mosquito to successfully reproduce. As with other blood-borne diseases, it can also be spread through blood transfusion, organ transplant and sharing dirty needles, and it can be passed from an expectant mother to her unborn child.

Of the five known species that can infect humans, four are specific to us while one is naturally hosted in macaque monkeys but can be spread to humans.[6]

Malaria is relatively rare in the developed world, particularly in temperate areas.

What Is Malaria?

Malaria is a serious, often deadly infectious disease caused by a single-cell protozoa of the *Plasmodium* genus. Like humans, *Plasmodium* are eukaryotes (organisms that have a cellular nucleus).[5] This makes them more closely related to paramecia or amoeba than bacteria, which lack a nucleus.

The four that are unique to humans are *P. falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*. *Plasmodium knowlesi* (*P. knowlesi*) is naturally hosted in macaque monkeys and is mostly found in Southeast Asia.[6]

Malaria is relatively rare in the developed world, particularly in temperate areas. The United States averages just

1,500 cases per year (about five of them fatal), with nearly all cases contracted by those who had traveled to other parts of the world.[7]

Globally, however, malaria remains a deadly scourge, with 228 million cases per year resulting in more than 400,000 deaths.[8] It is still endemic in more than 90 nations, leaving 40 percent of the globe's population at risk — and it is especially dangerous in young children.[9] (Another high-risk group is travelers from areas like the United States who are less likely to have developed immunity.[9])

P. falciparum is by far the most prevalent species, accounting for 90 percent of all cases.[8] As with the other four species, *P. falciparum* is spread to a human host via an infected female mosquito of the genus *Anopheles* — about four dozen species of which are known to carry malaria.[10]

The protozoa enter the bloodstream in a spore-like state when the mosquito injects infected saliva while feeding (a previously uninfected mosquito will become infected when feeding on an already-infected human host). These sporozoites migrate through the bloodstream to the liver, where they begin to rapidly multiply and are then rereleased back into red blood cells. After several cycles of this, these spores develop into gametes, and if the host is again bitten by a mosquito, these gametes will be transferred back to the mosquito where they will combine for sexual reproduction in the gut of the mosquito.[6]

Symptoms and Diagnosis

It is during the period when the sporozoites are multiplying in the liver and being released into the bloodstream that individuals will begin to feel sick. Symptoms are similar across all malaria variants, and can resemble those of viral infections:[11]

- Fever (often a high fever)
- Chills
- Unusual sweating
- Nausea
- Diarrhea
- Fatigue
- Abdominal pain
- Muscle and joint pain
- Cough
- Increased heart rate

If left untreated, malaria can cause significant side effects, several of which can prove fatal:

- Organ failure: The infection can cause the spleen to rupture or the kidneys or liver to fail.
- Cerebral malaria: The red blood cells increase in size when infected by the parasite, and these enlarged cells can block small blood vessels in the brain, causing a stroke or even coma.
- Anemia: If too many red blood cells are infected, there may not be enough healthy red cells left to deliver oxygen throughout the body.

Diagnosis is usually made by a blood smear, which can also identify the species of *Plasmodium* and how many are in the bloodstream, which is useful in plotting treatment.[12] Because of the rapidity at which malaria progresses, it is recommended that any undiagnosed fever be considered for malaria, as a fast diagnosis is key to effective treatment. Tests should be ordered immediately if patients report travel to areas of active malaria infection, or when tests for other diseases come back negative. If the first round of blood smear tests are negative, they should be repeated at 12 and 24 hours to confirm the negative diagnosis.

While several blood assays can indicate a malaria infection, they do not yet accurately indicate the species nor the parasite count, so a positive blood test should still be followed by a blood smear.

Since malaria is a reportable infection in the United States,[13] physicians who confirm a diagnosis will be in contact with public health authorities and have access to their information and resources when working with patients to chart their treatment.

While there is no vaccine, those who are traveling to an area where malaria is endemic can lower their risk by taking antimalarials.

Treatment

Treatment will primarily consist of prescription drugs to kill the invading parasite in patients' bodies. The main drug currently used in treating malaria is chloroquine phosphate; dosage and frequency will vary based on patients' age and severity of infection.

P. falciparum is developing resistance to chloroquine phosphate in many parts of the world, though, so now artemisinin-based combination therapies (ACT) are often recommended as the first-line treatment. These multi-drug cocktails gain their efficacy by killing the *P. falciparum* in all its different stages of development, from spore to gamete. Examples of ACT treatments include artemether-lumefantrine, artesunate-mefloquine and atovaquone-proguanil.[14]

Other drug treatments that may be used, depending on the species, resistance and previous bouts with malaria by patients, may include quinine sulfate (Qualaquin) with doxycycline or primaquine phosphate. In addition, the efficacy of quinine has been found to improve significantly when administered along with tetracycline or clindamycin.[15]

The Centers for Disease Control and Prevention (CDC) has a chart to aid physicians in treating malaria (available at www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table_202306.pdf). The chart organizes treatment based on the region in which a patient contracted the malaria, which species of *Plasmodium* is present (if detected in the blood smear test), whether the species is known to be drug-resistant and recommendations based on age.

If a patient is pregnant, quinine can still be used in combination with clindamycin during the first trimester to avoid developmental harm to the child.[15] The standard ACT treatments listed above can safely be used during the second and third trimesters.

For severe cases of malaria, the drugs need to get into a patient's system as quickly as possible. Prescriptions will typically be injected, either intravenously or intramuscularly, for 24 hours until high-dosage oral versions can be tolerated.[8] Again, the CDC chart provides specific, updated guidance for each combination of region, patient age and drug-resistance.

Because of the risk of rapid progression of the infection and the dangers of lethal complications, it is recommended that all *P. falciparum* and *P. knowlesi* patients be admitted to a hospital immediately.[8]

CDC maintains a hotline for physicians to call to get the latest information on treating malaria: (855) 856-4713 during East Coast regular business hours, and (770) 488-7100 on holidays, weekends and overnight.

Prevention

Prevention remains the best treatment option. While malaria was formerly endemic in parts of the United States, particularly in warmer regions in the Southeast, a coordinated effort organized by the federal government led to its elimination by 1951. This was accomplished by destroying the breeding habitat of the mosquitoes that transmitted malaria through wetlands drainage and spraying of insecticides.[16]

This federal effort was, in fact, what led to the formation of the CDC. However, many developing nations lack the resources to mount such a campaign.

While there is no vaccine to prevent malaria, those who are traveling to an area where malaria is endemic can lower their risk by taking antimalarials ahead of time and throughout the trip.[17] The specific drug or drugs to be prescribed will depend on their itinerary.

Even if travelers are taking precautionary prescriptions, avoiding infection should be their ultimate goal. Covering arms and legs and using repellents are all important parts of prevention, as are insecticide-treated netting to keep out the malaria-carrying mosquitoes.

Looking Forward

As with most diseases caused by protozoa, there is, as mentioned above, currently no vaccine for malaria. (Only three protozoa-caused diseases currently have an approved inoculation.[18])

However, given the severity and human cost of malaria worldwide, the U.S. Food and Drug Administration's clinicaltrials.gov website lists 300 recent or ongoing trials into a malaria vaccine. Still, until a vaccine is developed, even physicians in countries where malaria no longer exists in the wild will have to be prepared to treat patients who travel abroad and contract the disease.

Given the growing resistance of the *Plasmodium* parasites to existing antiprotozoal drugs, many of the 1,300 total clinical trials studying malaria are looking at new classes of drugs, or new combinations, some of which will undoubtedly enter the pipeline before too long.

Keeping that CDC hotline number handy will be the most effective way of determining state-of-the-art treatment when a blood smear comes back positive. ❖

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Myths & Facts: Sleep Disorders

Sleep disorders are responsible for a host of physical and mental health conditions, making it essential to dispel the myths surrounding them and to promote education and awareness about the importance of sleep health.

By Ronale Tucker Rhodes, MS

SLEEP SCIENCE has rapidly advanced in the past 20 years, providing expanded insight about the importance of sleep, the biological mechanisms that control sleep and the ways it can be disrupted.[1] In fact, a lack of sleep can cause various concerns with mental and physical health in the long term.

According to estimates, 50 million to 70 million people have ongoing sleep disorders, with the most common among them being insomnia, sleep apnea (a common condition in which breathing stops and restarts many times while sleeping) and narcolepsy (feeling very drowsy during the day).[2] Indeed, nearly one-third of U.S. adults report getting less than the recommended amount of sleep. Lack of sleep is linked to many chronic diseases and conditions such as type 2 diabetes, heart disease, obesity and depression, and it can lead to motor vehicle crashes and mistakes at work, which cause a lot of injury and disability each year.[3]

Yet, despite this advanced knowledge, false information about sleep is commonly spread online or by word of mouth, according to experts at the Sleep Foundation, who say "some of this false information is repeated so often that it becomes a widely held belief, many of which can lead to poor sleep habits and insufficient sleep."[1] So, not only can dispelling the myths surrounding sleep disorders help improve individuals' health, understanding more about sleep duration and sleep insufficiency can help organizations develop programs to prioritize efforts to improve sleep health.

Separating Myth from Fact

Myth: Insomnia means having trouble falling asleep.

Fact: Trouble falling asleep can be a sign of insomnia, but there are a lot more symptoms of insomnia, including waking up too early and not being able to get back

to sleep, frequent awakenings and waking up feeling exhausted.[4] According to the National Institutes of Health, short-term insomnia may be caused by stress or changes in one's schedule or environment, and it can last for a few days or weeks. On the other hand, chronic (long-term) insomnia occurs three or more nights a week, lasts more than three months and cannot be fully explained by another health problem.[5]

Common causes of insomnia include medications that interfere with sleep; dietary choices such as caffeine later in the day that interfere with sleep; stress thoughts; depression; recent upheavals in one's life such as divorce or the death of a loved one; hormone changes such as those accompanying menopause; bedtime habits that don't lead to restful sleep; sleep disorders; chronic pain; medical conditions such as acid reflux, thyroid problems, stroke or asthma; substances like alcohol and nicotine; and travel, especially between time zones.[6]

Myth: Men and women have equal risk of insomnia.

Fact: Actually, women are twice as likely to have insomnia than men, and older adults are more likely to experience insomnia.[7] Insomnia is also more common among shift workers who don't have consistent sleep schedules, people with low incomes, people who have a history of depression and those who don't get much physical activity.[6]

Myth: A lack of sleep causes narcolepsy.

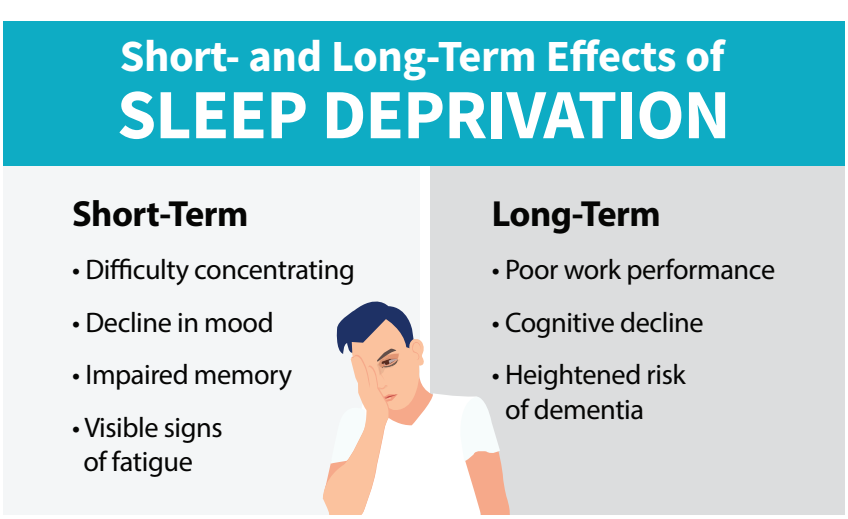
Fact: While a lack of restful sleep *can* be a cause of narcolepsy, there are many other causes as well. Narcolepsy is a sleep disorder that affects the brain's ability to regulate sleep-wake cycles and causes persistent daytime sleepiness. Symptoms include severe and persistent drowsiness that can cause impairments in school, work and social settings, as well as a heightened risk of serious accidents and injuries. Even though narcolepsy is rare compared to other sleep disorders, it affects hundreds of thousands of Americans, including both children and adults.

According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), there are two types of narcolepsy: narcolepsy type 1 (NT1) and type 2 (NT2). NT1 is identified by cataplexy (sudden loss of muscle tone) and the loss of neurons in the brain responsible for making hypocretin, also known as orexin, a chemical that helps regulate wakefulness and sleep. People with NT1 have a loss of 90 percent or more of the normal amount of hypocretin-making neurons. Researchers have also found that as many as 98 percent of people with NT1 carry a gene variation known as DQB1*0602, which could cause a genetic susceptibility to NT1, but it is not yet definitively proven. And, most individual cases of NT1 occur with no clear, direct cause. Some experts believe NT2 is a less pronounced loss of hypocretin-producing neurons, while others think NT2 may primarily be a precursor to NT1. However, cataplexy has only been observed to develop in about 10 percent of cases of people initially diagnosed with NT2, and once cataplexy develops, people can be rediagnosed with NT1. In some instances, NT2 has been reported following a viral infection, but most cases do not have an established cause. And, as with NT1, NT2 can arise because of other medical conditions such as head trauma, multiple sclerosis and other diseases affecting the brain.[8]

Myth: Individuals need a minimum of eight hours of sleep a night.

Fact: Everyone has different sleep needs based on factors such as age, activity levels and sleep patterns. Therefore, the eight-hour rule is not necessarily the "perfect amount" of sleep. In fact, trying to follow a set rule for an exact number of hours of sleep can cause sleep anxiety, leading to lower-quality sleep.[9] What's more important is the number of times a person goes through a sleep cycle and experiences the different stages of sleep: non-REM sleep and REM sleep. (REM is the acronym for rapid eye movement, named for the way the eyes erratically move behind the eyelids during this sleep stage.)

Non-REM happens first and includes three stages. Non-REM stage N1 is the typical transition from wakefulness to sleep and generally lasts only a few minutes. It is the lightest stage of sleep.



During this stage, eye movements are typically slow and rolling, heartbeat and breathing slow down, muscles begin to relax and low amplitude mixed frequency waves in the theta range (4 to 7 Hz) are produced. NREM stage N2 is the next stage of non-REM sleep, which comprises the largest percentage of total sleep time and is considered a lighter stage of sleep from which a person can be easily awakened. This is the stage before a person enters deep sleep. During this stage, heartbeat and breathing slow down further, there are no eye movements, body temperature drops, and sleep spindles and K-complexes are two distinct brain wave features that appear for the first time. NREM stage N3, the final stage of non-REM sleep, is the deepest sleep stage. During this stage, arousal from sleep is difficult, heartbeat and breathing are at their slowest rate, there is no eye movement, the body is fully relaxed, delta brain waves are present, tissue repairs and grows, cell regeneration occurs and the immune system strengthens.

There are two phases of REM sleep: phasic and tonic. Phasic REM sleep contains bursts of rapid eye movements, while tonic REM sleep does not. REM sleep occurs about 90 minutes after falling asleep and is the primary "dreaming" stage of sleep. It lasts roughly 10 minutes the first time, increasing with each REM cycle. The final cycle of REM sleep may last roughly between 30 to 60 minutes. During this stage, eye movements become rapid, breathing and heart rate increase and become more variable, muscles become paralyzed (but twitches may occur) and brain activity is markedly increased.[10]

Myth: The brain rests during sleep.

Fact: The *body* rests during sleep, but the brain remains active, gets recharged and still controls many body functions, including breathing. As previously stated, the brain typically drifts between two sleep states, REM sleep and non-REM sleep, making the brain active during sleep.[4]

REM sleep is the stage of sleep when people usually have vivid dreams. While it isn't the only stage of sleep when people can dream, it tends to be the stage in which people have the most intense dreams. During the REM stage of sleep, brain activity is similar to when people are awake, which may explain why vivid dreams occur.[9]

Myth: Older adults need less sleep.

Fact: Older adult sleep patterns change, but the amount of sleep they need doesn't. As people age, certain changes happen in their hormones and circadian rhythm, both of which affect sleep patterns. This may cause older adults to experience sleeplessness at night and wake up more often, which means they may spend more time awake.[9]

According to the Sleep Foundation, changes in the quality and duration of sleep in older adults occur due to changes in the body's internal clock, which is located in a part of the brain called the hypothalamus and is made up of approximately 20,000 cells that form the suprachiasmatic nucleus (SCN). The SCN controls 24-hour daily cycles, called circadian rhythms, that influence when people get hungry, when the body releases certain hormones and when a person feels sleepy or alert. Deterioration in the function of the SCN can disrupt circadian rhythms, directly influencing when people feel tired and alert. The SCN receives information from the eyes, and light is one of the most powerful cues for maintaining circadian rhythms. Unfortunately, research shows that many older people have insufficient exposure to daylight, averaging around one hour each day. In addition, changes in production of hormones such as melatonin and cortisol may also play a role in disrupted sleep in older adults. As people age, the body secretes less melatonin, which is normally produced in response to darkness and helps promote sleep by coordinating circadian rhythms.[12]

Myth: The body gets used to a lack of sleep.

Fact: This myth can be especially harmful because sleep deprivation can wreak havoc on diverse aspects of health, including metabolism, the cardiovascular system, the immune system, hormone production and mental health.[1]

Indeed, in a literature search conducted to provide a nonsystematic review of the health consequences of sleep deprivation, researchers found there are both short- and long-term consequences. Specifically, they found that "in otherwise healthy adults, short-term consequences of sleep disruption include increased stress responsivity, somatic pain, reduced quality of life, emotional distress, mood disorders and cognitive, memory and performance deficits. For adolescents, psychosocial health, school performance and risk-taking behaviors are impacted by sleep disruption. Long-term consequences of sleep disruption in otherwise healthy individuals include hypertension, dyslipidemia, cardiovascular disease, weight-related issues, metabolic syndrome, type 2 diabetes mellitus and colorectal cancer. All-cause mortality is also increased in men with sleep disturbances. For those with underlying medical conditions, sleep disruption may diminish the health-related quality of life of children and adolescents and may worsen the severity of common gastrointestinal disorders."[13]

Myth: Lack of sleep can be made up over the weekend.

Fact: Yes, it can feel good to sleep in on the weekend, but this change in sleep patterns can disrupt a person's sleep schedule. It's always better to go to bed

and wake up at the same time every day, even on the weekends.[9]

Myth: Napping makes up for a lack of nighttime sleep.

Fact: Sleeping only a few hours at night and taking multiple naps during the day is known as biphasic or polyphasic sleep, which can work for some people, but it's not healthy for extended periods of time.[4]

Biphasic sleepers sleep twice per day, whereas polyphasic sleepers sleep in multiple segments (three of more periods) per day. According to the Sleep Foundation, unintentional polyphasic sleep can be a sign of a sleep disorder or a neurodegenerative disease such as Alzheimer's. For those who do sleep this way intentionally, it is associated with negative physical and mental health outcomes.

Still, for some, biphasic sleep schedules come naturally. And, it is unknown whether biphasic sleep is better, worse or about the same as monophasic sleep (sleeping only one time per day). For instance, research has found that midday napping has consistently been linked to improved cognitive performance, shorter naps have been shown to reduce sleepiness and cause cognitive improvements that are felt almost immediately, and longer naps lasting more than 30 minutes produce cognitive benefits for a longer time period, but the person tends to experience a period of grogginess after waking up.[14]

Myth: The only thing that matters is the duration of sleep.

Fact: While getting enough sleep is important, even more important is sleep quality. Awakening numerous times during the night interferes with the sleep cycle, decreasing time spent in the most restorative stages of sleep.[1]

Myth: Alcohol before bed improves sleep.

Fact: Alcohol may make it easier to fall asleep at night, but can disrupt sleep later in the night and may cause periods of awakening that would otherwise not have been experienced. According to an article in the *Handbook of Clinical Neurology*, "Alcohol acts as a sedative that interacts with several neurotransmitter systems important in the regulation of sleep. Acute administration of large amounts of alcohol prior to sleep leads to decreased sleep onset latency and changes in sleep architecture early in the night, when blood alcohol levels are high, with subsequent disrupted, poor quality sleep later in the night. Alcohol abuse and dependence are associated with chronic sleep disturbance, lower slow wave sleep and more rapid eye movement sleep than normal, that last long into periods of abstinence and may play a role in relapse.[15]

Myth: Snoring while sleeping is harmless.

Fact: Snoring can actually be a sign of sleep apnea, a sleep disorder that is associated with other medical problems such as heart disease and diabetes. While it is a common condition that causes breathing to stop and restart many times while sleeping, it can prevent the body from getting enough oxygen.

There are two types of sleep apnea: obstructive and central. Obstructive sleep apnea, the most common type, occurs when the upper airway becomes blocked many times while sleeping, reducing or completely stopping airflow. This can be caused by anything that could narrow the airway such as obesity, large tonsils or changes in hormone levels. Central sleep apnea occurs when the brain fails to send the signals needed to breathe.[16]

There are many factors that raise the risks of both obstructive and central sleep apnea. Risks of obstructive sleep apnea include older age; endocrine disorders; family history and genetics; heart or kidney failure; large tonsils and a thick neck; lifestyle habits such as drinking alcohol and smoking; obesity; and sex (it is more common in men than women). Risks of central sleep apnea include older age; family history and genetics; lifestyle habits (again, alcohol and smoking); opioid use; health conditions that affect how the brain controls the airway and chest muscles such as heart failure, stroke, amyotrophic lateral sclerosis and myasthenia gravis; and premature birth.[17]

Myth: There is no treatment for sleep disorders other than lifestyle modifications.

Fact: While lifestyle modifications can certainly help to treat sleep disorders, there are many other treatments available:[18]

Light therapy. Sitting in front of a light box that produces bright light similar to

The Connection Between Emotional Health and Sleep[1]

- 40% of people with insomnia may have a diagnosable mental health condition.
- 70% of adults with seasonal affective disorder (SAD) feel tired in the winter, compared to 44% of those without it.
- Individuals with SAD who practice light therapy during the winter are 36% less likely to experience a depressive episode.
- 83% of adults with depression may have at least one symptom of insomnia.
- 54% of adults say stress and anxiety were the top reasons they have trouble falling asleep. Sunday was the night of the week in which they had the most trouble falling asleep.
- As much as 91% of adults with post-traumatic stress disorder (PTSD) have symptoms of insomnia.
- 80% of people with PTSD have nightmares within three months of experiencing trauma.

sunlight can help to adjust the amount of melatonin the body needs to reset the sleep-wake cycle. A light box can be used in the morning to help reduce daytime sleepiness or in the afternoon or early evening to help treat advanced sleep-wake phase disorder, shift work disorder and jet lag. In place of a light box, light visors and light glasses can also be effective.

Orofacial therapy. Exercising the mouth and facial muscles can help treat sleep apnea in children and adults.

Cognitive behavioral therapy for insomnia (CBT-I). CBT-I is a six- to eight-week treatment plan to help individuals learn how to fall asleep faster and stay asleep longer. It is recommended as a first-line therapy with a healthcare provider, nurse or therapist. CBT-I involves five parts: 1) cognitive therapy, 2) relaxation or meditation therapy, 3) sleep education, 4) sleep restriction therapy and 5) stimulus control therapy.

Prescription medicines. These include benzodiazepine receptor agonists such as zolpidem, zaleplon and eszopiclone; melatonin receptor agonists such as ramelteon; orexin receptor antagonists such as suvorexant; and benzodiazepines if other treatments and medicines haven't worked. In addition, stimulants and depressants such as sodium oxybate can be prescribed.

Off-label medicines. In some cases, medications often used for other health conditions but not approved by the U.S. Food and Drug Administration to treat insomnia can be prescribed. These include antidepressants, antipsychotics and anticonvulsants.

Over-the-counter (OTC) medicines. Many OTC products can help with sleep disorders, including antihistamines, melatonin supplements and dietary supplements.

Devices. Both over-the-mouth and in-the-mouth devices can help treat sleep disorders. A continuous positive airway pressure (CPAC) device works by using mild air pressure to keep airways open while sleeping. The CPAP machine includes a mask the fits over the nose and mouth and a tube that connects the mask to the machine's motor.

Oral devices that are worn in the mouth are often custom-made by a dentist or orthodontist. There are two types that open the upper airway while sleeping: 1) mandibular advancement devices that cover the upper and lower teeth and hold the jaw and 2) tongue retaining devices that hold the tongue in a forward position.

Surgical procedures. When CPAP machines or oral devices don't work, one of four types of surgery may be needed: 1) adenotonsillectomy surgery removes the tonsils and adenoids, 2) an implant to help monitor breathing patterns and control certain muscles, or a nerve stimulant to control the tongue muscles, can prevent the airway from becoming blocked, 3) removing the soft tissue from the mouth can make the upper airway larger and 4) maxillary or jaw advancement surgery moves the upper jaw and lower jaw forward to make the upper airway larger.

Dispelling the Myths Now

Getting enough sleep is not a luxury — it is something people need for good health. Lack of sleep can have short- and long-term consequences, and it has detrimental effects on mental health, metabolism, the immune system and more. On the other hand, getting enough sleep makes people feel healthier and rested during the day.

Fortunately, sleep is receiving increasing attention in public health. In a recent viewpoint article published in *The Lancet*, the authors proclaim that "despite the strength of evidence showing that sleep has a critical influence on all aspects of human health, the importance of sleep health remains under-recognized globally." They recommend that sleep health "be promoted as an essential pillar of health, equivalent to nutrition and physical activity … with a focus on education and awareness, research and targeted public health policies." In addition, they recommend developing sleep health educational programs and awareness campaigns; increasing, standardizing and centralizing data on sleep quantity and quality; and developing and implementing sleep health policies across sectors of society.[19] ❖

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Anxiety

A Patient's Perspective

By Trudie Mitschang

A LIFELONG anxiety sufferer, our featured patient in this issue explains how extreme introversion and anxiety often go hand-in-hand. During our interview, this individual admitted that the prospect of sharing his name and photo in print and online made him very uncomfortable — "like being asked to walk around naked in public." Out of respect for his wishes, we've agreed to keep his identity anonymous.

BSTQ: How old were you when you first experienced symptoms of an anxiety disorder?

Patient: I have had anxiety disorder for as long as I can remember. To this day, I can vividly recall having extreme fear about going to school as a young preschool student. My heart was always pounding, and my mind felt overwhelmed with an unreasonable amount of worry about how I would fare in public.

BSTQ: Do you have an official diagnosis?

Patient: I was diagnosed with social anxiety in 2017.

BSTQ: Can you describe what happens during an anxiety attack?

Patient: When I'm in public or in groups numbering more than two, I am self-conscious to a crippling extent, going as far as stammering, my throat becoming dry and my hands beginning to tremor (especially if I feel triggered). Then, I am constantly fearful about how people will judge me. All these mental turbulences wreak havoc on my cognitive ability. I frequently end up having brain fog and struggle to retain new information. Focus and concentration go down the drain. It becomes impossible to even read. When anxiety is in full swing, the slightest of daily tasks feel like an uphill mountain climb.

BSTQ: What treatment options have you tried?

Patient: There is no end to the list of treatments I have tried. Medication, mindfulness, slow breathing techniques and constantly trying to ram positive thoughts into my subconscious. Nothing has helped.

BSTQ: How are your symptoms today?

Patient: Sadly, worse than ever. Anxiety disorder runs rampant in my family's gene pool. My mom also had it and succumbed to it in 2016.

BSTQ: You started a YouTube channel to shed light on life with anxiety. Tell us about that.

Patient: I wanted to articulate what goes on in the tumultuous mind and daily life of anxiety disorder sufferers. It has come to my mind that social media platforms are inundated with gurus and their literature on how to cope with mental disorders. There is not even a handful of content posted by the sufferers themselves.

BSTQ: What do you wish friends and family understood about anxiety disorder?

Patient: That people who have this condition need all the love, care and understanding in the world. People with anxiety disorder are much more intelligent, logical, pragmatic and down-to-earth than you realize. Rationality and logic have been consistent tools we use to calm our minds when they have the tendency to cripple us with fear and trauma. Our logical half is locked in a perpetual effort to calm our unreasonably anxious other halves.

BSTQ: What has struggling with anxiety taught you?

Patient: That we are complex. That others cannot understand this condition if they have not had it themselves. Anxiety and anxiety disorder are completely different. Let the term "disorder" sink in if you have ever had the impulse to say "just snap out of it" to people like me. I have learned that many people like to pridefully state that they have had anxiety in certain phases of their lives, and they have overcome it. That's not an anxiety disorder. This condition is not just circumstantial. It's actually a part of you.

BSTQ: What coping skills can you share with others?

Patient: There is not much in our power during an attack, but other times we can have the upper hand. The key lies in getting as much self-replenishment in between episodes as possible. Distraction techniques are helpful. We can do things we love and talk to people who understand us. In my case, I watch movies on my phone. The other thing I've found helpful is self-acceptance and knowing I'm not alone. I also think it's important to read, research and gain knowledge about our condition as much as possible. Knowledge is power and by knowing about our enemy, we can minimize its power to take us by surprise or bring us to our knees.

To learn more about life with anxiety, visit the Anxiety Survivors YouTube channel at www.youtube.com/@thesurvivor156. ❖

Anxiety: *A Physician's Perspective*

ANDREA KULBERG, PhD, CEDS, is a licensed psychologist with more than 25 years of experience in treating anxiety and eating disorders, and is also a certified eating disorder specialist. She has been trained through the International OCD Foundation in the use of exposure with response prevention (ERP), the number one treatment for anxiety. Dr. Kulberg is also the clinical director at Anxiety Experts in Santa Barbara, Calif.

BSTQ: What is generalized anxiety disorder (GAD), and how is it diagnosed?

Dr. Kulberg: Anxiety disorders are named for situations in which people experience anxiety (such as social phobia — a sense of entrapment and fear of negative evaluation in social situations). However, GAD is characterized by excessive worry about average things that may keep them up at night or may intrude upon their minds during normal daily activities.

BSTQ: What are common symptoms of anxiety in adults?

Dr. Kulberg: Everyone experiences anxiety that results in paranoid thoughts and body sensations such as nausea, heart racing, sweating, shallow breathing, etc. Anxiety disorders are diagnosed only when the anxiety interferes with people's ability to live the lives they want because it results in avoidance behaviors, reassurance-seeking or rituals.

BSTQ: Can GAD be cured or only managed?

Dr. Kulberg: The goal of effective anxiety treatment never involves ridding people of anxiety, but rather getting better at understanding the feared thoughts and body sensations to help them get over it more quickly.

BSTQ: When is medication recommended and/or helpful?

Dr. Kulberg: If my clients are not responding well to non-medicinal treatment, I will refer them to a psychiatrist for medication management. Depending upon the severity of symptoms, I may even refer them for a medication consultation at the outset of treatment to avoid a higher level of care. Unfortunately, instead of trying psychiatric medications, many individuals with anxiety turn to taking something habit-forming when they are distressed (e.g., THC in cannabis, benzodiazepines or alcohol), all of which perpetuate the lie that the anxiety can harm them. Of course, when the substance leaves their systems, the individuals are left with a spike of anxiety that is often worse than before, and they usually end up using the substance more frequently and in greater amounts.

BSTQ: Tell us about your two primary treatment protocols at Anxiety Experts.

Dr. Kulberg: We employ ERP and acceptance and commitment therapy (ACT). ERP, a type of cognitive behavioral therapy, is considered the number one treatment for all anxiety-spectrum disorders. The focus of ERP is to interrupt the associated behaviors of GAD and help clients learn to accept the uncertainty and discomfort that people with lower levels of anxiety are better able to manage. We slowly expose people to the things that make them anxious in hierarchical fashion such as thinking thoughts that they have been trying to avoid or going into anxiety-inducing situations. Then, we focus on response prevention by having the clients invite anxiety while refraining from engaging in the usual behaviors. Over time, it becomes easier to resist these behaviors, and baseline anxiety is gradually reduced.

ACT teaches people to make their own happiness in life by going after things they value. ACT focuses on accepting thoughts and emotions while committing to living by values anyway. This means that people can still do something meaningful while experiencing distressing thoughts and emotions. With ACT, we learn to pursue a rich, full, meaningful life while tolerating the pain that inevitably comes with it.

BSTQ: Are there any promising studies on anxiety that shed light on this increasingly common diagnosis?

Dr. Kulberg: The top researcher on these matters is Jonathan Abramowitz at the University of North Carolina at Chapel Hill. His book *Exposure Therapy for Anxiety* discusses the important research showing the efficacy of exposure-based therapies. The recently released movie "Anxious Nation" also explains the problem very well in our society. I fear children are leaving school in record numbers due to accommodation of normal childhood anxiety because we are so afraid of requiring children to face average stressors and discomfort. This "prevalence inflation hypothesis" is discussed in a recent article titled "Are Mental Health Awareness Efforts Contributing to the Rise in Reported Mental Health Problems?"[1] ❖

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Cryoprecipitate, Fibrinogen Concentrates and New Pathogen Reduced Cryo Product Vie for Use in Massive Hemorrhage

By Keith Berman, MPH, MBA

WHETHER THE result of severe trauma, major surgery, childbirth or some other acute event, massive hemorrhage requires the earliest possible replacement of shed blood components, ideally through transfusion of packed red blood cells (pRBCs), plasma and platelets or, where available, low-titer type O whole blood. But an added common concern for massively bleeding patients is acquired hypofibrinogenemia, secondary to fibrinogen consumption and hemodilution from any replacement of lost blood with coagulation factor-deficient fluids, as well as a dynamic fluid shift from the interstitial to the intravascular compartment.

The next most plentiful plasma protein after human albumin, fibrinogen is converted by thrombin (factor II) at sites of vascular injury to form a tough, insoluble fibrin mesh-like clot, which in turn stabilizes and strengthens primary platelet and retained RBC hemostatic plug (Figure 1). Because fibrinogen is the key effector protein in the coagulation process, it is also the first coagulation protein to reach critically low levels during severe hemorrhage. Impaired hemostasis due to hypofibrinogenemia in turn results in increased ongoing bleeding, which in turn increases the risk of multiorgan failure and death.

The causal association between low fibrinogen level and increased transfusion requirements and mortality risk is well-established. In the controlled setting of cardiopulmonary bypass (CPB) surgery, for example, a large single-center study found that the risk-adjusted odds of requiring large-volume transfusion (≥5 units of pRBCs) was 80 percent higher for patients with a post-CPB fibrinogen level <2.0 g/L relative to those with a post-CPB level of >2.0 g/L.[1] A recent Australian trauma registry study evaluating nearly 4,800 patients confirmed that low circulating fibrinogen was a strong independent risk factor for massive transfusion, as well as increased in-hospital mortality: The mortality odds for patients with a fibrinogen nadir less than 1 g/L and 1-1.5 gram/liter (g/L) were, respectively, 3.28 and 2.08 times that of patients whose fibrinogen levels remained in the normal range (2 to 4 g/L).[2]

Does Fibrinogen Replacement Work?

Since it was first developed in the 1960s, fibrinogen-rich human cryoprecipitate* (cryo) has been administered in an effort to restore fibrinogen levels in extensively bleeding surgical, trauma and obstetric patients with laboratory-confirmed or presumptive hypofibrinogenemia. Prepared by thawing fresh frozen plasma (FFP) and recovering the cold-insoluble centrifugate, each bag of cryo contains a minimum of 150 mg of fibrinogen suspended in 5 mL to 20 mL of added plasma, as well as significant levels of factor VIII, factor XIII and von Willebrand factor.[3] Typically, five or 10 cryo units are pooled into a single bag for frozen storage and, once thawed, must be transfused within six hours.

Over the last decade, two purified fibrinogen concentrates (FCs) approved

* Technically called cryoprecipitated antihemophilic factor (cryoprecipitated AHF).

as replacement therapies for treatment of congenital fibrinogen deficiency — CSL Behring's RiaSTAP and Octapharma's Fibryga — have also been widely used off-label in lieu of cryo to treat hypofibrinogenemia in massively bleeding coagulopathic patients. The lyophilized protein powder is simply reconstituted with sterile water for injection, implying that FCs can be ready to infuse much faster than cryo.

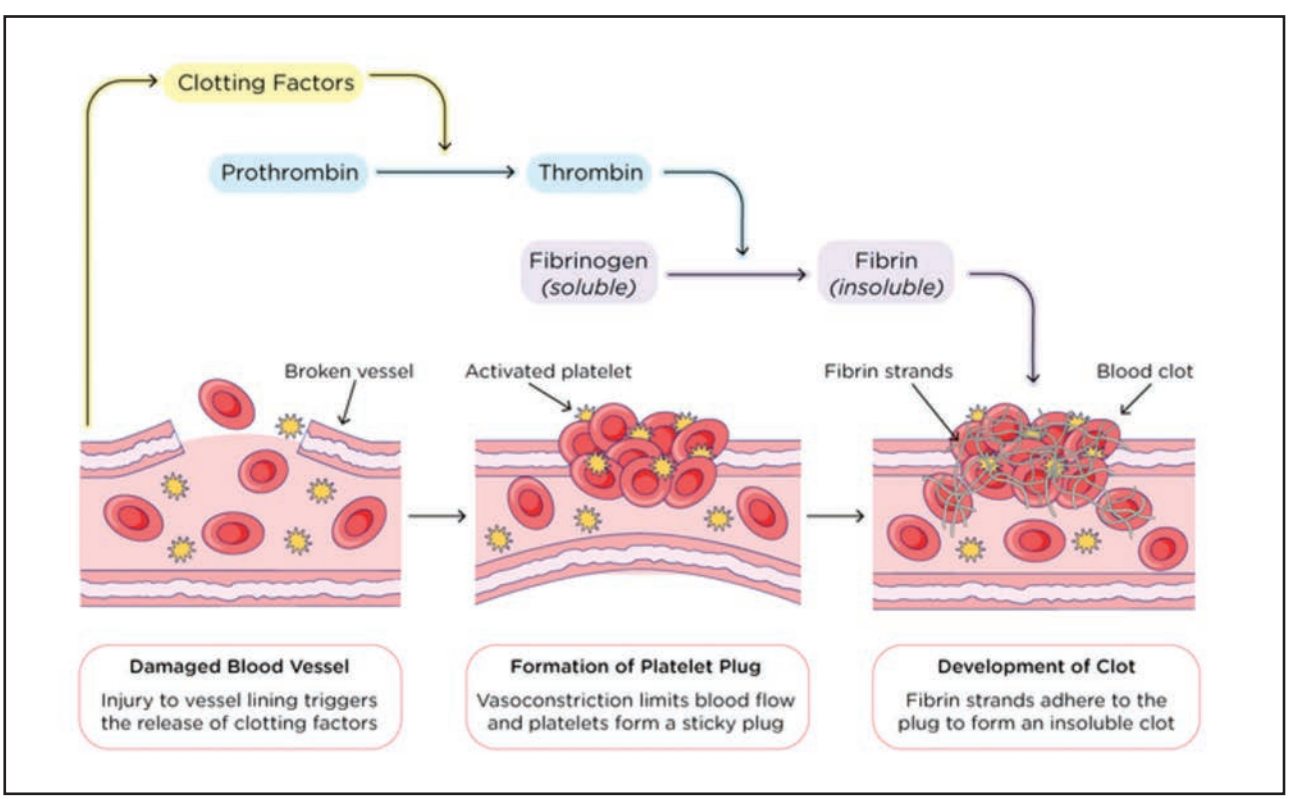
But while there is a straightforward therapeutic rationale for using either cryo or FCs to replete fibrinogen massively bleeding hypofibrinogenemic patients, there is limited and conflicting evidence to support the ability of either product to reduce transfusion requirements or mortality.

A recent systematic review of 26 clinical studies and a meta-analysis of five randomized controlled trials evaluating the use of FCs for trauma-related hemorrhage found no benefit from the use of FCs with respect to mortality or usage of packed RBCs, FFP or platelet transfusion requirements. The study authors acknowledged that the quality of evidence was graded as low to moderate, and called out the need for high-quality, adequately powered clinical trials.[4] And they astutely added that new trials need to prioritize administration of FCs "as early as possible from the point of entry into the trauma system of care."

A two-year analysis of the American College of Surgeons-Trauma Quality Improvement Program data set came to a very different conclusion. The investigators examined records of 4,945 massively transfused patients who received cryo and 14,698 others who did not receive cryo. Patients in the cryo group received a lower volume of plasma and pRBCs, and on multivariate logistic regression, the use of cryo was associated with decreased odds of in-hospital mortality (odds ratio, 0.79 [95% confidence interval, 0.77-0.87]; p=0.01).

A separate 2017 sub-analysis of the landmark PROPPR study demonstrated that mortality declines with fewer elapsed minutes between massive transfusion protocol (MTP) activation and delivery of blood-containing coolers.[5] While this study focused on blood component therapy generally, it and similar reports have convinced many surgeons and anesthesiologists that each minute of delay to administration of fibrinogen

Figure 1. Schematic of Basic Hemostasis to Resolve Bleeding from Damaged Blood Vessels



Source: Coagulation, Clotting Mechanisms. Accessed at jackwestin.com/resources/mcat-content/circulatory-system/coagulation-clotting-mechanisms.

concentrates translates into prolonged coagulopathic hemorrhage and increased risk of death.

Accordingly, a growing consensus is now aligned behind a simple explanation for why some massive transfusion studies report survival and transfusion avoidance benefits with use of fibrinogen-containing products and some do not: The infusion-ready product must arrive and be administered very early to rapidly restore hemostasis and limit further bleeding-related complications.

Delivery Timing of FCs vs. Cryo: No Contest

Prompted by wider awareness that earlier blood product administration saves more lives, investigators are now focusing on how much time actually transpires before FC or cryo is on hand and ready to infuse.

Published in 2021, the "Fibrinogen Early In Severe Trauma studY" (FEISTY), conducted at four major Australian trauma centers, examined the time interval in minutes from the blood draw for fibrinogen level testing to the commencement of first administration of either FC or cryo.[6] A total of 100 major trauma patients were identified based on clinical evidence or suspicion of major active hemorrhage, and were randomly assigned to the FC or cryo arms. Sixty-two of these patients were determined to be hypofibrinogenemic and received either FC (n=35) or cryo (n=25). Dosing was guided by the degree of hypofibrinogenemia.

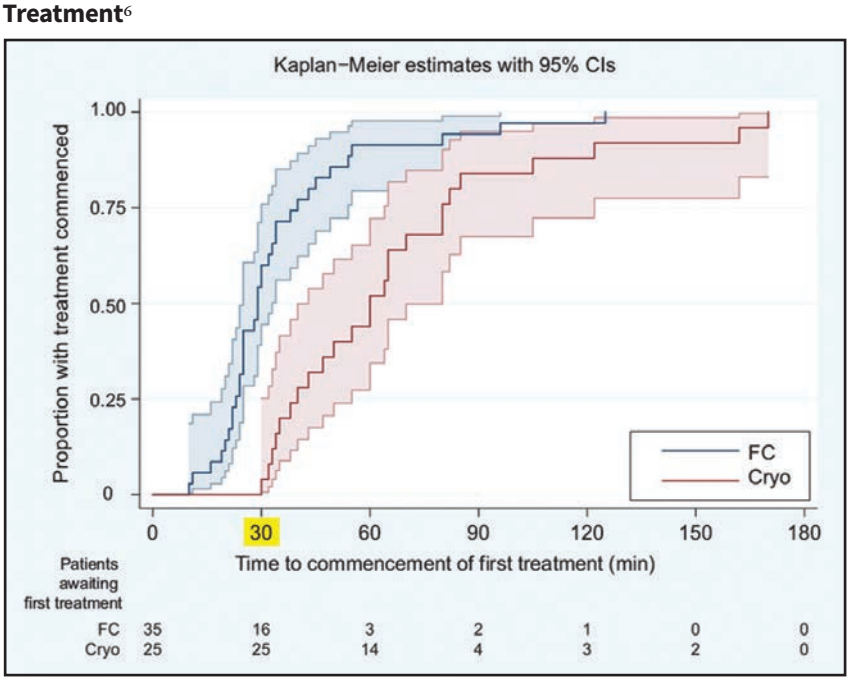
The median time to initiation of FC administration from the time of blood sampling for functional fibrinogen testing was 29 minutes, compared to 60 minutes for cryo administration. Within 30 minutes, more than half of patients in the FC replacement had started to receive their infusions. By contrast, no patient in the cryo group had been started at 30 minutes (Figure 2). Further, the median duration of FC administration was four minutes (interquartile range [IQR] two to eight minutes), compared to 12.5 minutes (IQR eight to 24 minutes) for cryo.

This same Australian team separately reported that, in 36 consecutive severe hemorrhagic trauma patients who received FCs, it took a median of 22 minutes (IQR 17 to 30 minutes) from the time that thromboelastometry results confirming hypofibrinogenemia triggered an order for FC to its administration,[7] during which the product was reconstituted and pooled.

Their findings are consistent with a report from a Canadian tertiary care hospital, where aseptic reconstitution and pooling of 1-gram FC concentrates to prepare a 6-gram dose was completed in about 20 minutes by trained blood bank technologists.[8] A pilot trial at five United Kingdom (UK) hospitals separately showed that FC could be ordered, prepared and administered to most severe hemorrhagic trauma patients within 45 minutes of admission (a median of 37.5 minutes for all participants).[9]

By contrast, reported real-world experience with cryo reveals that it often arrives for administration long after the first units of RBCs and plasma have been transfused, if it arrives at all before the patient exsanguinates or dies from other causes. In a prospective observational study of 146 massively hemorrhaging patients in 22 UK hospitals, the median time to delivery of cryo after arrival was 2.2 hours — long after the first unit of pRBCs was transfused at a median of 41 minutes after admission. Just under 50 percent of patients with massive hemorrhage did not receive any cryo within the first 24 hours.[10] In a secondary

Figure 2. Fibrinogen Early In Severe Trauma studY" (FEISTY): Time to Initiation of First Fibrinogen Concentrate (FC) or Cryoprecipitate (Cryo) Treatment[6]



analysis of the much-referenced U.S. PROMMTT trial, the median time from admission to first cryo unit was 2.7 hours (IQR 1.7 to 4.5 hours) — similar to the median time of 2.6 hours to hemorrhagic death. By the median time that cryo was finally administered, patients had already received a median of eight units of pRBCs.

Nevertheless, some clinicians continue to prefer cryo over purified FCs, citing its high concentrations of other clotting factors, in particular factor FXIII, which both acts to cross-link fibrin strands and stabilize the clot by cross-linking fibrinolytic inhibitors into the forming fibrin network.[11] But recent findings from a large head-to-head trial in Canada cast doubt on the presumptive inherent superiority of cryo relative to FCs: Investigators randomized 827 bleeding hypofibrinogenemic patients following cardiac surgery to FC or cryo and found that FC was noninferior to cryo; the mean numbers of 24-hour post-bypass allogeneic transfusions were 16.3 in the FC group and 17.0 in the cryo group ($P<0.001$ for noninferiority).[12]

However, this apparent therapeutic equivalency of FC and cryo in the controlled, typically non-emergent postoperative cardiac surgery setting has little if any bearing on the "is FC or cryo better" question for patients experiencing massive acute hemorrhage, who may arrive or very quickly become hypofibrinogenemic and seriously coagulopathic, and who need fibrinogen replacement therapy as quickly as possible.

Additionally, thanks to the recent arrival of an entirely new cryo-like product with remarkable post-thaw stability and storage flexibility, standard cryoprecipitate could soon be obsolete, making the "FC vs. cryo" question for massive transfusion moot.

> While there is a straightforward therapeutic rationale for using either cryo or FCs to replete fibrinogen massively bleeding hypofibrinogenemic patients, there is limited and conflicting evidence to support the ability of either product to reduce transfusion requirements or mortality.

The Newest Option: A Ready-to-Use Cryo

In late 2020, California-based Cerus Corp. received FDA approval for a process that now enables community blood centers to manufacture a new pathogen-inactivated version of cryo, formally known as the INTERCEPT Pathogen Reduced Cryoprecipitated Fibrinogen Complex (INTERCEPT Fibrinogen Complex, or IFC). IFC can be supplied as single or pre-pooled units from up to 10 donors. In addition to a fibrinogen content comparable to standard cryo, IFC contains high concentrations of factor XIII and von Willebrand factor.

Like standard cryo, IFC is intended for the treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency.** But unlike cryo, which must be transfused within six hours of thawing, IFC can be stored in a thawed state at room temperature for up to five days (120 hours), which entirely eliminates the roughly 20- to 30-minute thawing time and need for transfer from the hospital blood bank.

Now, instead of an average of an hour or more from admission to delivery of cryo, the immediate availability of IFC could cut that time down to as little as 30 minutes while awaiting confirmatory fibrinogen and/or clot strength testing results. In circumstances in which the physician suspects the patient is hypofibrinogenemic based on presenting signs and symptoms, IFC can be transfused contemporaneously with the first round of blood component products instead of waiting until a later transfusion round while cryo is thawing in the blood bank.[13] IFC additionally offers the opportunity to reduce product wastage: In instances where it is ordered but not transfused, IFC's five-day shelf life allows it to be used for a different patient, instead of being discarded as sometimes occurs with six-hour shelf life standard cryo.

** As it contains significant levels of factor XIII and von Willebrand factor (vWF), INTERCEPT pathogen reduced cryoprecipitated fibrinogen complex (IFC) is also intended for control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or vWF are not available, and as second-line therapy for von Willebrand disease. This product should not be used for replacement of factor VIII.

Which Fibrinogen Product: New Trials Needed

In the design and conduct of clinical investigations in the hemorrhagic trauma population, choices of patient inclusion criteria, fibrinogen-containing product(s) and dosage protocol may yield results that answer the research question posed by the investigators, but which may not help to define what is optimal therapy for every patient. A prime example is the recently reported 26-center randomized CRYOSTAT-2 trial, which evaluated the addition of "early" empiric high-dose cryo (three five-unit pools; six grams) to standard resuscitative care in 1,604 patients with trauma and bleeding who required activation of a major hemorrhage protocol.[14]

> Prompted by wider awareness that earlier blood product administration saves more lives, investigators are now focusing on how much time actually transpires before FC or cryo is in hand and ready to infuse.

The investigators found no difference in all-cause 28-day mortality between standard care and standard care plus "early" empiric high-dose cryo (26.1 percent vs. 25.3 percent). Nor was there a significant difference in transfusion requirements across the two study groups. While the intention was to administer cryo as early as possible, the study authors acknowledged that "multiple challenges in rapidly delivering the intervention led to variability of timing of cryoprecipitate administration." Of 665 patients in the cryo group who received cryo within 24 hours of hospital admission, only about 11 percent received it within 45 minutes, and under one-third within an hour of admission. All the rest waited for between one and two hours or longer to receive their cryo infusions, hardly what one would characterize as "early." Further, the lack of a placebo group, as well as low patient numbers, precluded an assessment of mortality in the minority of patients who did receive cryo within the first 45 minutes or hour of admission.

"Although the study aimed for early cryoprecipitate administration," the co-authors admitted, "the median time to first transfusion was more than an hour after arrival, reflecting the logistical challenge of preparing and administering a frozen blood component stored in a blood laboratory remote from the patient."[14]

Now, with the availability of a pathogen-reduced IFC product that can be transfused immediately, one could argue that it is no longer necessary or justifiable for any U.S. hospital to provide only standard cryo for empiric treatment of any trauma, obstetric or other patient experiencing severe acute hemorrhage and suspected hypofibrinogenemia. A case for use of IFC in lieu of standard cryo can also be made for *any* patient for whom fibrinogen and/or clot strength testing is ordered: Why risk a potential delay in treatment to resolve low fibrinogen in an actively bleeding patient in the event that blood bank staff need extra time to prepare standard cryo?

Does the relatively short preparation time for fibrinogen concentrates make them a reasonable option in lieu of IFC in defined patient populations experiencing massive hemorrhage? This question can only be answered by large-scale clinical trials. Given the life-and-death stakes involved, the earlier such trials can be organized, completed and reported out, the better. ❖

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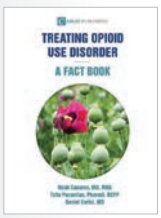
[1]https://www.cdc.gov/poxvirus/molluscum-contagiosum/index.html
[2]https://www.fda.gov/consumers/consumer-updates/safely-treating-molluscum-common-skin-condition#:~:text=The%20FDA%20has%20approved%20Ycanth,only%20by%20health%20care%20professionals.

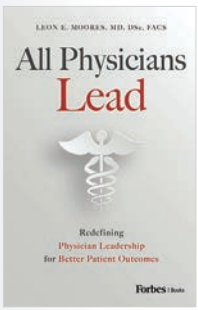


Treating Opioid Use Disorder — A Fact Book

Authors: Noah Capurso, MD, MHS, Talia Puzantian, PharmD, BCPP, and Daniel Carlat , MD

This Carlat Fact Book provides physicians with the tools and information needed to assess and treat patients who are struggling with opioid use disorder. Unlike traditional textbooks, this book distills each critical aspect of clinical decision-making into a single sheet, with tips and bullet points that can be used at the point of care. Topics covered include conducting an initial assessment, treating opioid withdrawal symptoms, psychosocial approaches to treating opioid use disorder and relapse prevention strategies.

www.amazon.com/Treating-Opioid-Disorder-Fact-Book/dp/B0CSM8W14Z/ref=sr_1_1



All Physicians Lead: Redefining Physician Leadership for Better Patient Outcomes

Author: Leon E. Moores, MD, DSc, FACS

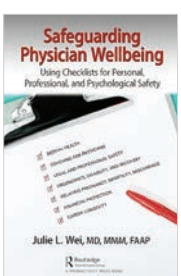
Primarily aimed at physicians, this book offers an introductory course in physician leadership, using a "concentric circles" model: As a physician, progressing from learning to lead yourself, to leading other individuals, to leading teams and, finally, to leading organizations, can improve healthcare team performance and patient outcomes. The book also speaks to those in charge of medical schools, healthcare organizations and physicians' professional associations, arguing that leadership should be considered a core competency throughout every doctor's career and structured education in leadership fundamentals should begin the first day as a medical student.

www.amazon.com/All-Physicians-Lead-Redefining-Leadership-ebook/dp/B0CLT231WM

Safeguarding Physician Wellbeing, 1st Edition

Author: Julie L. Wei, MD, MMM, FAAP

The critical shortage of physicians coupled with an unhealthy physician workforce results in longer wait times for access, increased healthcare costs, decreased quality of care and worsening patient experience. Effective solutions to mitigate physician burnout, protect current working physicians and keep them from leaving medicine require a shift and a more individualized approach. This book uses a "checklist" approach to empower medical students, residents, fellows and practicing physicians to create and experience psychological, personal and professional safety and wellbeing. Not only can physicians choose and use these checklists themselves, but those who live with, love and cherish one or more physicians in their families and/or lives can use this book to understand physician realities and their risks.



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Oxford Handbook of Clinical Medicine (Oxford Medical Handbooks), 11th Edition

Authors: Ian B. Wilkinson, PhD, Tim Raine, MD, Kate Wiles, MD, Peter Hateley, MD, Dearbhla Kelly, MBBChBAO, MSc, DPhil, MRCPI, and Iain McGurgan, MBBChBAO, MSc

This handbook is a complete and concise guide to the core areas of medicine that also encourages thinking about the world from the patient's perspective to develop a holistic approach to care with a passion for practice. Now in its 11th edition, it has been fully updated to reflect the latest changes in clinical practice and best management. Three new authors have joined the writing team, bringing a fresh perspective to the content. The chapters on emergencies, endocrinology and diabetes, hematology, oncology and surgery have been completely revamped, and every page has been reviewed by a consultant and a trainee to ensure it continues to be accurate, relevant and user-friendly. Figures and illustrations have been revised and updated in response to reader feedback, and key references fine-tuned to include only the most up-to-date and pertinent.

www.amazon.com/Handbook-Clinical-Medicine-Medical-Handbooks/dp/0198844018

Emicizumab Prophylaxis Efficacious and Well-Tolerated in Infants with Severe Hemophilia A Without Inhibitors

Due to challenges with intravenous factor VIII administration, many infants with severe hemophilia A do not receive prophylaxis until 1 year of age or older. Emicizumab (HEMLIBRA) can be administered subcutaneously following initial hemophilia A diagnosis, which may reduce risk of spontaneous and traumatic bleeds, importantly including intracranial hemorrhage. The Phase IIIb multicenter, open-label HAVEN 7 study evaluated the efficacy, safety and pharmacokinetics of emicizumab in infants 12 months of age or younger with severe hemophilia A without factor VIII inhibitors.

The median age of the 55 male study participants was 4 months. All received emicizumab for at least 52 weeks, with a median treatment duration of 100.3 weeks (range 52-18 weeks). Of a total of 207 bleeds (treated or untreated) reported in 46 participants (83.6%), 42 treated bleeds — all traumatic — were reported in 25 participants (45.5%). The annualized treated bleeding rate was 0.4 bleeds (95% confidence interval, 0.30-0.63 bleeds). Thirty infants (54.5%) experienced no treated bleeds, 52 infants (94.5%) had no treated joint bleeds and all 55 infants (100%) had no treated spontaneous bleeds.

Nine of the 55 participants had one or more emicizumab-related adverse events, all of which were grade 1 injection-site reactions. No adverse event led to treatment changes or withdrawal. Sixteen participants reported 30 serious adverse events, none of which were considered emicizumab-related. Pharmacokinetics profiles were similar to those in previous studies in adult populations treated with emicizumab.

"This primary analysis of HAVEN 7 confirms that emicizumab is efficacious and well-tolerated in infants with severe hemophilia A without factor VIII inhibitors," the investigators concluded. ❖

Pipe, S, Collins, P, Dhalluin, C, et al. Emicizumab Prophylaxis in Infants with Severe Hemophilia A Without Factor VIII Inhibitors: Results from the Primary Analysis of the HAVEN 7 Study. American Society of Hematology Annual Meeting (Oral Session 322; Abstract 505), Dec. 10, 2023.

Albumin Administration Superior to Ringer's Lactate for Maintaining Normovolemia During Major Surgical Hemorrhage

With the aim of better understanding the plasma volume expansion effects of albumin solutions during surgery associated with major hemorrhage, Swiss investigators at the Bern University Hospital conducted a single-center randomized clinical trial to quantify and compare the PVE properties of iso-oncotic 5% albumin, hyper-oncotic 20% albumin and Ringer's lactate (RL) in patients undergoing radical cystectomy.

To combat intraoperative hypovolemia, 42 consecutive patients were randomly allocated to receive 5% albumin (12 mL/kg) or 20% albumin (3 mL/kg) over 30 minutes of the hemorrhagic phase of their surgery, together with RL to replace blood loss at a 1:1 ratio, or RL alone to replace blood loss in a 3:1 ratio. The median hemorrhage volume across all patients was 848 mL (interquartile range 615-1145 mL).

The RL solution expanded the plasma volume by 0.18 times the infused volume, while 5% and 20% albumin solutions, respectively, attained plasma volume expansion of 0.74 and 2.09 times the infused volume. While the RL-only group experienced modest hypovolemia (a mean of -313 mL), the 5% and 20% albumin solutions were more effective in filling the vascular system, with calculated blood volume changes of only +63 mL and -44 mL, respectively. The two albumin solutions also 1) increased central venous pressure relative to RL and 2) achieved long-lasting plasma volume expansion with median half-times of 5.5 hours and 4.8 hours, respectively.

The study investigators pointed out that administration of albumin combined with restricted administration of RL reduces positive fluid balance. "This is

of importance as excessive postoperative fluid balance has been related to poorer outcomes, including postoperative complications like anastomotic leakage in major surgery involving intestines or colon," they added. ❖

Jardot, F, Hahn, RG, Engel, D, et al. Blood Volume and Hemodynamics During Treatment of Major Hemorrhage with Ringer Solution, 5% Albumin, and 20% Albumin: A Single-Center Randomized Controlled Trial. *Critical Care*, 2024 Feb 5;28(1):39.

Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2024, through June 30, 2024

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$982.81	$967.05
	BIVIGAM	ADMA Biologics	J1556	$145.93	$143.59
	GAMMAGARD SD	Takeda	J1566	$156.93	$154.41
	GAMMAPLEX	BPL	J1557	$110.02	$108.25
	OCTAGAM	Octapharma	J1568	$93.96	$92.45
	PANZYGA	Octapharma/Pfizer	J1576	$129.90	$127.81
	PRIVIGEN	CSL Behring	J1459	$95.72	$94.18
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$86.45	$85.06
	GAMMAKED	Kedrion	J1561	$97.77	$96.20
	GAMUNEX-C	Grifols	J1561	$97.77	$96.20
SCIG	CUTAQUIG	Octapharma	J1551	$138.00	$135.79
	CUVITRU	Takeda	J1555	$158.27	$155.73
	HIZENTRA	CSL Behring	J1559	$129.07	$127.00
	HYQVIA	Takeda	J1575	$169.41	$166.69
	XEMBIFY	Grifols	J1558	$141.32	$139.05

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Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g, 25 g
	OCTAGAM Liquid, 10%	Octapharma	ITP, DM	2 g, 5 g, 10 g, 20 g, 30 g
	PANZYGA Liquid, 10%	Octapharma/Pfizer	PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	IVIG: PI, MMN SCIG: PI , CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g, 10 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g 1 g PFS, 2 g PFS, 5 g PFS, 10 g PFS
	HYQVIA Liquid, 10%	Takeda	PI, CIDP	2.5 g, 5 g, 10 g, 20 g, 30 g
	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
DM Dermatomyositis
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease
PFS Prefilled syringes

2023-2024 Influenza Vaccines

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Product	Manufacturer	Presentation	Age Group	Code
Quadrivalent				
AFLURIA (IIV4)	Seqirus	0.5 mL PFS 10-bx	3 years and older	90685
AFLURIA (IIV4)	Seqirus	5 mL MDV	6 months and older	90685
FLUAD (IIV4)	Seqirus	0.5 mL PFS 10-bx	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUBLOK (ccIIV4)	Sanofi	0.5 mL PFS 10-bx	18 years and older	90682
FLUCELVAX (ccIIV4)	Seqirus	0.5 mL PFS 10-bx	6 months and older	90674
FLUCELVAX (ccIIV4)	Seqirus	5 mL MDV	6 months and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUMIST (LAIV4)	Astrazeneca	0.2 mL nasal spray 10-bx	2-49 years	90672
FLUZONE (IIV4)	Sanofi	0.5 mL PFS 10-bx	6 months and older	90686
FLUZONE (IIV4)	Sanofi	5 mL MDV	6 months and older	90685
FLUZONE HIGH-DOSE (IIV4)	Sanofi	0.7 mL PFS 10-bx	65 years and older	90662

ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

COVID-19 Vaccines

Product	Manufacturer	Presentation	Age Group	Code
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL PFS Blister 10-pk	12 years and older	91322
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL SDV 10-pk	12 years and older	91322
MODERNA COVID-19 Vaccine, mRNA	Moderna	0.25 mL SDV 10-pk	6 months to 11 years	TBD
NOVAVAX COVID-19 Vaccine, Adjuvanted	Novavax	0.5 mL SDV 10-pk	12 years and older	91304
COMIRNATY COVID-19 Vaccine, mRNA	Pfizer-BioNTech	0.3 mL PFS 10-bx	12 years and older	91320

Respiratory Syncytical Virus (RSV) Vaccines

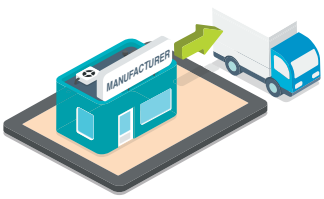
Product	Manufacturer	Presentation	Age Group	Code
ABRYSVO	Pfizer	0.5 mL Kit 1-ctn	60 years and older	90678
ABRYSVO	Pfizer	0.5 mL Kit 5-ctn	60 years and older	90678
AREXVY	Pfizer	0.5 mL SDV 10-bx	60 years and older	90679

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

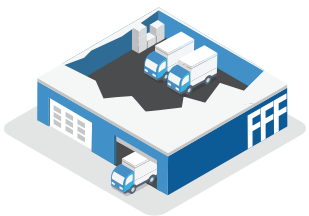
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss.



STEP 3

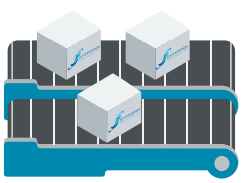
Specialty Packaging

At FFF, we use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

STEP 4

Interactive Allocation

FFF's unique capability of interactive allocation allows us to do that through our field sales team's close relationship with our customers. Our team understands customers' ongoing requirements, responds to their immediate crises, and allocates product in real-time to meet patients' needs.



Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

Our delivery guidelines are in compliance with the State Board of Pharmacy requirements. Products we deliver must only be transported to facilities with a state-issued license, and only to the address on the license. We make no exceptions. And we will not ship to customers known to have a distributor's license.

STEP 6

Methods of Delivery

We monitor for extreme weather conditions, and when the need arises, we ship overnight to maintain product efficacy. We also track patient need during life-threatening storms to make sure products are delivered when and where patients need them most.

STEP 7

Verification

In compliance with U.S. Drug Supply Chain Security Act (DSCSA) requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History, and Transaction Statement.

STEP 8

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

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