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QUARTERLY
SPRING 2023 SAFETY

OPIOID CRISIS

SAFEGUARDING AGAINST COUNTERFEIT MEDICINES

FDA Oversight
OF PHARMACEUTICAL WITHDRAWALS AND RECALLS

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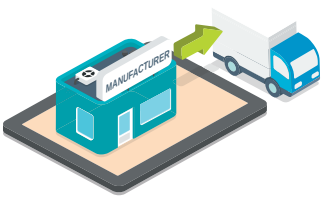
GuaranteedChannelIntegrity®

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

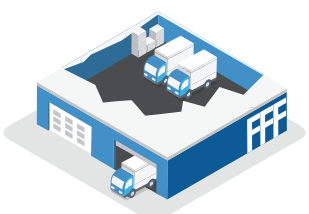
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



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

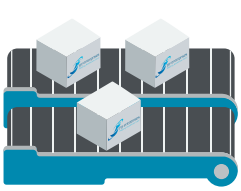
Specialty Packaging

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

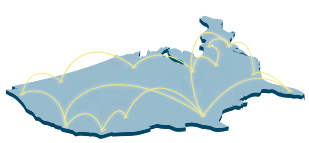
Verification

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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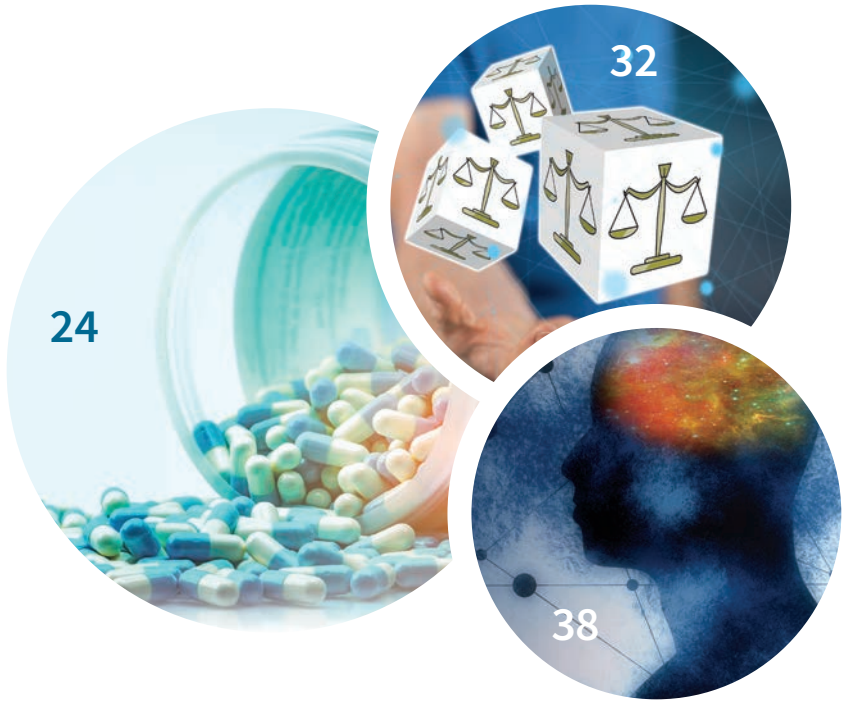

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Opioids, Recalls and Medical Error at the Forefront of Patient Safety

TODAY, PATIENT safety is at the forefront of the medical profession. The issues most pressing are the urgency of addressing the proliferation of both prescription and illicit drugs taken both wittingly and unwittingly by consumers that are obtained from online pharmacies or other means; the ability of the U.S. Food and Drug Administration (FDA) to monitor the safety of prescription medicines after they enter the market; and the need to accurately track the number of deaths caused by medical mistakes.

While the opioid crisis has been a growing problem for some time due to addiction and overdose, the issue is now being compounded by synthetic opioids, most notably fentanyl, that are often taken for recreational purposes, but are also sometimes added to counterfeit pills made to look like legitimate prescription narcotic medications. As we explain in our article "The Opioid Crisis: Fentanyl and the Safety of Prescription Drugs" (p.16), while legitimate prescriptions are many times obtained via legal means, there is growth of rogue online pharmacies selling fentanyl-laced fake pills made to look like the real drug, and consumers often can't tell the difference until it's too late. Data show that teens increasingly obtain counterfeit prescription opioids via social media sites that target this population. And, due to the high cost of medication in the U.S., a growing number of consumers unknowingly rely on rogue online pharmacies because of their purported convenience, including lower costs and home delivery. Even though the U.S. drug supply is "among the safest in the world," according to FDA, a safety net is critical to curtail the number of deaths. Enter: naloxone (generic for Narcan), which reverses the effects of opioids. Naloxone is available free of charge through various programs nationwide and is covered by Good Samaritan laws.

Aside from opioids, pharmaceuticals in general can pose health risks for a number of reasons. Thousands of drugs are recalled or withdrawn from the market every year in the U.S. We outline the reasons for this in our article "Pharmaceutical Market Withdrawals and Recalls: Expect the Unexpected" (p.24), which explains FDA's role, including overview and reporting, and manufacturers' role, including notification of the public and, most importantly, standard operating procedures they must have in place, especially since unanticipated issues often arise.

Unfortunately, unsafe medicines are not the only cause of patient death. Since 2016, reports of deaths due to medical error and misdiagnosis have made alarming headlines, mounting criticism on the healthcare system. But, as we examine in our article "Tracking Medical Error and Misdiagnosis" (p.28), whether these numbers are correct is a matter of intense dispute. Questions have been raised about significant flaws in the research methodology used to arrive at these numbers. To account for this, the Agency for Healthcare Research and Quality was established to issue annual reports on patient safety, but the agency's reporting system has yet to publish actual numbers of deaths from medical error. So, without any proof of these numbers' validity, physicians will continue to fight conjecture without any recourse.

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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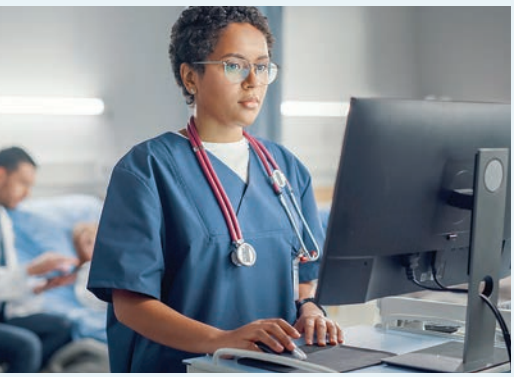
HHS Invests $13 Million to Grow and Strengthen the Nursing Workforce



The U.S. Department of Health and Human Services (HHS), through the Health Resources and Services Administration (HRSA), has awarded $13 million to bolster nursing education and training to grow the nursing workforce and improve access to nursing education. The awards are part of a series of investments across HHS and the Department of Labor to support pathways into good-quality nursing jobs. Investing in the nursing workforce pipeline is a key pillar of an action plan to improve the safety and quality of care in the nation's nursing homes.

"Nurses are an essential part of our nation's healthcare system," said HHS Secretary Xavier Becerra. "We are committed to growing the next generation of nurses and ensuring the education and training they receive prepares them to provide high-quality culturally competent care. Supporting nurses and other frontline health professionals providing care in our communities is critical to improving our nation's health and well-being."

One significant factor constraining admissions to nursing schools is the limited availability of nursing preceptors (experienced licensed clinicians who supervise nursing students during their clinical rotations). Nursing preceptors are a critical bridge between training and practice, providing direct instruction to nursing students in the clinical setting. Without sufficient preceptors, nursing schools cannot admit as many students, new students are delayed in starting their clinical rotations and prospective nursing students may be stymied and choose other career paths.

This investment works to reverse this trend. HRSA is awarding more than $8.4 million to 10 awardees through the Clinical Faculty and Preceptor Academies Program. These awards will support partnerships among academics, clinicians and the community designed to support clinical nursing faculty and preceptors, which will help increase the capacity of programs to train more nurses.

HRSA is also awarding $4.75 million to 14 awardees through the Registered Nurse Training Program to increase the number of nursing students trained in acute care settings. This program aims to improve health outcomes and health equity by strengthening the capacity and skillset of undergraduate student nurses prepared to provide high-quality, culturally sensitive care in underserved communities. ❖

HHS Invests $13 Million to Grow and Strengthen the Nursing Workforce. U.S. Department of Health and Human Services press release, Oct. 21, 2022. Accessed at www.hhs.gov/about/news/2022/10/21/hhs-invests-13-million-grow-and-strengthen-nursing-workforce.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=october-23-2022.

$245 Million Awarded by HHS to Support Youth Mental Health

The U.S. Department of Health and Human Services (HHS) has awarded nearly $245 million in Bipartisan Safer Communities Act funding — $185.7 million from the Substance Abuse and Mental Health Services Administration (SAMHSA) and nearly $60 million from the Health Resources and Services Administration to support the integration of mental health training into the training of primary care clinicians, with a specific focus on preparing primary care providers to treat the mental health needs of children and adolescents.

SAMHSA's Bipartisan Safer Communities Act awards include:

- $73.6 million for Project Advancing Wellness and Resiliency in Education to help develop and support school-based mental health programs and services;
- $57.7 million in Mental Health Awareness Training grants to prepare and train school personnel, emergency first responders, law enforcement and others to recognize the signs and symptoms of mental health challenges to enable early intervention;
- $14.9 million for School Based Trauma-Informed Support Services and Mental Health Care for Children and Youth to increase student access to evidence-based and culturally relevant trauma support services and mental health care;
- $19.5 million for the National Child Traumatic Stress Initiative to improve treatment and services for children, adolescents and families who have experienced traumatic events; and
- $20 million in Resiliency in Communities after Stress and Trauma grants to promote resilience and equity and prevent violence in communities that have recently faced civil unrest, community violence and/or collective trauma. ❖

HHS Awards Nearly $245 Million to Support Youth Mental Health and Help the Health Care Workforce Meet Families' Mental Health Needs. U.S. Department of Health and Human Services press release, Jan. 9, 2023. Accessed at www.hhs.gov/about/news/2023/01/09/hhs-awards-nearly-245-million-support-youth-mental-health-and-help-health-care-workforce-meet-families-mental-health-needs.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=january-15-2023.

HHS Issues Bulletin to Highlight Online Tracking Technology Obligations Under HIPAA Rules

In December, the Office for Civil Rights (OCR) at the U.S. Department of Health and Human Services issued a bulletin to highlight the obligations of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) on covered entities and business associates ("regulated entities") under the HIPAA Privacy, Security and Breach Notification Rules (HIPAA Rules) when using online tracking technologies. Online tracking technologies such as Google Analytics or Meta Pixel collect and analyze information about how Internet users are interacting with a regulated entity's website or mobile application.

The bulletin is in response to some regulated entities that regularly share electronic protected health information (ePHI) with online tracking technology vendors in a manner that violates the HIPAA Rules, which apply when the information that regulated entities collect through tracking technologies or disclose to tracking technology vendors includes ePHI. Regulated entities are not permitted to use tracking technologies in a manner that would result in impermissible disclosures of ePHI to tracking technology vendors or any other violations of the HIPAA Rules.

The bulletin addresses potential impermissible disclosures of ePHI by HIPAA-regulated entities to online technology tracking vendors. It explains what tracking technologies are, how they are used and what steps regulated entities must take to protect ePHI when using them to comply with the HIPAA Rules. Specifically, the bulletin provides insight and examples of tracking on webpages and within mobile apps, along with HIPAA compliance obligations for regulated entities when using tracking technologies.

"Providers, health plans and HIPAA-regulated entities, including technology platforms, must follow the law. This means considering the risks to patients' health information when using tracking technologies," said OCR Director Melanie Fontes Rainer. "Our bulletin answers questions for those using tracking technologies, importantly how to protect the privacy and security of the health information they hold."

The bulletin can be read at www.hhs.gov/hipaa/for-professionals/privacy/guidance/hipaa-online-tracking/index.html. ❖

HHS Office for Civil Rights Issues Bulletin on Requirements Under HIPAA for Online Tracking Technologies to Protect the Privacy and Security of Health Information. U.S. Department of Health and Human Services press release, Dec. 1, 2022. Accessed at www.hhs.gov/about/news/2022/12/01/hhs-office-for-civil-rights-issues-bulletin-on-requirements-under-hipaa-for-online-tracking-technologies.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=december-4-2022.

NIH Provides $5.3 Million Grant to Study Down Syndrome

The first clinical trial for Down syndrome regression disorder, a rare and debilitating condition that affects adolescents and young adults with Down syndrome, is being funded by a five-year, $5.3 million grant from the National Institutes of Health Eunice Kennedy Shriver National Institute for Child Health and Human Development. The randomized controlled trial, which is taking place at Children's Hospital Los Angeles (CHLA) and Children's Hospital Colorado, will investigate the safety and effectiveness of three different treatments, as well as examine the role of the immune system in the disorder.

The new trial will enroll a total of 60 patients between the two centers, with all patients randomized to receive one of

three therapeutic options:

- Lorazepam, an anti-anxiety medication that treats catatonia and other symptoms
- Intravenous immune globulin, an immune-regulating therapy
- Tofacitinib, a type of drug called a JAK inhibitor that suppresses the immune system

Tofacitinib was chosen because it previously has been used to successfully treat people with Down syndrome who have other autoimmune diseases.

"Until recently, there had been no research on this condition since it was first described in 1946," says Jonathan Santoro, MD, director of the neuroimmunology program at CHLA and co-principal investigator for the study. "We're excited to launch this first trial to advance our understanding of this disorder and how to best treat it." ❖

A First Clinical Trial for Down Syndrome Regression Disorder Earns $5.3 Million NIH Grant. Children's Hospital Los Angeles news release, Jan. 23, 2023. Accessed at www.newswise.com/articles/a-first-clinical-trial-for-down-syndrome-regression-disorder-earns-5-3-million-nih-grant.

Potential Disruptors: 2023 and Beyond

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

FINANCIAL CHALLENGES remain a consistent and growing concern for the healthcare industry, so taking actionable steps to produce tangible results can assist the industry in righting itself after uncertain times of financial instability.

Health-Related COVID-19 Federal Emergency Declarations Ending

The Centers for Medicare and Medicaid Services (CMS) has released updated fact sheets for Medicare and Medicaid providers on the status of COVID-19 blanket waivers and flexibilities, some of which will end and some of which will continue after the COVID-19 public health emergency. Although ending the emergency is helping public health officials to focus their resources on the people who remain most vulnerable, it also limits access to tests, vaccines and treatments, especially for uninsured Americans, some of whom are no longer eligible for Medicaid.

The following changes are scheduled for emergency declarations implemented in the early days of COVID-19:

1) Public health emergency initially declared by the Department of Health and Human Services (HHS) in late January 2020 and renewed several times: Expires May 11, 2023

2) National emergency declaration issued March 2020: Expires May 11, 2023

3) A separate emergency use authorization, a mechanism to facilitate availability and use of medical countermeasures determined to be safe and effective but have not yet been formally approved, issued pursuant to Section 564 of the Federal Food, Drug and Cosmetic Act: Conclusion to be determined

4) A declaration under the Public Readiness and Emergency Preparedness Act, providing liability immunity for activities related to COVID-19 medical countermeasures: Expires Oct. 1, 2024, in most cases (with some exceptions)

Healthcare providers are encouraged to review the implications of these changes at www.kff.org/coronavirus-covid-19/issue-brief/what-happens-when-covid-19-emergency-declarations-end-implications-for-coverage-costs-and-access.

Preapproval Information Exchange (PIE) Act of 2022

The PIE Act of 2022 (H.R. 7008) was passed to improve patient access to emerging therapies by improving the communication exchange between manufacturers and payers ahead of U.S. Food and Drug Administration (FDA) approval. It creates a statutory safe harbor for the proactive dissemination of certain clinical and economic information to health payers regarding new therapies or new indications of existing therapies not yet approved by FDA. It was believed that by having information ahead of FDA approval, payers would be able to better anticipate new indications and, in turn, increase the speed of coverage decisions, granting access to patients in need. Professional organizations such as the Academy of Managed Care Pharmacy have long supported initiatives to improve preapproval communication, saying: "The need for proactive PIE communication is especially important as the healthcare system continues to evolve from a fee-for-service payment system to a value-based system rewarding quality, improved patient outcomes and cost efficiency."

Although FDA had provided some PIE guidance as early as 2018, it was unclear whether manufacturers could proactively share information with payers or whether payers needed to request the data, creating legal grey areas and uncertainty for both entities. Now that the PIE Act has passed, health payers ahead of FDA approval can incorporate new therapies into their formularies for the plan year in which approval is anticipated.

FDA Proposes Revising the National Drug Code (NDC) Format

Drug codes are the link between correctly and completely telling a patient's story and payers understanding which products are being billed for. A revision to the NDC is intended to minimize the potential impact of running out of the current 10-digit NDC combinations as new products come to market. The proposal adopts a single, uniform 12-digit format for FDA-assigned NDCs with three distinct and consistent segments and one uniform format. The revision also includes a change to the drug product barcode label requirements.

Although these changes are not imminent, incorporating them into all parts of dispensing software and bar code scanning on administration involves careful planning long in advance, so now is a good time to purge charge description masters and pharmacy drug masters of duplications and discontinued products.

340B Considerations

Previous cuts to Medicare Part B reimbursement are due for remediation. How this will be carried out is under intense discussion that has many

implications. Since the process is deigned to be budget-neutral, repayment may have negative implications on other areas of reimbursement over a yet undefined period of time. If repayment is required, facilities need to be able to resubmit claims. This entails being able to identify traditional Medicare 340 B-eligible patients who received status indicator K drugs in an outpatient setting during the defined period. And, facilities must determine whether they can do this for every patient or if they need to establish a cutoff value.

Other items under considerations are 340B administrative dispute panels and the Protect 340B Act of 2021 with antidiscrimination provisions and a clearinghouse to prevent duplicate discounts.

Pharmacy Benefit Managers (PBMs): Old and New

The rising list prices of drugs are being linked to rising rebates from PBMs. It's estimated that three major PBMs — Express Scripts, CVS Caremark and OptumRx — control nearly 80 percent of U.S. prescription benefit transactions. PBMs profit from rebates and discounts, failing to pass on an estimated $120 billion back to consumers.

New market entrants (EmsanaRx, a not-for-profit venture owned by the Purchaser Business Group on Health; CostPlus PBM, a startup funded by venture capitalist and Dallas Mavericks owner Mark Cuban; Prescryptive Health, a blockchain-powered prescription data platform; and CapitalRx) are likely to disrupt this pattern, as are the new regulations governing PBMs that have been enacted in several states.

Equitable Community Access to Pharmacist Services (ECAPS) Act

The ECAPS Act enables Medicare patients to receive timely and consistent treatment from pharmacists for pandemic-related health services and allows pharmacists to respond to ongoing and future public health threats. It adds pharmacists as eligible providers for Medicare Part B beneficiaries of pharmaceutical services related to the COVID-19 pandemic and specific infectious diseases such as testing (for COVID-19, flu, respiratory syncytial virus and strep throat), treatment (for COVID-19, flu and strep throat) and vaccinations (for COVID-19 and flu). It also prepares for future emergencies by establishing Medicare coverage and payment for pharmacy- and pharmacist-provided services when there is a public health need such as during a public health emergency or similar event. And, it authorizes the HHS secretary to identify services as needed, including to close gaps in health equity. While this act is limited to states' scope of practice or physicians' services (or more broadly if provided under a Public Readiness and Emergency Preparedness Act declaration), it enables pharmacists to provide services to Medicare beneficiaries to address COVID-19 and other pressing health needs in all areas of the country.

2024 Medicare Advantage (MA) and Medicare Part D CMS Advance Notice

If the 2024 Advance Notice for the MA and Part D prescription drug programs passes, payment policies will be updated to strengthen beneficiary protections and incorporate provisions from the Inflation Reduction Act of 2022. Additionally, it will eliminate cost-sharing for Part D prescription drugs in the catastrophic phase and expand eligibility for full cost-sharing and premium subsidies under the low-income subsidy program. The goal is to continue efforts by CMS to provide more equitable, high-quality and person-centered care that is affordable and sustainable, including maintaining strong value and choice for people with Medicare. It also proposes updates to MA payment growth rates and to the MA and Part D payment methodologies. This includes technical updates to the MA risk adjustment model to keep the model up to date and improve payment accuracy such as by fully transitioning to the International Classification of Diseases (ICD)-10 system, which has been in use since 2015. The payment policies for 2024 were scheduled to be finalized and published no later than April 3, 2023. ❖

Resources

1. Cubanski, J, Kates, J, Tolbert, J, et al. What Happens When COVID-19 Emergency Declarations End? Implications for Coverage, Costs, and Access. Kaiser Family Foundation, Jan. 31, 2023. Accessed at www.kff.org/coronavirus-covid-19/issue-brief/what-happens-when-covid-19-emergency-declarations-end-implications-for-coverage-costs-and-access.
2. Centers for Medicare and Medicaid Services. Announcements and Documents: 2024 Advance Notice. Accessed at www.cms.gov/files/document/2024-advance-notice.pdf.
3. Centers for Medicare and Medicaid Services. 2024 Medicare Advantage and Part D Advance Notice Fact Sheet. Accessed at www.cms.gov/newsroom/fact-sheets/2024-medicare-advantage-and-part-d-advance-notice-fact-sheet.
4. A Celerian Group Company. MLN Connects Newsletter: Prescription Drug Inflation Rebate Program Guidance — Feb. 9, 2023. Accessed at www.cgsmedicare.com/articles/cope134823.html.
5. Centers for Medicare and Medicaid Services. COVID-19 Public Health Emergency (PHE) New Overview Fact Sheet. Accessed at www.cms.gov/outreach-and-education/outreach/ffsprovpartprog/provider-partnership-email-archive/2023-02-27-oce.

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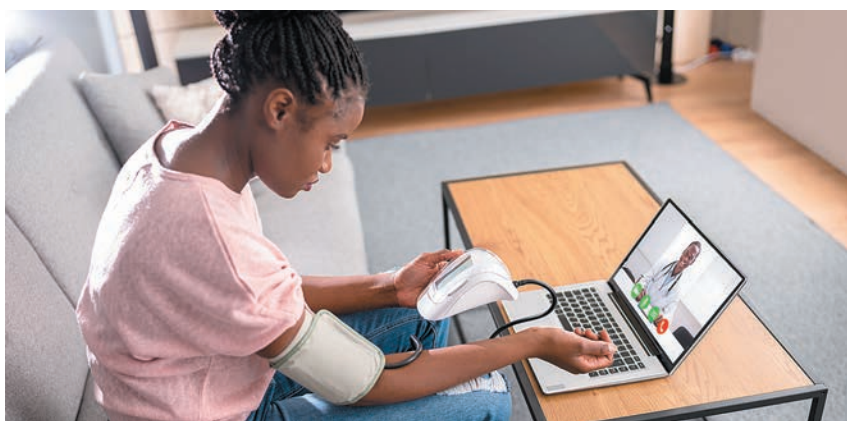
Expanding the Use of Telehealth and Virtual Care

How healthcare industry stakeholders are working to make telehealth and virtual care permanent delivery systems.

By Diane L.M. Cook



TELEHEALTH IS defined as a healthcare delivery system that digitally connects patients and healthcare providers when in-person care is not necessary or possible. Using telehealth services, patients can receive care, consult with a healthcare provider, get information about a condition or treatment, arrange for prescriptions and receive a diagnosis.[1] Telehealth and virtual care have existed in the United States for about 30 years, but they functioned on patchwork policy until the COVID-19 pandemic catalyzed expansion with exceptional results.

According to the American Telemedicine Association, "Expanding telehealth and virtual care can increase access to care for rural communities, underserved and vulnerable patient populations, and to individuals unable to secure in-person care, ensuring that everyone has access to safe, effective and appropriate care when and where they need it."[1]

Here's how major healthcare industry associations are working to expand telehealth and virtual care services in the coming years.

American Association of Colleges of Nursing (AACN)

Representing nursing schools from 850 universities and colleges combined, AACN is a national association of deans and faculty dedicated to advancing nursing education. According to AACN, "To prepare graduates for the evolving healthcare system, programs will need to encompass didactic, simulated and clinical field learning opportunities in diverse settings, including community, primary care, long-term care, acute care, hospice and virtual care settings (telehealth)."[2] AACN further observes that "the increasing use of telehealth, as well as the growth of nonhospital settings, will affect the RN [registered nurse] and APRN [advanced practical registered nurse] nursing workforces."[2]

To help equip them for these challenges, AACN recently presented two telehealth training webinars to its nursing students and alumni. The first, *Telehealth: Nurses Called to Action* (February 2020), explores the current telehealth landscape and examines essential telehealth components that influence nursing practice and the ability to reach patients with vital healthcare services by telehealth. The second, *Consumer Health: Preparing Nurse Graduates for Telehealth and Informatics* (April 2022), defines consumer health, health informatics and nursing informatics, explains how the consumerization of healthcare impacts nurses' roles and prepares future nurses on the current state of informatics, including telehealth and mobile wellness applications.

Given the rapid expansion of telehealth — particularly in rural communities — AACN expects telehealth to expand, and encourages nursing schools to develop learning experiences that will help nurses leverage telehealth in their professional practice.

American Nurses Association (ANA)

ANA represents the nation's 4.4 million registered nurses. According to the association, "Nurses are highly trained and well-educated to effectively use telehealth technologies, supervise remote patient monitoring activities and provide quality care using tools that promote access to timely care without the burdens often existing in remote geographic locations or appointment shortage areas."[3]

In 2019, ANA updated its Core

Principles on Connected Health, which contains 13 principles that act as a guide for healthcare professionals who use connected health technologies to provide quality healthcare.[4]

"There is robust evidence demonstrating that telehealth technologies make healthcare more effective and efficient by electronically connecting clinicians to clinicians, patients to clinicians and patients and caregivers to other resources. This approach facilitates remote diagnosis and treatment, continuous monitoring and adjustment of therapies, support for patient self-care and the leveraging of providers across large populations of patients," adds ANA.[3]

American Medical Association (AMA)

AMA is a professional association and lobbying group of physicians and medical students with more than 270,000 affiliated physicians, two million nurses and other caregivers. According to AMA trustee Jack Resneck, MD, "Telehealth is a critical part of the future of effective, efficient and equitable delivery of healthcare in the United States."[5]

The association believes it is essential that physicians and other healthcare providers are licensed in the state where the patient is located to ensure telemedicine services are provided in a secure environment. AMA also believes efforts should be made to increase membership in the Interstate Medical Licensure Compact.[5]

However, this policy is more flexible when it believes the physician should be licensed or otherwise authorized by the state where the patient is located, and it has a new policy regarding working with states on exemptions. According to AMA, it is not about licensing per se, but rather how to ensure patient safety and appropriate oversight over the practice of medicine in interstate situations made possible by telehealth.

AMA strongly supported the two-year waiver extension for telehealth provisions that was included in the omnibus bill that was passed on Dec. 29, 2022, and it will continue to seek permanent repeal of these outmoded statutory restrictions.

Further, AMA says its Return on Health research identified many healthcare organizations that are moving to hybrid models of care that combine virtual, in-person and remote monitoring services.

American Telemedicine Association (ATA)

ATA is a nonprofit organization that represents a network of healthcare delivery systems, academic institutions, technology solution providers and payers, as well as partner organizations and alliances, which work to advance industry adoption of telehealth. The association's nine policy principles promote a healthcare delivery system in which everyone has access to safe, effective and appropriate care when and where they need it, while enabling clinicians to do more good for more people.[6] ATA, and its affiliate trade organization, ATA Action, are working with lawmakers and policymakers to determine the best path forward to integrate virtual healthcare into an omnichannel healthcare system that includes in-person and virtual healthcare delivery in the future.

In December 2022, ATA and ATA Action launched Vision 2030: The Future of Telehealth in the United States. The vision contains six roadblocks that patients, providers, policymakers and digital solution companies need to tackle to create a pathway toward a future of telehealth for everyone.[7]

Further, in 2022, ATA Action launched Patient Voices for Telehealth Coalition (PVTC) to ensure patient perspectives are prominent in the debate for telehealth permanency. PVTC represents diverse patient communities providing perspectives on federal and state policies related to virtual healthcare and participates in activities to support the advancement of telehealth.[8]

And, in 2021, ATA launched Telehealth Awareness Week, featuring a series of national and regional events exploring the role of telehealth in healthcare delivery, providing new educational resources focused on the key advantages of hybrid healthcare and elevating the voices of patients and healthcare professionals who depend on telehealth to receive and deliver care.[9] ❖

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Guidelines

CDC Adds COVID-19 Vaccine to Its Routine Immunization

In February, the Centers for Disease Control and Prevention (CDC) updated its schedule of recommended immunizations to include COVID-19 shots and boosters for children, adolescents and adults after a recommendation by the agency's Advisory Committee on Immunization Practices and other healthcare organizations, including the American Academy of Pediatrics.

"This means COVID-19 vaccine is now presented as any other routinely recommended vaccine and is no longer presented in a special 'call out' box as in previous years," say Neil Murthy, MD, MPH, MSJ, and A. Patricia Wodi, MD, authors of the report recommending COVID-19 vaccines be added to the schedule. "This, in a sense, helps 'normalize' this vaccine and sends a powerful message to both healthcare providers and the general public that everyone ages 6 months and older should stay up to date with recommended COVID-19 vaccines (including a booster, when eligible), just as they would with any other routinely recommended vaccine."

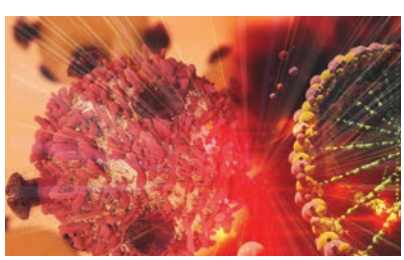
Specifically, the new schedule says children aged 6 months to 4 years can choose between a two-dose Moderna primary series, followed by a bivalent Moderna booster, or a three-dose Pfizer-BioNTech primary course. For 5-year-old children, the schedule recommends two doses of Moderna, followed by a bivalent mRNA booster, or two doses of Pfizer-BioNTech followed by the company's bivalent booster. For children aged 6 to 11, CDC recommends two doses of the Moderna vaccine or two doses of the Pfizer-BioNTech shot, in both cases followed by an mRNA booster. Those aged 12 to 18 years can choose between a two-dose Moderna series or a two-dose series from Pfizer-BioNTech or Novavax, followed by a bivalent booster for either. And, adults can choose a two-part primary series, followed by a bivalent booster dose.

The report also includes guidance for children, adolescents and adults who are immunocompromised, as well as new and updated guidance for the influenza, pneumococcal and measles, mumps and rubella vaccines. ❖

Vlachou, M. CDC Adds COVID Vaccines to Recommended Immunizations for Children, Adults. Yahoo News, Feb. 10, 2023. Accessed at finance.yahoo.com/news/cdc-adds-covid-vaccines-recommended-124016503.html.

Research

Study Links Persistent Tumor Mutation with Therapeutic Response to Immunotherapy Schedule



Investigators at the Johns Hopkins Kimmel Cancer Center and its Bloomberg-Kimmel Institute for Cancer Immunotherapy have found that a subset of mutations within the overall tumor mutation burden (TMB), termed "persistent mutations," are less likely to be edited out as cancer evolves, rendering tumors continuously visible to the immune system and predisposing them to respond to immunotherapy. This persistent mutation load may help clinicians more accurately select patients for clinical trials of novel immunotherapies or predict a patient's clinical outcome with immune checkpoint blockade, a type of immunotherapy.

In the study, the investigators hypothesized that tumors with a high persistent TMB (pTMB) would be most visible to the immune system and, therefore, would regress after exposure to immunotherapy. They evaluated the potential of pTMB, multicopy and single-copy mutations to predict response to immune checkpoint blockade among 542 patients with melanoma, nonsmall cell lung cancer, mesothelioma and head and neck cancer, and discovered that tumors with a high pTMB attained higher rates of therapeutic responses to the immunotherapy, while TMB, the number of loss-prone mutations, or tumor aneuploidy, less optimally distinguished tumors that responded from those that did not respond. In addition, when comparing tumor samples prior to immunotherapy and at the time of acquired resistance, the team observed a more than 60-fold lower probability of loss for persistent mutations. Persistent mutation load showed promising performance in predicting immunotherapy response when pTMB was computed from targeted next-generation sequencing, which is the testing modality routinely used in clinical practice.

According to the researchers, future steps include additional large-scale validation of the findings, as well as prospective analyses to evaluate the role of persistent mutation load to select patients for cancer immunotherapy. ❖

Persistent Tumor Mutation Burden Linked with Therapeutic Response to Immunotherapy. News Medical Life Sciences, Jan. 26, 2023. Accessed at www.news-medical.net/news/20230126/Persistent-tumor-mutation-burden-linked-with-therapeutic-response-to-immunotherapy.aspx.

Research

Blood-Based Biomarkers Can Detect Alzheimer's 10 Years Before Disease Onset

A new study conducted by researchers at Karolinska Institutet on an inherited form of Alzheimer's shows that a protein called glial fibrillary acidic protein (GFAP) is a possible biomarker for very early stages of the disease, which could one day lead to an earlier detection of this serious and common disease.

For the study, the researchers analyzed 164 blood plasma samples from 33 mutation carriers and 42 relatives without the inherited pathogenic predisposition. The data were collected between 1994 and 2018. Results reveal clear changes of several blood protein concentrations in the mutation-carriers. "The first change we observed was an increase in GFAP approximately 10 years before the first disease symptoms," says the study's last author Caroline Graff, professor at the department of neurobiology, care sciences and society at Karolinska Institutet. "This was followed by increased concentrations of P-tau181 and, later, NfL (neurofilament light protein), which we already know is directly associated with the extent of neuronal damage in the Alzheimer's brain. This finding about GFAP improves the chances of early diagnosis."

"Our results suggest that GFAP, a presumed biomarker for activated immune cells in the brain, reflects changes in the brain due to Alzheimer's disease that occur before the accumulation of tau protein and measurable neuronal damage," says the study's first author Charlotte Johansson, doctoral student in the same department at Karolinska Institutet. "In the future, it could be used as a noninvasive biomarker for the early activation of immune cells such as astrocytes in the central nervous system, which can be valuable to the development of new drugs and to the diagnostics of cognitive diseases." ❖

Karolinska Institutet. Blood-Based Markers May Reveal Alzheimer's Disease Ten Years Before Symptoms Show. Neuroscience News, Jan. 10, 2023. Accessed at neuroscience news.com/gfap-alzheimers-blood-22219.

Research

New Approach May Better Treat SLE

Findings in a recent study conducted at Vanderbilt University Medical Center suggest that targeting iron metabolism in immune system cells may offer a new approach for treating systemic lupus erythematosus (SLE) — the most common form of the chronic autoimmune disease lupus. Specifically, blocking an iron uptake receptor reduces disease pathology and promotes the activity of anti-inflammatory regulatory T cells in a mouse model of SLE.

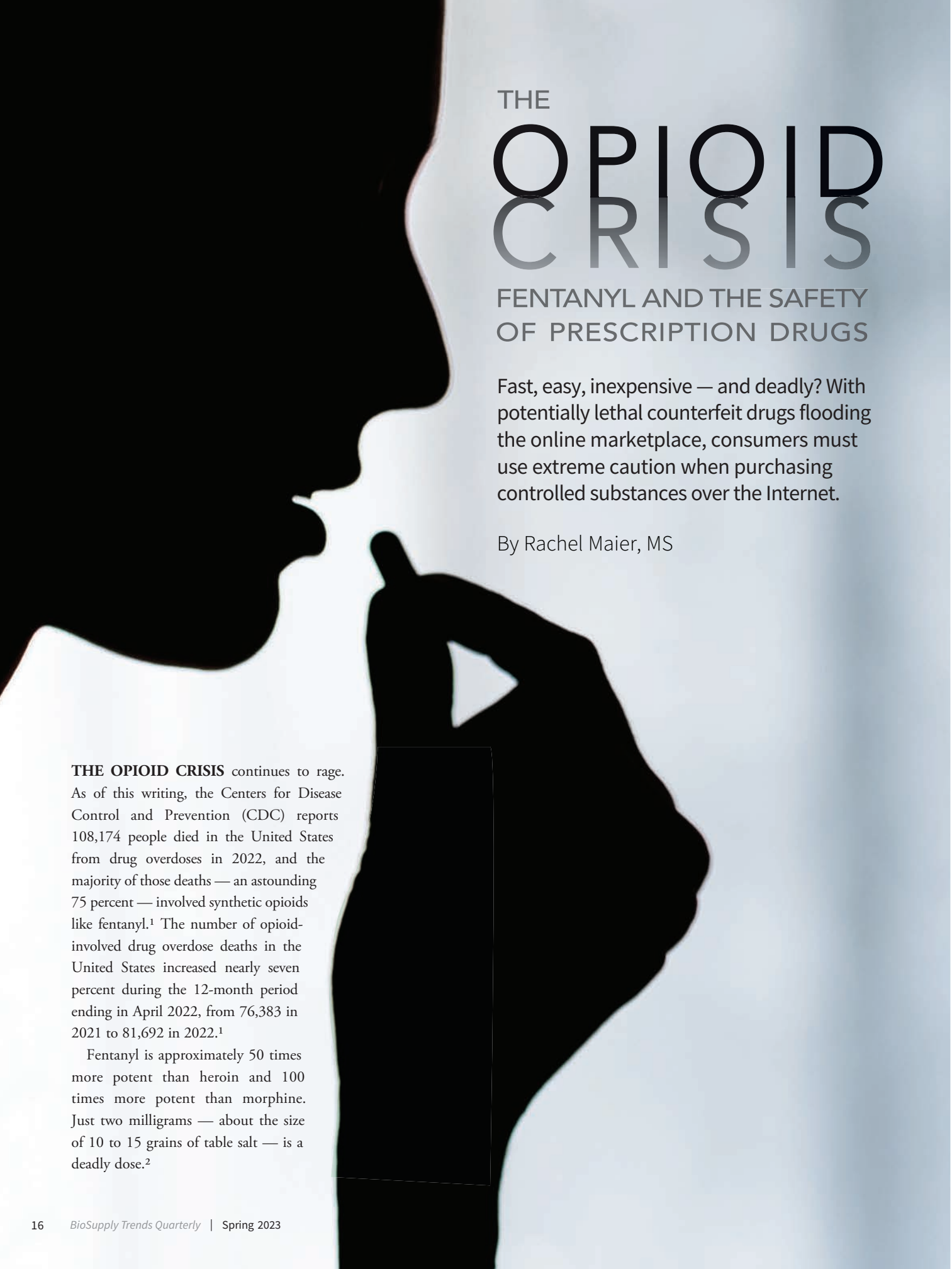
The study was conducted based on postdoctoral fellow Kelsey Voss, PhD, who found iron appeared to be a "common denominator in many of the problems in T cells." To explore T cell iron metabolism in lupus, Dr. Voss and Jeffrey Rathmell, PhD, professor of pathology, microbiology and immunology and Cornelius Vanderbilt chair in immunobiology, used a CRISPR genome editing screen to evaluate iron-handling genes in T cells. They identified the transferrin receptor, which imports iron into cells, as critical for inflammatory T cells and inhibitory for anti-inflammatory regulatory T cells. They also found that the transferrin receptor was more highly expressed on T cells from SLE-prone mice and T cells from patients with SLE, which caused the cells to accumulate too much iron.

According to Dr. Voss, an antibody that blocks the transferrin receptor reduced intracellular iron levels, inhibited inflammatory T cell activity and enhanced regulatory T cell activity. Treatment of SLE-prone mice with the antibody reduced kidney and liver pathology and increased production of the anti-inflammatory factor, IL-10.

"It was really surprising and exciting to find different effects of the transferrin receptor in different types of T cells," Dr. Voss said. "If you're trying to target an autoimmune disease by affecting T cell function, you want to inhibit inflammatory T cells but not harm regulatory T cells. That's exactly what targeting the transferrin receptor did."

In T cells from patients with lupus, expression of the transferrin receptor correlated with disease severity, and blocking the receptor in vitro enhanced production of IL-10. The researchers are interested in developing transferrin receptor antibodies that bind specifically to T cells to avoid any potential off-target effects (the transferrin receptor mediates iron uptake in many cell types). They are also interested in studying the details of their unexpected discovery that blocking the transferrin receptor enhances regulatory T cell activity. ❖

Study Identifies Potential New Approach for Treating Lupus. The Print, Jan. 15, 2023. Accessed at theprint.in/science/study-identifies-potential-new-approach-for-treating-lupus/1315377.



THE OPIOID CRISIS

FENTANYL AND THE SAFETY OF PRESCRIPTION DRUGS

Fast, easy, inexpensive — and deadly? With potentially lethal counterfeit drugs flooding the online marketplace, consumers must use extreme caution when purchasing controlled substances over the Internet.

By Rachel Maier, MS

THE OPIOID CRISIS continues to rage. As of this writing, the Centers for Disease Control and Prevention (CDC) reports 108,174 people died in the United States from drug overdoses in 2022, and the majority of those deaths — an astounding 75 percent — involved synthetic opioids like fentanyl.[1] The number of opioid-involved drug overdose deaths in the United States increased nearly seven percent during the 12-month period ending in April 2022, from 76,383 in 2021 to 81,692 in 2022.[1]

Fentanyl is approximately 50 times more potent than heroin and 100 times more potent than morphine. Just two milligrams — about the size of 10 to 15 grains of table salt — is a deadly dose.[2]

Synthetic opioids like fentanyl are often used recreationally along with heroin and/or cocaine to increase the drug's euphoric effects, sometimes with the user's knowledge and sometimes without it.[3] But it doesn't stop there: Fentanyl is increasingly being folded into counterfeit pills that look like legitimate prescriptions for controlled substances such as OxyContin, Xanax and Percocet, among others, without consumer knowledge or consent. Counterfeit pills pose an alarming risk to the health and life of everyday Americans, since the majority of them contain a potentially lethal dose of fentanyl, according to the U.S. Drug Enforcement Agency (DEA), and it's difficult to discern which pills are real and which are fake.[4]

Compounding the problem are illegal, unregulated "rogue" online pharmacies selling fake pills made to look like the real thing. Unsuspecting consumers — even patients with credible medical needs and legitimate documented doctors' orders — are at grave risk for incidental ingestion of a life-threatening dose of fentanyl they don't even know is there.

But how does the fentanyl get into the pills in the first place, and how can consumers be sure their prescription pills are safe?

Legitimate vs. Counterfeit Pills

To answer that question, we must first sort out the difference between legitimate prescription pills and counterfeit pills.

Legitimate prescription pills are medicines regulated by the U.S. Food and Drug Administration (FDA), made in registered pharmaceutical production facilities, prescribed by medical providers and dispensed by state-board certified pharmacies. They contain the correct amount of active ingredients needed to elicit a desired therapy. When used correctly under a healthcare provider's supervision, legitimate prescription medications are safe and effective, but misuse of them carries a slew of risks, including abuse, addiction and overdose.[5]

Counterfeit pills are made to look like real brand-name medications, but they have different ingredients than their legitimate counterparts.[6] While the active ingredient(s) may be present, the amount is often incorrect; but the active ingredient might not be present at all, and the pills may contain harmful substances instead. Counterfeits are illegal, unlicensed, sold without a prescription and not regulated; of unknown origin, safety and effectiveness; dispensed without adequate directions for safe use; and do not include FDA-required consumer warnings about the serious health risks associated with the prescription drug.[7]

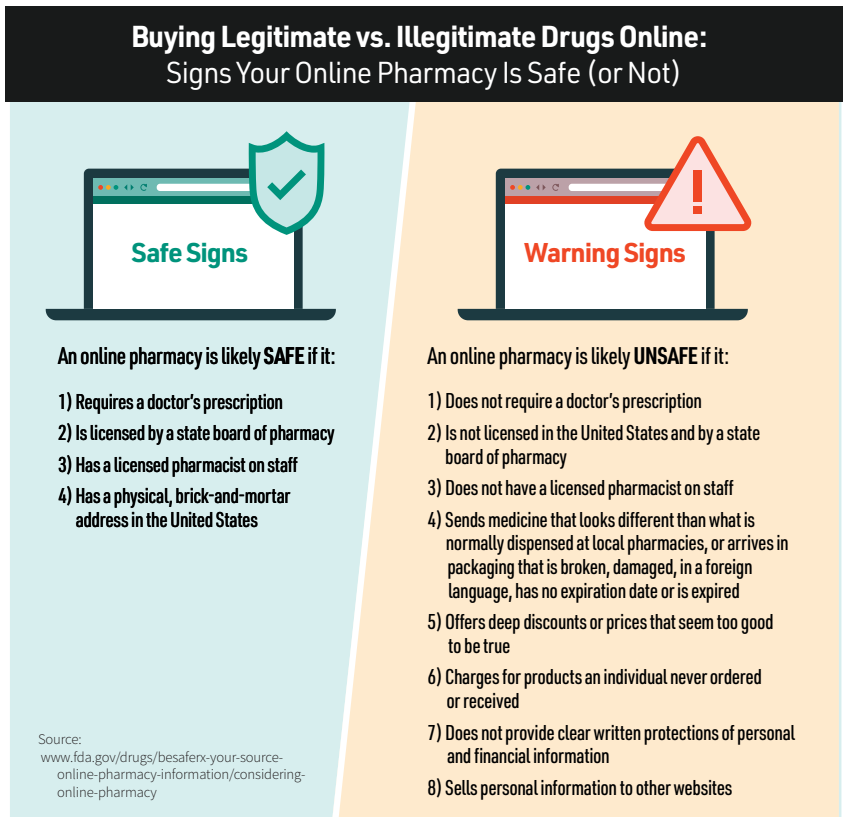
Perhaps what's most concerning, though, is not what's missing from the counterfeit pills but what may be added to them. According to Interpol, "some fake medicines have been found to contain mercury, arsenic, rat poison or cement."[8] Counterfeit prescriptions pose a threat to the health and safety of consumers regardless of whether they are laced with fentanyl or not, but when they do contain fentanyl, the danger to consumers sharply increases.

DEA found that of the fentanyl-laced fake prescription pills seized and analyzed in 2022, six out of 10 contained a potentially lethal dose of fentanyl. This is an increase from DEA's previous announcement in 2021 that four out of 10 fentanyl-laced fake prescription pills were found to contain a potentially lethal dose.[4] According to the agency, the sharp surge in pills laced with fentanyl can be traced to Mexican drug cartels that buy precursor chemicals from China or India, convert them into fentanyl, then press lethal doses into pills made to look like legitimate prescription pills.[9] In addition to including dangerous ingredients, counterfeits are also typically produced in substandard conditions without quality control protocols, and they are often labeled to look like real medications. The pills are then illegally trafficked into the United States where they are often sold online, primarily via social media.[6,10]

According to the National Association of Boards of Pharmacy's July 2015 report, 96 percent of online pharmacies are noncompliant with federal and state laws or its own safety and practice standards.

Rogue Online Pharmacies

Internet-based pharmacies sound ideal: lower costs, faster service, no lines and home delivery. Shopping for prescription medications online sounds like a practical solution to sky-high drug prices, and sometimes it is. When an online pharmacy is legitimate, consumers can use it with confidence. But not all online pharmacies are the real deal. In fact, according to the National Association of



Boards of Pharmacy's July 2015 report, 96 percent of them are noncompliant with federal and state laws or their own safety and practice standards.[11]

Rogue online pharmacies illegally capitalize on consumers who either want easy access to controlled substances without a prescription (for either medicinal purposes or recreational use) or want convenient access to legitimate prescriptions at a lower cost. According to a 2021 survey conducted by the Association for Safe Online Pharmacies (ASOP), one in five Americans relies on online platforms or social media sites to find an Internet-based pharmacy.[12] While some legitimate online pharmacies are regulated by FDA, rogue online pharmacies are not, and they intentionally target unsuspecting consumers to illegally sell counterfeit drugs. Consumers who purchase from these illegitimate retailers are likely not getting the active ingredient they want or need, and if they do, it is often not in the amount needed to make a meaningful difference, which significantly impacts patient outcomes for those genuinely using prescription drugs for therapeutic purposes.[8]

But despite the dangers, ASOP found many Americans assume online sales of prescription medications are legitimate, regulated and safe. While nearly half of the study participants acknowledged it is at least somewhat risky to purchase medications on the Internet, the majority also mistakenly believe FDA has oversight of any medication sold there.[12] The survey also showed nearly half of Americans aged 18 years and older have ordered prescription medication over the Internet, either for themselves or someone in their care, and 29 percent said they would likely buy prescription medications online without consulting a medical provider first.[12] Risk did not seem to be a significant deterrent to the behavior, while cost and convenience were primary drivers of it.

The Snare of Social Media

Medical use of prescription medication is risky enough when pills are obtained through rogue online pharmacies, but nonmedical use of prescription medication (NUPM) makes an already risky practice more dangerous, especially when the pills are obtained through social media. Rogue online pharmacies are increasingly using sites such as TikTok, Twitter and Snapchat (among others) to target customers — particularly young people — to make counterfeit prescription-strength drugs such as Xanax, Percocet and Vicodin, among others, incredibly easy, inexpensive and somewhat anonymous to obtain.

Data shows the overwhelming majority of teens have regular access to and use of the Internet, and the majority of them regularly use social media. According to a 2018 report from the American Academy of Child and Adolescent Psychiatry, two-thirds of teens have their own mobile devices with Internet capabilities; 90 percent of teens ages 13 to 17 have used social media; 75 percent report having at least one active social media profile; and 51 percent report visiting a social media site at least daily.[13]

Further complicating matters, CDC reported that the estimated prevalence of NUPM among high school students is 20.7 percent, and the U.S. Department of Justice says one in six teens have used a prescription drug to deliberately alter their mood or get high.[14,15] A 2021 study of trends in drug overdose deaths among teens aged 14 to 18 reported that in 2010, 518 died from drug overdoses. By 2021, that number more than doubled

to 1,146, and fentanyl was identified in 77.14 percent of the deaths.[16] While the study did not discuss how victims had obtained the drugs, the National Center on Addiction and Substance Abuse identified an increased risk associated with substance abuse for youth who use social media.[17]

The phenomenon of illegally obtaining controlled substances via social media is not new, nor is it limited to teenagers. In 2011, the National Survey on Drug Use and Health showed young adults aged 18 to 25 have the highest annual and monthly rates of NUPM of any age group in the United States.[18] Ryan Haight was one such young adult. The 18-year-old honors student and varsity athlete died from an overdose of Vicodin, an opioid drug available by prescription only. He obtained the drug via an illicit online environment.[17] His death led to the passage of the 2008 U.S. federal legislation, formerly known as the Ryan Haight Online Pharmacy Consumer Protection Act, but now known as the Ryan Haight Act (RHA), which established regulatory provisions and tools for DEA to control the sale and dispensing of controlled substances over the Internet.[17]

But the provisions of the Act did not adequately deal with the problem. By 2013, the International Narcotics Control Board (INCB) warned that illegitimate, rogue online pharmacies use social media to target young audiences, hoping to sell illicit drugs to the vulnerable population.[19] Hamid Ghodse, president of INCB, noted that "illegal Internet pharmacies have started to use social media to get customers for their websites, which can put large, and especially young, audiences at risk of dangerous products, given that the World Health Organization has found that over half of the medicines from illegal Internet pharmacies are counterfeit."[19]

In the years since the INCB's warning regarding social media and teen substance abuse, the problem has just gotten worse, and some experts say the COVID-19 pandemic may have exacerbated the problem. During that time, "many young people felt isolated due to limitations of attending school, engaging in activities or seeing friends," says Kelsey Bradshaw, PhD, licensed clinical psychologist and intern supervisor at Sharp's Mesa Vista's Child and Adolescent Unit. "For some, this may have increased consideration of trying drugs as something to do or to cope with distressing emotions. The challenge with fentanyl is that some young people may not intend to use fentanyl but end up with it, thinking it is something safer."[20]

Illegitimate online pharmacies are increasingly using sites such as TikTok, Twitter and Snapchat (among others) to target customers — particularly young people — and making counterfeit prescription-strength drugs such as Xanax, Percocet and Vicodin, among others, incredibly easy, inexpensive and somewhat anonymous to obtain.

Twenty-two-year-old Sam Cioffi is one such young person who did not intend to use fentanyl but ended up with it anyway. On May 1, 2022, he took what he believed to be a Percocet, which he had purchased from a dealer he knew from the social media sites Instagram and Snapchat. He was dead the next morning; a toxicology report showed Sam had ingested fentanyl.[21] Sam's story is just one of many that underscores the importance of DEA's urgent message: "Never take a pill that wasn't prescribed directly to you. Never take a pill from a friend. Never take a pill bought on social media. Just one pill is dangerous and one pill can kill."[22]

What About Naloxone?

But doesn't naloxone reverse the effects of fentanyl and other opioids?

It does, and there is a growing push to combat the surge of opioid-involved overdoses by making naloxone (generic for Narcan) widely available nationwide, getting it to the people who need it, where they need it, before they need it (and hoping they never do). And it's no wonder: Naloxone blocks the effects of opioids and can reverse an overdose within minutes. It restores normal breathing in a person whose breath has slowed or stopped due to opioid overdose. But time is of the essence: It must be administered quickly. (And, it's important to note that when overdose is due to stronger opioids like fentanyl, more than one dose of naloxone may be required.[23])

In many states, naloxone is available at pharmacies without a prescription. Many community-based naloxone

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distribution programs also provide naloxone kits to anyone who requests them for free. Carrying naloxone is increasingly common among law enforcement officials and first responders to preemptively prepare for responding to accidental overdoses, including those that occur due to accidental exposure to fentanyl in the course of duty.[24] Even everyday citizens are being asked to regularly carry doses of naloxone with them so the emergency medication is on hand where and when it is needed. Good Samaritan laws protect bystanders from negative repercussions of administering it to someone they suspect is overdosing on opioids.[23]

Getting naloxone in the hands of those who are most likely to overdose on opioids is already a tall order, but predicting when and where otherwise low-risk individuals may need it is far more difficult. People who unknowingly purchase what turn out to be counterfeit pills from illegitimate pharmacies don't realize they may need naloxone because they don't suspect their pills are fake in the first place, let alone that fentanyl could be hidden inside them. While naloxone is increasingly easy to get without a prescription, those who are merely trying to save money by filling a legitimate prescription online may not see a need for it themselves, let alone preemptively get a "just in case" dose to carry with them. While co-prescribing naloxone for people at high risk of opioid overdose (such as those who are taking high doses of opioid medication that have been prescribed by their doctor, and especially those struggling with opioid use disorder) is an effective strategy to get lifesaving naloxone in their hands in case they ever need it, unknowingly buying counterfeit pills from rogue online pharmacies precludes that layer of protection for people who never intend to take opioids at all.

Safeguards for Prescription Medications

Even amid the alarming influx of fentanyl into the United States, especially in the form of counterfeit prescription pills, FDA emphasizes its focus is on ensuring the quality of legitimate prescription drugs and safeguarding the integrity of pharmaceutical distribution to Americans, stating "FDA implements key provisions of the Drug Supply Chain Security Act (DSCSA), which outlines steps to achieve interoperable, electronic tracing of product at the package level to identify and trace certain prescription drugs as they are distributed in the U.S."[25] The Act is meant to enhance FDA's ability to help protect consumers from "exposure to drugs that may be counterfeit, stolen, contaminated or otherwise harmful."[25]

While DEA is focused on targeting rogue online pharmacies for prosecution and shutting down the illegal websites, DSCSA prevents harmful drugs from entering the legitimate supply chain in the first place, detects harmful drugs if they do enter the supply chain and enables rapid response when such drugs are found.[26] Legitimate pharmaceutical producers work within the confines of DSCSA to determine whether trading partners (including manufacturers, repackagers, wholesale distributors, third-party logistics providers and other pharmacies) are licensed or registered. Pharmacies must only accept medicines accompanied by three pieces of product tracing documentation, including transaction information, transaction history and transaction statement. This information must be stored for six years

and provided when selling a prescription drug to a trading partner.[25]

When suspected illegitimate drugs are found, pharmacies must quarantine and investigate them; work with the manufacturer to ensure they are not distributed to patients; and notify FDA and trading partners from whom they bought them and to whom they sold the drug products.[26]

Additionally, all imported shipments of FDA-regulated drug products are reviewed electronically by FDA, and they must meet FDA's standards for quality, safety and effectiveness. "FDA verifies compliance with the following requirements as applicable: registration, listing, drug application, drug labeling and drug current good manufacturing practices [...] FDA also randomly samples and tests imported products."[25]

Further, FDA issued a draft guidance for industry on anti-counterfeiting for pharmaceutical manufacturers who may want to use physical-chemical identifiers (PCIDs) in solid oral dosage forms. A PCID is a substance or combination of substances possessing a unique physical or chemical property that unequivocally identifies and authenticates a drug product or dosage form.[25]

FDA: Legitimate Drugs Remain Safe

Illegitimate, counterfeit drugs pose a major threat to the health and well-being of the American people — no doubt about that. But despite the danger, FDA insists that "the U.S. drug supply is among the safest in the world," and emphasizes that consumers can be confident their prescription drugs are safe and effective when obtained with a valid prescription by a credentialed medical provider through state licensed pharmacies.[25]

The best strategies to guard against mistakenly purchasing fraudulent medications are to 1) never buy from a social media site; 2) never accept or take pills from anyone else (one should always purchase his or her own medications from a verified pharmacy); and 3) always verify online pharmacies are state licensed before purchasing medications. Consumers who wish to purchase medication online should only use pharmacies that require a doctor's prescription, have licensed pharmacists on staff, have a physical, brick-and-mortar address in the United States and are licensed by a state board of pharmacy. The FDA state boards of pharmacy online search tool is a great resource to verify legitimacy (See www.fda.gov/drugs/besaferx-your-source-online-pharmacy-information/locate-state-licensed-online-pharmacy).

But perhaps more importantly, talk openly and often to young people about the extreme danger of buying pills over the Internet, especially via social media. Reinforce DEA's "one pill can kill" message and emphasize the risk just isn't worth it. If controlled substances are necessary for a medical need, doctors should emphasize the importance of obtaining a legitimate prescription — and verifying the pharmacy is the real deal before filling it. ❖

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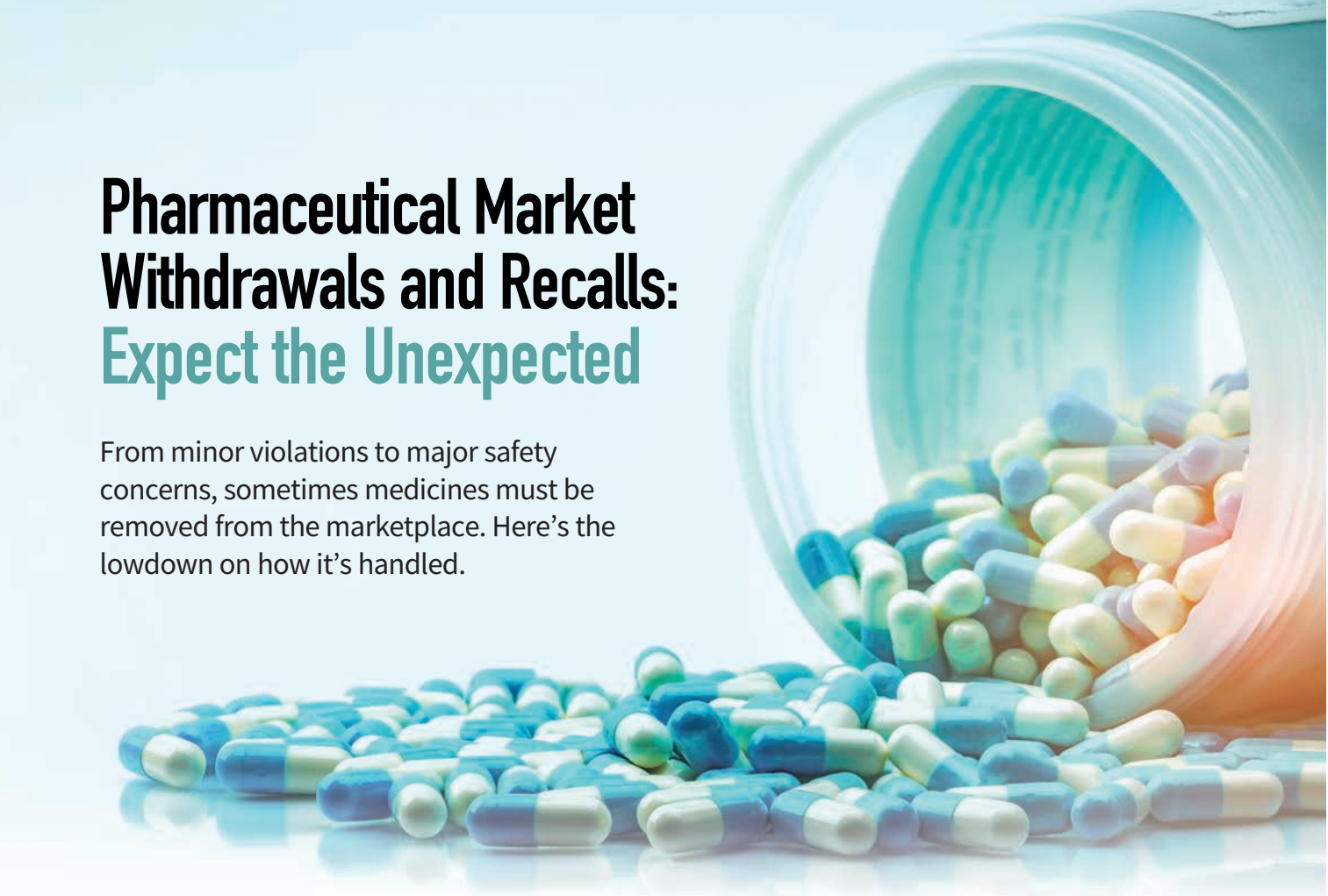
Pharmaceutical Market Withdrawals and Recalls: Expect the Unexpected

From minor violations to major safety concerns, sometimes medicines must be removed from the marketplace. Here's the lowdown on how it's handled.



By Amy Scanlin, MS

A PATIENT'S PATH toward heath outcome goals is rarely linear. Even the best treatment plans can become sidetracked, waylaid by interruptions in pharmaceutical supply chains and risks posed by the very pharmaceuticals themselves. Thousands of drugs are withdrawn or recalled from the marketplace annually for any number of reasons. The main differentiator in a manufacturer's decision to withdraw or recall a product is the risk that product poses to those who take it.

When a drug product is withdrawn or recalled, it requires vigilance: Drug products must be removed from the marketplace, and manufacturers, healthcare providers and pharmacists — all patient-facing entities — must work together to get the job done. It also requires pivots to care plans and constant communication to ensure patients are well-informed of changes and how to handle them.

Market Withdrawals

Products are withdrawn from the marketplace, generally, for one of two reasons: when the manufacturer identifies a minor problem (known in U.S. Food and Drug Administration (FDA) parlance as a "minor violation") with the product; when the manufacturer rotates stock or discontinues a product, perhaps due to declining sales; or as a result of a more effective drug product receiving a new FDA approval. A market withdrawal may also be initiated when product or manufacturing equipment adjustments are made.

Market withdrawals are only used in instances when there is no evidence FDA laws have been violated by the manufacturer or distributor and when the risk of consumer harm is extremely low.

Product Recalls

Product recalls occur when a drug product is in violation of FDA law.[2] This may be a problem with its strength or potency, a mislabeling violation or product contamination. Most recalls are voluntary and initiated by the manufacturer, but FDA has statuary authority to request and even require product recalls. FDA will also seize products if recalls are not executed in an approved manner or

when the agency determines the violative products are still being manufactured. However, FDA product seizures are rare.

Recalls are classified by the risk the product poses and the likelihood of potential danger to the patient (see FDA Recall Classifications). When determining which classification will be used, FDA looks at a number of variables, including whether any disease or injuries have already occurred that can be attributed to the violative product; whether the recall and subsequent lack of product availability is likely to contribute to negative health outcomes for those who use the product; the degree of seriousness of those negative health outcomes; and any consequences, both immediate and long-term. A medical safety alert is used in place of a recall for violative medical device products. This may include combination drug-device products when the device component presents an unreasonable safety risk.

Recall Plans

The recalling company, typically the manufacturer, is responsible for developing a recall plan, although FDA will guide the recalling company on the specifics of recall requirements. The depth of the recall is dependent on the risks the product poses and how widely the product was distributed.

The recall plan will include customer communication methods and frequency; content and frequency of FDA-required recall status reports; and instructions for product disposal or reconditioning.

The agency will consider terminating the recall only when it determines efforts to warn customers and identify and remove affected lots from the marketplace are complete. FDA will also need confirmation that all affected products were destroyed or reconditioned as required. An analysis of why the violation occurred followed by the implementation of effective corrective actions must also be completed prior to a recall termination.

Communication Is Key

FDA facilitates communication of recalls through weekly enforcement reports found on the agency's website. Product withdrawals will not be included in FDA's weekly enforcement report, since these reports include only products found to be in legal violation of FDA regulations (products that have been recalled).

Additional recall notification sources include state boards of pharmacy and state health departments, compounder outsourcing facilities and other vendors in addition to the drug manufacturer itself. FDA recommends manufacturers initiate direct customer communications concerning product recalls only with those who received the affected lots to avoid "recall fatigue."

in repository of information related to pharmaceuticals, including recalls, and is powered by the American Society of Health-System Pharmacists, IBM Watson and other medical information suppliers.

Should the recalling company wish to issue a public statement regarding the recalled product, FDA requests a draft submission of the proposed warning be first submitted to the agency for its review and comment. FDA will only issue a public warning of a recalled product when urgency dictates the need for additional communication beyond that of the recalling company. However, FDA also notes that it may delay publication of a recall notification in its weekly enforcement reports should the agency determine that a public notification in advance of providers having an opportunity to discuss the recall with their patients may cause unnecessary and harmful anxiety.

The main differentiator in a manufacturer's decision to withdraw or recall a product is the risk that product poses to those who take it.

Providers and patients also have opt-in communication options for receiving recall notifications such as the Patient Notification System (PNS) led by the Plasma Protein Therapeutics Association and developed with support from the Immune Deficiency Foundation. This PNS, specific to plasma products, requires an online registration and sends alerts via the registrant's preferred communication method. More information on the PNS can be found at www.patientnotificationsystem.org. The drugs.com database is another opt-

Once notification of a withdrawal or recall is received, communication with in-house supply chains that distribute the affected drug must be initiated quickly. Physicians, prescribers, pharmacists and medication administrators will review customers and dispensing records to identify those who have been prescribed the drug. Patients will undoubtedly have questions, so it is important for public-facing providers to be prepared.

Patients should also be encouraged to play a proactive role in keeping track of their drugs, including recording the

names and lot numbers of the products they are using. This can help them to quickly determine whether their drugs are affected by a recall, possibly even in advance of outside communication.

If the recalled drug might result in a product shortage, the recalling company is required to explain the situation to its customers, as well as draft a plan to address the shortage. While suitable alternative treatment options are being identified, it is important to remind patients that any changes to medications and dosing should first be discussed with their healthcare professionals.

Identifying Recalled Products

While communication outreach is underway, an inspection of healthcare facilities, storage areas and locations where drugs are prepared or dispensed, including off-site clinics, must be simultaneously conducted. This includes a review of all purchasing records and sample logs to determine if any of the affected drug lots are present in the facilities or on order. A comparison of National Drug Code numbers, lot numbers, etc., will confirm whether the drug in question matches what is on providers' or patients' shelves. As part of the recall announcement, drug manufacturers must provide copies of the affected labels and other identifying information. Any identified medications must be removed, returned or destroyed per the instructions found in the recall notice. Additionally, incoming medication shipments should be monitored to prevent recalled products from entering the facility.

Documentation of efforts to identify and recall the affected drugs must be provided to the manufacturer that will in turn prepare an FDA recall compliance report. A facility report will include the date the recall notice was received, the dates any and all subsequent actions were taken and the specifics of those actions, including quantities removed and what was done with them. Communication efforts with prescribers, patients and any other requirements included in the recall notice must also be documented.

Patients should also be encouraged to play a proactive role in keeping track of their drugs, including recording the names and lot numbers of the products they are using.

FDA, state boards of pharmacy, health departments and other official entities all have an interest in ensuring recalls are conducted in accordance with the FDA-approved plan. All may initiate compliance inspections and recall effectiveness checks and fine entities determined to be out of spec.

Expect the Unexpected

It is best practice for manufacturers to establish and document a recall plan as part of a standard operating procedure (SOP). The plan should cover all aspects of a recall from start to finish and be regularly practiced so the response is automatic when unanticipated issues arise. In short, manufacturers should expect the unexpected.

An effective recall SOP includes and addresses the following key points:

- Name of the person in charge of overseeing the entire recall process. Ideally, that person will be available to orchestrate the recall; however, the SOP should be explicit enough that all staff can easily and independently complete their tasks, reporting their progress up the chain using good documentation practices.
- List of all locations where drugs flow through the system: receiving and inspection areas, floor stocks and automated dispensing stock cabinets, preparation areas, pharmacy carts, clinics and outpatient practices — any area that might hold or dispense pharmaceuticals. And, those locations must be cross-referenced with the affected lot numbers.

FDA Drug Recall Classifications[2]

Class I	Class II	Class III
A dangerous or defective product that could cause serious health problems or death	A product that might cause a temporary health problem, or pose a slight threat of a serious nature	A product that is unlikely to cause any adverse health reaction, but that violates FDA labeling or manufacturing laws

• Instructions for identifying affected patients and their providers through a review of dispensing records.

• Location of a designated, quarantined in-house collection area for the recalled product and post-signage so mistakes are not made by unknowing staff.

• Details for a patient notification system (for both inpatients and outpatients), along with a tracking system to confirm when they were contacted, by whom and by what method, as well as the outcome. And, those contacts must be cross-referenced with product dispositions, if applicable, per the manufacturer's instructions.

• Documentation of the date products were disposed of or returned to the manufacturer.

• Instructions for monitoring incoming shipments to prevent new product from entering the facility.

• Benchmark for what recall success should look like based on risk, per the recall classification.

• An understanding of all applicable laws and compliance with additional state- and/or county-specific requirements. New York state, for example, requires pharmacies to contact patients in the event of a Class I recall within seven days of a recall notice. Often a last line of communication for patients regarding their prescriptions, pharmacies may feel a particular responsibility for timely communications placed upon them.

Be Ready to Respond

There is no time to waste when executing a recall plan. Identification and removal of the affected product, notification of patients and providers, along with documentation of how the recall was executed will demonstrate a facility's level of compliance. All of these steps are conducted while simultaneously determining appropriate alternative drugs for patients, each unique to their individual needs. The execution of a recall must be seamless and complete to be effective.

Product market withdrawals and recalls are stressful events. But, through a concerted effort and diligent attention to detail, the affected drugs can be quickly removed from circulation, protecting patients from the potential of future harm. ❖

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Tracking Medical Error and Misdiagnosis

While studies have reported about the high number of deaths due to medical error and misdiagnosis in the U.S., how these numbers are calculated and whether they are correct is a matter of debate.

By Jim Trageser

NO ONE DISPUTES that physicians and other medical professionals make mistakes. They are, after all, human beings — as fallible as any of us. Training, well-designed protocols and discipline can reduce the number of medical errors, but they will never eliminate them. Yet, how often are mistakes made, and how many people die because of them? That topic is the source of great dispute and debate, with several high-profile studies generating plenty of headlines, while divulging relatively little in the way of hard numbers.

For physicians charged with running a medical practice or hospital, trying to measure the risks posed to both patients and the fiscal solvency of the business is difficult — especially without the kind of numbers readily available for, say, healthcare-associated infections (HAIs) or falls. Indeed, practices, hospitals, clinics and other healthcare facilities have access to the statistics on HAIs and falls because both are regularly reported to and tracked by local and state health agencies and the Centers for Disease Control and Prevention (CDC). But, this is not so with deaths due to medical error and misdiagnosis. CDC does not have a mechanism in place for reporting these deaths, which makes gauging the severity of the issue little more than a series of educated guesses. It's an actuary's nightmare.

Tracing the Numbers

The issue of mortality from human error in the healthcare profession first came to the attention of the general public in the spring of 2016, when Johns Hopkins researchers published a meta-analysis that claimed more than a quarter million Americans die due to medical misdiagnosis or error every year.[1] The mainstream media quickly picked up on that startling claim, with headlines and newscasters proclaiming that going to the doctor was among the riskiest things one could do. In fact, the numbers suggested by that study would make medical error and misdiagnosis the third-leading cause of death in

Source: Adapted from The Joint Commission's 2023 National Patient Safety Goals. Accessed at www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2023/2023-hap-npsg-goals-102122_simple.pdf.

this country, behind only cancer and cardiovascular disease. If HAIs and falls in a healthcare setting were added to the Johns Hopkins claim, that would make an eye-catching number of roughly 400,000 Americans every year dying while under medical care.

Another group of Johns Hopkins researchers followed up that meta-analysis in December 2022 with a study focused specifically on diagnostic errors during emergency room visits. That study concluded that 250,000 deaths a year are attributable to medical errors in the emergency room alone.[2]

While the 2016 Johns Hopkins meta-analysis was the first time most laypeople had heard about medical error, it's important to note that the authors relied on a survey of previous studies that had suggested medical error was underreported, and their numbers were extrapolated from those studies. Indeed, one of those earlier studies is still cited: a 1999 study from the Institute of Medicine (IOM) (since renamed the National Academy of Medicine) that estimated as many as 98,000 Americans die each year from preventable mistakes.[3] And that study was based on data from a 1984 study of patients treated in New York hospitals and another from Colorado at about the same time.[4]

Raising Concerns About Those Numbers

The Johns Hopkins study didn't raise nearly the same level of enthusiasm among the mainstream media about the concerns skeptics immediately raised about the 2016 Johns Hopkins meta-analysis. A few weeks after the meta-analysis was released, Medscape published an article reporting on it and then ran an analysis of the feedback it had received. Many physicians were among the 500 Medscape readers who posted criticisms about the methodology of the meta-analysis, with comments such as:[5]

- Correlation was confused with causation.
- Unavoidable complications were classified as errors.
- Gravely ill patients who were facing an imminent death regardless of treatment were included in the studies.
- Some high-risk conditions offer no easy nor universally agreed-upon treatment.

Just a few months after the publication of the meta-analysis, the same journal that had published it ran a rebuttal, pointing out that, scientifically speaking, the Johns Hopkins claims weren't even contained in an actual study: "Though the paper by Makary and Daniel was widely cited as 'a study,' it presented no new data nor did it use formal methods to synthesize the data it used from previous studies. The authors simply took the arithmetic average of four estimates since the publication of the IOM report, including one from HealthGrades, a for-profit company that markets quality and safety ratings, a report from the U.S. Office of the Inspector General and two peer-reviewed articles. The paper did not apply any established methodology for quantitative synthesis, nor did it include a discussion either of the intrinsic limitations of the studies used or of the errors associated with the extrapolation process."[6]

In the years since the 2016 meta-analysis was released, other researchers have combed through it and brought forth even more pointed criticism of both its methods and conclusions. An analysis in 2019 referred to the Johns Hopkins estimates of deaths from medical error as "outlandish."[7] Another analysis in 2021 by a Canadian researcher at McGill University observed, "The idea that medical error is the third-leading cause of death in the U.S. is indeed a fiction, an overestimation that has negative consequences."[8]

Similar to the pushback to the 2016 meta-analysis, the 2022 Johns Hopkins study also has physicians questioning its methodology, as well as the scale of its claims. In the Dec. 30, 2022, edition of the *Wall Street Journal*, Kristen Panthagani, MD, PhD, an emergency physician at Yale New Haven Hospital, argued that the statistical analysis underlying the study was based on too small a sample size for any kind of meaningful extrapolation.[9] It should be noted that two of the study authors responded to Dr. Panthagani's opinion piece with a letter to the editor in the Jan. 5, 2023, edition of the *Wall Street Journal*, rebutting her arguments, and countering that she misrepresented their methodology.[10]

And going back to the beginning, the original 1999 IOM study also had its methods and conclusions questioned. The medical school at Indiana University identified several significant flaws in the study, including the fact that all the patients in the source study were classified as "very sick," as well as the lack of a control group to provide comparison.[11] A month later, another analysis of the IOM study found that the estimated number of deaths seemed subjective, and that there was little supporting evidence for the claim that up to half of those deaths were preventable.[12] Most damaging, in 2005, the author of one of the studies cited by the IOM study weighed in, arguing that the IOM authors had inflated the risks in their extrapolations from his work, and had underplayed the increasing patient safety in hospitals.[13]

In Search of Hard Numbers

It goes without saying that an actual medical error has the potential to

cause great human and financial harm. We've all heard or read anecdotal stories about patients who had the wrong leg removed during surgery, who received the wrong dosage of a medication or who was otherwise a victim of what can only be described as malpractice.

But anecdotes do not make data. And without hard numbers, doing something — anything — about the problem is impractical: If we don't know what the numbers are to begin with, how on earth can we measure the efficacy of any solution? Further, if we don't have solid data, we can't even prioritize our response to the problem because we don't know how serious it is, what the costs are or how much of our limited resources should be put into addressing the problem.

Fortunately, while CDC still does not list medical error on its cause-of-death reporting forms, another agency has been attempting to quantify the scope of the issue. Shortly after the original IOM study was published, Congress designated the Agency for Healthcare Research and Quality (AHRQ) (under the Department of Health and Human Services) to issue annual reports on patient safety.[14] AHRQ commissioned a project in 2008 to explore alternative methods of documenting real cases of medical error. Its resultant report recommended allowing patients to report incidents they felt represented a failure of their medical providers that resulted in an adverse reaction.[15]

Still, in the decade since that report spelled out the parameters of how a parallel reporting system could be established to track deaths from medical error that the CDC does not capture, it does not seem the AHRQ has issued any reports on actual numbers of deaths from medical error.

Addressing Errors

While hard numbers remain scarce, that doesn't mean the issue of medical error can't be addressed. One organization working to reduce medical error is the The Joint Commission, a nonprofit agency that accredits hospitals and other medical facilities. The Joint Commission's "National Patient Safety Goals" were established in 2002 to assist in providing guidance and goals for member facilities, and they are updated each year.[16] The goals are fine-tuned for different kinds of facilities: acute-care hospitals (see 2023 National Patient Safety Goals for Hospitals), outpatient facilities and assisted living facilities. The Joint Commission then provides a formal protocol that any member can adopt as a baseline for its own program — covering basic issues that need to be addressed in a disciplined manner such as ensuring the right patient is brought in for surgery, ensuring a patient's prescriptions are accurate and assigned to the right patient, setting response time for fall-prevention alarms, etc.

Many state licensing boards have instituted similar protocols in the wake of the IOM study and the 2016 Johns Hopkins meta-analysis.

Looking Ahead

Given the widespread mainstream media reporting on the Johns Hopkins' meta-analysis and study and their claims of deaths from medical error, physicians will be dealing with patients who accept these numbers as uncritically as the media reports on them. And in the age of social media, "medical error as meme" is likely here to stay for many years to come — whether or not those numbers are scientifically founded or statistically valid.[17]

Until the governing agencies are able and willing to track medical error and misdiagnosis similar to what they do with HAIs and falls, physicians will continue to face all kinds of conjecture without having recourse to the kinds of hard data that can refute it. Committing to procedures and protocols that minimize the possibility of medical error remains the best way to reassure patients and secure the financial security of practices and facilities. ❖

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COVID-19 Year Three: How Medical Professionals Can Balance Life, Family and Practice

Is finding a healthy work-life balance possible in the post-pandemic world?

By Meredith Whitmore

EVEN BEFORE THE PANDEMIC upended the U.S. healthcare system, many medical professionals already lacked a sense of healthy balance between their work and personal lives. But the COVID-19 virus's chaotic arrival changed the very way that medical facilities and providers function, and the disorientation meant a flood of extra work and stress for everyone on the front line. Now, three years later, the aftermath of the taxing workload is striking.

For example, before COVID-19, 75 percent of U.S. physicians stated they were happy while at work, but today only 48 percent can say that, and 84 percent of U.S. physicians stated they were happy outside of their workday, but that percentage is down to 58.[1] Further, even though the end of the pandemic has approached, staffing shortages, burnout and exhaustion continue to leave many providers struggling to manage all of their responsibilities in both clinical settings and at home.

It's no wonder that when asked in a 2022 survey conducted by health staffing firm CHG Health, 85 percent of new physicians said work-life balance is the top factor to consider when choosing a new job. Released early this year, the survey says that number shows a noteworthy uptick (22 percent) since the 2018 survey. "This increase is significant but not surprising," a firm representative explains, "when compared to similar surveys that have found physicians' attitudes toward the importance of wellness and work-life balance are changing in the wake of the pandemic." Work schedule and location were tied at 83 percent for the second

most important factors when doctors were selecting a first job.[2]

It's not just medical professionals that need a healthy standard for living well: Any professional would benefit from finding ways to develop peace and contentment with the way they live their lives each day. But if people have attempted to find this ostensible nirvana for decades, why haven't more of them discovered that elusive space? Maybe it has to do with the fact that society is often trapped in old mindsets. Insanity, as Einstein allegedly said, is doing the same thing over and over and expecting different results.

It's time to look at why the "work-life balance" concept is unhelpful, and to consider fresh alternatives to the punishing perception with a more helpful and realistic mindset.

Rethinking Standards

Since the 1970s and 1980s, when the term "work-life balance" was coined, its nebulous ideal has been held up as the gold standard by which people's work success and overall well-being are judged. Its basic premise could be boiled down to this: The less time one spends at work, the more time one has for more important and fulfilling areas of "real" life such as family, friends, hobbies and themselves.

Not to put too fine a point on it, but this idea of work-life balance is crazy. In fact, it's an impossible standard to meet, and sets people up for guilt and shame. Under this unspoken mandate of "balance," a person can be forced into all-or-nothing thinking. To illustrate, imagine someone misses several of their children's extracurricular sports to provide coverage during a staffing shortage or to help during another crisis at work. Even if this happens only a handful of times per season, that person still might feel as if they're failing their kids — and in failing their kids, they might feel that they're failing themselves and the rest of their family. Depending on how much credence that person gives to the idea of achieving an ideal work-life balance, catastrophizing the situation sets in. They might even begin to wonder if their life is emptier because of their "failure."

Yes, that seems extreme — and for many, it is. Still, it happens to those who strive to achieve the mythical "balance" that is continually pushed by magazines and talk shows. This type of either/or mindset is unhealthy, although it seems to be the pall under which millions of Americans operate. In reality, it's odd and awkward to separate one's "real" life from one's work life. Separating the two is a bit like separating platelets from red blood cells: Neither operate on their own, and they are both important parts of the whole. Any type of work is an integral part of one's overall life, not just a fragmented piece of it. Work is not a burden that somehow encroaches on "real" life.

Still, American culture tends to arbitrarily prescribe a certain amount of vacation or other time off for pleasure that each professional "must" take to escape work. If someone doesn't take that time, then, again, he or she might be judged — and even judge themselves — as failing their families and, somehow, not living up to society's "best life" standards. Erroneously, workaholism "must" be a factor for such people.

A healthier perspective is less punishing or black-and-white: The integration of work and life into one cohesive whole is a perspective that realizes no one can ever have it all and do it all, let alone perfectly. Simply put, it is possible for people to use their time more equitably. Yes, there will be days when healthcare professionals work 16-hour shifts (or more), and they will have to devote less time to other areas of life that day, but a tradeoff may be a four-day workweek or an additional day off. One must simply make adjustments as needed.

If this sounds easier said than done, it may be helpful to note that human resources (HR) departments across the country are gradually working to view this more holistically. Rather than seeing work hours in terms of what they take away from employees' other responsibilities, family time and hobbies, HR is increasingly redirecting employees' mindsets, helping them to see their lives as a whole, and not as divided into identically sized sections that must be continuously maintained equally to achieve success.

Asking Questions and Seeing Alternatives

How, then, do people begin to change the way they view the integration of work and life, and then do something about it? In his article "Work Life Balance Is Becoming Work Life Integration," author, speaker and futurist Jacob Morgan wrote that it's virtually impossible to avoid merging work with life. People, therefore, would be smart to align their goals and experiences to create the life they want.[3] And creating the life they want comes down to decisions — what one wants more of and what one wants less of — and then approaching each day with those decisions in mind. No matter the choices one makes, one must fully accept the fact that their decisions and desires will never line up perfectly with their ideals for each day, every day. Each day is different, and each person is different. Every day is an opportunity for people to continue the self-correcting journey of weighing what's most important for that moment.

Questions to Ask and Answers to Consider

When attempting to make mindful, realistic lifestyle choices to create an intentional, peaceful life, it can help to consider the following questions and their inevitable answers:

1) What am I trying to balance? (Knowing that, whatever it is, the balance will never be 50/50.)

Each day is different, and each person is different. Every day is an opportunity for people to continue the self-correcting journey of weighing what's most important for that moment.

2) What do I want *more* of? (Knowing that, whatever it is, the desire will never be perfectly attainable.)

3) What do I want *less* of? (The keyword here is "less." "None" is rarely, if ever, part of the equation.)

4) What is preventing me from having the life I want? (Whatever it is, it will likely never fully disappear, but it's possible to learn to navigate around it.)

5) Who am I trying to impress, if anyone?

6) What is driving my choices?

Many people might be surprised at what they learn from asking themselves these questions and considering their answers. No one likes to admit it, but the desire to keep up with the Joneses is alive and well for many. And although people's motives are often good, what drives them still might be a bit tainted by jealousy or anger, especially when proving a point to someone who doubted them, which makes enjoying life difficult.

More Myths, and the Truths

It's also helpful to look at some of the myths surrounding "work-life balance" in light of the truths that debunk them.

Myth: *Everything in life can be well-balanced.*

Truth: If people believe that it is possible for everything in life to always be well-balanced, they might consider investing stock in dotcoms. (In other words, efforts to achieve perfection will inevitably fail.)

Myth: *Working less equals feeling happier.*

Truth: Quantity does not trump quality. It's not about how many hours people work versus how many hours they spend doing something they love. It's about the quality of how they're spending their time regardless of circumstance.

Myth: *People can and should always be able to avoid distractions and stress.*

Truth: No one can completely avoid distractions or stress, but they can be selective about how they spend their time and energy, and they can determine the right actions to take at the right time.

Summing It Up

Striving to fit all the things we *have* to do, as well as all the things we *want* to do, into one day or week is nearly impossible, so it's no wonder trying to do so typically leads to guilt or frustration — or both (especially for young professionals with growing families since the additional obligations during that stage of life are many).

People will rarely if ever feel effortlessly comfortable navigating the demands of all their daily tasks. It often feels more like juggling balls or spinning plates on a stick than balancing responsibilities with poise — and that's OK. Determining what's most important from one day to the next is hard! But culture does not get to dictate how you do it, what your success should look like or how you feel about it. That is unique to each individual, and no one can make those decisions for anyone else. And no matter your choices, you must radically accept the fact that your choices will not line up perfectly with the traditional, arbitrary time slots that seem to dictate your days. You might get into a good routine, but things will inevitably line up irregularly sometimes, and you must learn how to surf the waves of each day. Every one of them is a new opportunity to self-correct as you navigate the never-ending journey of determining what you want "more of" and "less of" in your life. Each day brings new challenges and luxuries, and every day is a juggling act to determine which aspect of life gets your attention when.

Picture a seesaw: It's perfectly balanced for roughly half a second before it's "disturbed" again. It's constantly adjusting, and that's what it's supposed to do. That's not a bad metaphor for all aspects of our obligations, wants and needs, actually. The trick is not to try to keep the seesaw perfectly balanced, but instead learn how to enjoy the ride. ❖

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Update on Toxoplasmosis

Because there is no cure or vaccine for this widespread parasitic infection, knowing how toxoplasmosis is spread and best practices for preventing transmission remains important.

By Jim Trageser

THE CONCEPT OF PARASITES seems far removed from our modern world. It's the kind of thing one gets eating undercooked food while on an exotic vacation, or that one might read about in the tabloids or see on a "National Geographic" special on TV. And yet, more than 800,000 people will contract toxoplasmosis — a disease caused by the single-cell parasite *Toxoplasma gondii* — this year in the United States alone.[1] Of those infected, many will be blinded, several hundred will die and thousands will require hospitalization.

Particularly at risk are two populations: those with weakened immune systems and unborn babies. Among the immunocompromised, encephalitis is the greatest risk, along with an unchecked spread of the disease throughout the body — which can be fatal. Unborn babies can get toxoplasmosis from their mothers (there are approximately 4,000 cases of this per year in the United States). Toxoplasmosis can lead to miscarriage, blindness, epilepsy and learning disabilities.[1]

There is presently no cure for toxoplasmosis. Once infected, a person is infected for life. Still, the vast majority of people who contract it will have only a brief, mild flu-like reaction during the initial infection. And, human beings cannot pass it on (with the exception of mothers passing it to their unborn children).

What Is *Toxoplasma gondii*?

Toxoplasma gondii is a single-cell organism in the Sarcocystidae family. Each one is roughly 10 micrometers in length, about the same size as a typical bacteria. However, unlike bacteria, *Toxoplasma gondii* are eukaryotes that have nuclei, mitochondrion, ribosomes, Golgi complex and other complex organelles universal to eukaryotes.[2]

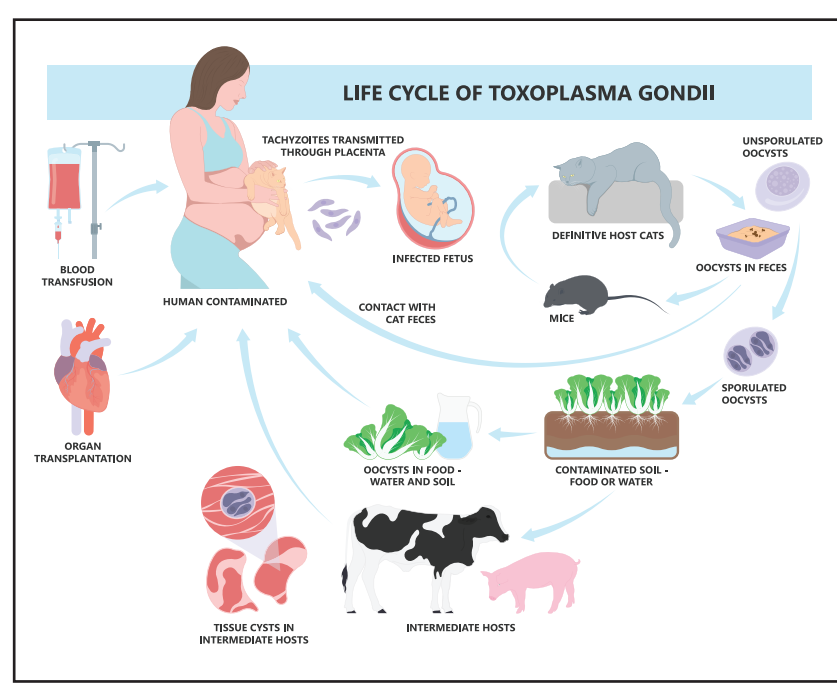
While *Toxoplasma gondii* is a near-universal parasite able to infect almost all mammals and birds, it can only sexually reproduce in cats, which are its primary host.[3] All other hosts are considered secondary hosts, since they cannot reinfect others (except for a mother passing it on to her unborn child).

After *Toxoplasma gondii* sexually reproduces inside a cat's body, it creates a resistant stage (known as an oocyst), which is released in the feces; when infected feces gets into soil or onto plants, it can stay there for months until it is ingested by another host.[3]

When a mammal or bird ingests an oocyst, the *Toxoplasma gondii* can reproduce asexually in two different forms: 1) tachyzoite, in which it reproduces rapidly before spreading throughout the host, or 2) bradyzoite, a dormant form that develops inside cysts in the host after the tachyzoite stage, and reproduces much more slowly.[4,5]

How Is Toxoplasmosis Spread?

As mentioned, the primary method that *Toxoplasma gondii* spreads to new hosts is through oocysts. It can be transmitted to humans when they work in soil that has been contaminated, or by eating fruits or vegetables that have come in contact with infected soil.[1] Cleaning a pet cat's litter



box can also transmit the disease.

However, there are instances in which the tachyzoite and bradyzoite cysts can transmit the disease even without the sexual reproduction cycle limited to infection in a cat.

Unfortunately, as stated at above, *Toxoplasma gondii* is able to cross the placental barrier between a mother and her unborn child.[6] It is not fully understood how the parasite breaches this protective barrier, but research is ongoing.

While there is no cure for toxoplasmosis, most people will recover from their symptoms with no treatment beyond getting extra rest and drinking plenty of fluids.

People can also contract the disease when they eat meat from infected livestock or poultry without fully cooking it (which kills off the *Toxoplasma gondii*). This is perhaps the most common way humans contract the disease, which makes transmission wholly preventable. (Cats become infected when they catch and eat a secondarily infected rodent or bird.)

Another way it can be transmitted without involving the oocysts is via organ transplant or blood transfusion from an infected donor.

Symptoms and Diagnosis

Many, perhaps most, cases of toxoplasmosis will be asymptomatic, and patients may go through life never knowing they have it. For patients who do exhibit symptoms, common ones are:[7]

- Fever
- Headache
- Body or muscle aches
- Rash
- Swollen lymph nodes

If the *Toxoplasma gondii* has infected the eye, symptoms may include:

- Pain in the eye
- Worsened vision
- Floaters

For patients with weakened immune systems, the infection may be more severe, and symptoms will depend on where in the body the parasite is growing. In addition, as long as a patient is immunocompromised, there is a significant risk that a latent infection can reactivate. A recurring infection can cause organ damage as it spreads throughout the body.[8]

Toxoplasmosis in the lungs can lead to breathing difficulties or cough. Toxoplasmosis that has invaded the brain can lead to encephalitis, which may manifest as confusion, reduced coordination, seizures, brain fog or muscle weakness.[7]

Any time a physician suspects exposure to *Toxoplasma gondii*, a blood test for specific antibodies can confirm or rule out that diagnosis. There are two antibody tests: one for an active infection and one that indicates a previous infection.

Treatment

While there is no cure for toxoplasmosis, most people will recover from their symptoms with no treatment beyond getting extra rest and drinking plenty of fluids. High-risk patients and their physicians also have several treatment options to help the body control the infection.

A patient who is pregnant and has an active toxoplasmosis infection may be prescribed pyrimethamine, sulfadiazine and/or folinic acid, which is administered to reduce the side effects of the pyrimethamine.[9] (While pregnancy induces some manifestations of immunosuppression, one study indicated that women who have a latent case of toxoplasmosis, in which the *Toxoplasma gondii* is in the bradyzoite or dormant stage, do not seem statistically inclined to have a reactivation of toxoplasmosis during pregnancy.[10])

After birth, a newborn will likely be treated with the same drug combination as the infected mother for a period of up to two years. Additional therapies may be used to treat any associated birth defects from the toxoplasmosis, including vision problems, physical development issues and learning disabilities.

Those with compromised immune systems will also receive the previously mentioned drugs, but the treatment period will last longer — until the patient's condition has stabilized or they are no longer immunocompromised. Those with HIV generally will receive treatment for the rest of their lives.[11]

Notably, there is some evidence that *Toxoplasma gondii* is developing resistance to pyrimethamine, which is a clear worry for researchers and physicians alike.[12]

Prevention

There is currently no vaccine for toxoplasmosis in humans or cats. (There is, however, a vaccine called Toxovax, which is only available for sheep and goats, both of which suffer high rates of miscarriage during infection.[13])

Most methods of transmission of *Toxoplasma gondii* are easily prevented by

using the following strategies:

• Washing hands with hot water and soap after gardening or changing a litter box, and wearing protective gloves during both activities.

• Thoroughly cleaning fruits and vegetables before consuming them.

• Cooking meat thoroughly. Using a meat thermometer, the internal temperature should be measured in the thickest part of the cut for at least three minutes as follows: meat to 145 degrees Fahrenheit, ground meat to 160 degrees Fahrenheit and poultry to 165 degrees Fahrenheit.

• Avoiding eating uncooked shellfish, since shellfish can contract *Toxoplasma gondii* from runoff.

In addition, the Centers for Disease Control and Prevention suggests pregnant women refrain from cleaning the litter box or adopting a new cat. People with compromised immune systems should avoid adopting a new cat as well, and keep existing pet cats indoors to prevent them from contracting *Toxoplasma gondii*.

The only transmission vectors that are difficult to control are maternal transmission across the placenta, organ transplant and blood transfusion.

Research

As one of the most prevalent parasitic diseases in the world — up to one-third of all human beings on the globe are infected, plus uncounted livestock and pets — that carries significant health risks for those with weakened immune systems, it might seem that there would be a fairly large number of ongoing clinical trials seeking treatments for toxoplasmosis. And yet, there are fewer than four dozen ongoing or recently completed studies listed on the U.S. Food and Drug Administration's (FDA's) clinical trials website.

The largest contingent of these studies were looking at faster, more accurate diagnostic tests or fine-tuning the use of the existing pharmaceutical treatments.

One study conducted nearly eight years ago in Paris examined whether shortening the period of treatment for newborns with asymptomatic congenital toxoplasmosis to three months would have any impact on the disease's progress.[14]

Others were looking at whether prescribing pyrimethamine to HIV-positive patients could help prevent reoccurance of toxoplasmosis.

FDA's clinical trials website does not track veterinary research. That is overseen by the Agriculture Department's Center for Veterinary Biologics, which does not have a public database similar to clinicaltrials.gov. There are, however, several public databases similar to clinicaltrials.gov tracking veterinary medicine research, including one operated by the American Veterinary Medical Association (ebusiness.avma.org/aahsd/study_search.aspx[15]). A search of these also failed to turn up clinical trials testing a vaccine for cats.

The lack of many ongoing trials into proposed vaccines for humans or cats could be due to the fact that there have been dozens — maybe hundreds — of previous attempts, none of which have yielded success. In testing on mice, live attenuated vaccines have provoked antibody response, but have not prevented infection. MRNA, DNA and other alternative vaccines have proved similarly ineffective to date.[16]

Looking Ahead

The ideal development would be an affordable, effective feline vaccine. Preventing cats from contracting *Toxoplasma gondii* would be a critical breakthrough, because it would seriously diminish the raw numbers of *Toxoplasma gondii* in the environment. Without feline hosts, *Toxoplasma gondii* cannot continue to reproduce outside their hosts. However, it seems that researchers are still waiting for some kind of technological or theoretical advance before such a vaccine can be developed and available.

In the meantime, a significant number of people will continue to contract toxoplasmosis. Education about preventing transmission — by properly cooking food, practicing good hygiene after gardening and cleaning up after pets — is currently the most effective means of combating the spread of *Toxoplasma gondii*. ❖

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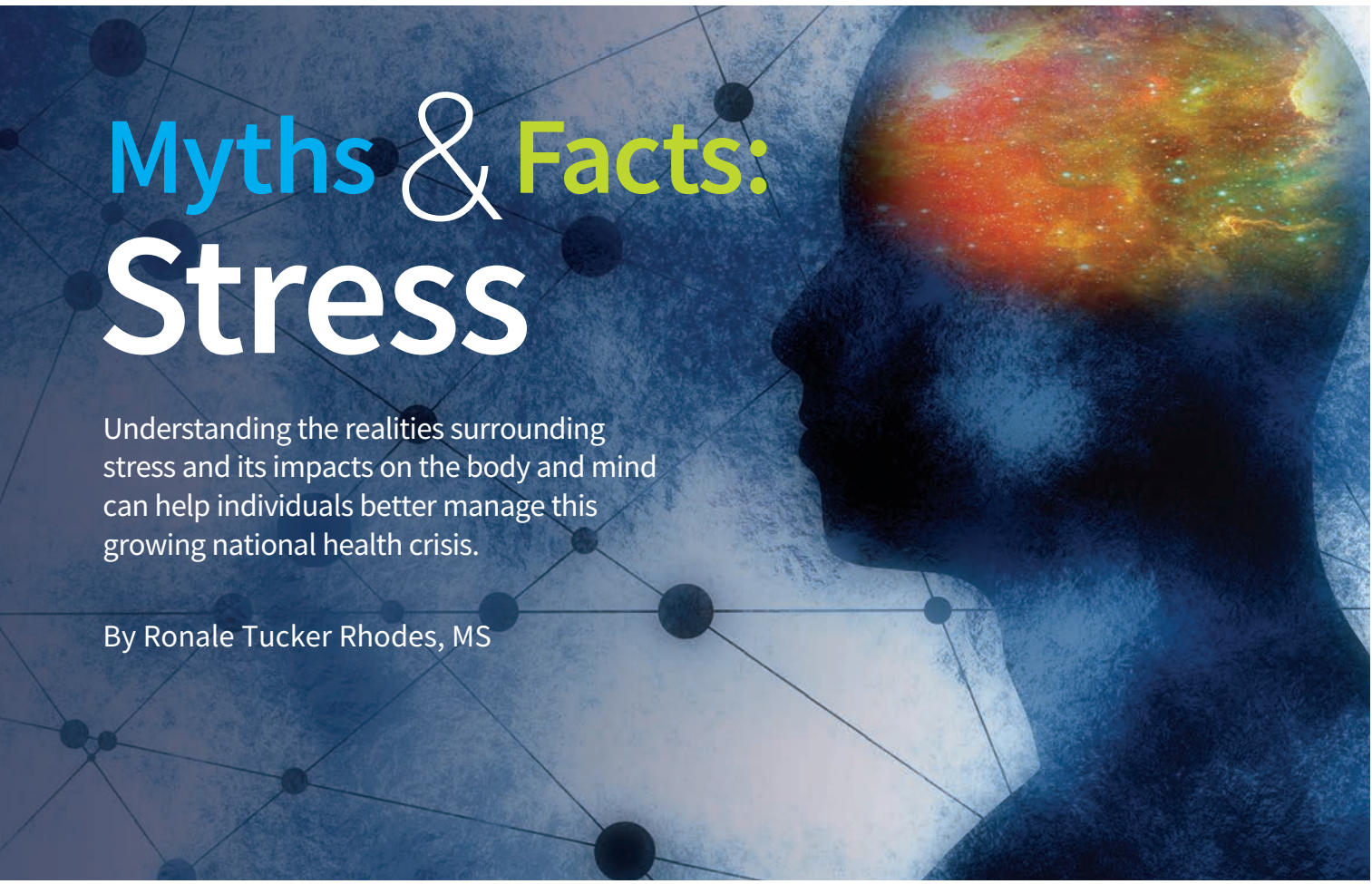

Myths & Facts: Stress

Understanding the realities surrounding stress and its impacts on the body and mind can help individuals better manage this growing national health crisis.

By Ronale Tucker Rhodes, MS

MOST PEOPLE associate the term "stress" with its negative effects. And, while most of the time stress can be harmful, triggering unwanted side effects, in other circumstances, stress can be beneficial. A nearly universal human experience, stress can be broken down into two types: acute and chronic. Acute stress is short-term and occurs in situations such as having a fight with a loved one or doing something new and exciting. Chronic stress such as losing a job, dealing with an unhappy relationship or having money problems often lasts for weeks or months and can often go unrecognized and lead to serious health problems.[1] Importantly, stress can be either eustress or distress. Eustress occurs in response to daily living activities such as getting married, getting a promotion, having a baby and winning money, and it comes with positive connotations. Distress, on the other hand, also occurs in response to daily living activities such as getting divorced, getting injured or having financial problems, but it has negative connotations.[2]

Just about everyone is affected by stress at some time in their lives, but some demographics experience higher rates of stress than others, including ethnic minorities, women, single parents and people responsible for their family's healthcare decisions. According to the American Institute of Stress:[3]

- About 33 percent of people report feeling extreme stress.
- Seventy-seven percent of people experience stress that affects their physical health.
- Seventy-three percent of people have stress that impacts their mental health.
- Forty-eight percent of people have trouble sleeping because of stress.

What's more, the association reports that for about half of all Americans, levels of stress are getting worse instead of better.

What are the reasons for this current high rate of stress? The American Psychological Association conducts

an annual Stress in America survey to measure attitudes and perceptions of stress among the general public and to identify leading sources of stress, common behaviors used to manage stress and the impact of stress on people's lives. In its 2022 survey, the top sources of stress were the rise in prices of everyday items due to inflation (e.g., gas prices, energy bills, grocery costs, etc.) (cited by 87 percent), followed by supply chain issues (81 percent), global uncertainty (81 percent), Russia's invasion of Ukraine (80 percent) and potential retaliation from Russia (e.g., in the form of cyberattacks or nuclear threats) (80 percent).[2]

Clearly, Americans need some coping mechanisms to deal with the stress they are experiencing. Yet, perhaps the key to successfully handling stress is to understand what is fact and what is fiction.

Separating Myth from Fact

Myth: Stress is always bad.

Fact: The assumption has always been that stress is bad. But, as mentioned previously, it has been found that, in some circumstances, stress can be beneficial. For instance, acute stress and eustress cause a release of epinephrine (endorphins) that makes it easier to perform tasks and enhances performance and problem-solving skills. Epinephrine can also help prepare the body to handle a threat or flee for safety by increasing pulse, breathing rate and muscle tension. In addition, acute stress can motivate people to complete a project or take a test. In one study, researchers tracked 2,804 participants for just over a week. Prior to the study, all participants completed a cognition test. Then, participants were interviewed nightly for eight consecutive nights. Researchers asked participants questions about their chronic conditions, physical symptoms, mood and the number of stressors they experienced during the day, as well as how many positive experiences they had within the previous 24 hours. Approximately 10 percent of the participants who did not report experiencing stress during the study period were more likely to experience positive moods and less likely to have chronic health conditions. On the other hand, those same participants scored lower on the cognition test than those who did experience stress during the study, equating to a cognitive decline of approximately eight years of aging. And, participants who did not report any stress also experienced fewer positive events than those who did report stress, and they were less likely to give or receive emotional support. "I think there's an assumption that negative events and positive events are these polar opposites, but in reality, they're correlated," said senior author of the study David M. Almeida, a professor of human development and family studies at Penn State.[4]

On the other hand, studies show that chronic, or long-term, stress can negatively affect every system in the body. Indeed, chronic stress can become debilitating and can increase the risk of serious health complications. Research also shows that people who don't have enough coping mechanisms have a strong reaction to stress that can cause health problems.[4] Chronic stress can lead to high blood pressure, heart disease, diabetes, obesity, depression and anxiety, skin problems such as acne or eczema, post traumatic stress disorder, sleeping difficulties, stomach upset and menstrual problems.[1] And, long-term chronic stress can be a contributing factor in many leading causes of death, including heart disease, cancer, lung disease, accidents, cirrhosis of the liver and suicide. It can also lead to substance abuse.[3]

Myth: Stress is universal, affecting everyone the same way.

Fact: Everyone reacts differently to stressful situations. In fact, the circumstances that lead to stress are not the cause of the stress, but rather how a person reacts to the circumstances. Some people who experience several stressors are able to handle them without leading to a severe stress reaction, while others suffer a severe reaction to only one stressor. For instance, one person might get stressed out by a high-pressure job, while another may thrive on it.[5]

Myth: People are only stressed if symptoms are apparent.

Fact: Just because a person isn't experiencing symptoms doesn't mean that person isn't stressed. For instance, medication can mask the symptoms of stress. And, a person may not "feel stressed" emotionally. In fact, even though stress is a psychological effect, most people experience physiological more than psychological symptoms.[6]

Myth: Most symptoms of stress are obvious.

Fact: While some common signs

Key U.S. Stress Statistics[2]

- 55 percent of Americans are stressed during the day.
- Stress causes 57 percent of U.S. respondents to feel paralyzed.
- Sixty-three percent of workers are ready to quit their job to avoid work-related stress.
- Chronic stress is commonplace at work with 94 percent of workers reporting feeling stress at work.
- Montana is the least stressed state with a total stress score of 26.81, while Louisiana is the most stressed with a score of 59.94.

Common Effects of Stress on Mental Health[7]

- A sense of dread
- Anger
- Anxiety and nervousness
- Disinterest in life
- Feeling depressed
- Losing one's sense of humor
- Feeling neglected or lonely
- Feeling overburdened or overwhelmed
- Feeling wound up
- Impatience
- Irritability
- Racing thoughts that can't be "turned off"
- Unable to enjoy things
- Worsening symptoms of existing mental health problems

Physical Side Effects of Stress[7]

- Blurred eyesight or sore eyes
- Changes in menstrual period or cycle
- Chest pains
- Constipation or diarrhea
- Developing rashes or itchy skin
- Difficulty breathing
- Existing health problems worsen
- Fatigue
- Feeling sick, dizzy or fainting
- High blood pressure
- Indigestion or heartburn
- Muscle aches and headaches
- Panic attacks
- Sleep problems
- Sudden weight gain or weight loss
- Sweating

of stress on mental health such as mood swings, rapid speech or socially withdrawing are obvious, other symptoms such as excessive worrying, anxiety and depression may not be apparent to others.[7]

There are also symptoms that many may not consider related to stress but are. For instance, stress can cause acne. One study found that individuals with higher stress scores also had a higher acne severity. In fact, it's known that stress can trigger corticotropin-releasing hormone and sebum — the oily substance on people's skin — both of which can cause acne. Other not-so-obvious symptoms that may be caused by stress include a low sex drive (chronic stress can cause even lower testosterone levels and sperm production in males); menstrual irregularities such as a late or skipped period; an inability to recall details in the moment or remember things long-term; and even amplified allergies.[3] Physicians can help their patients to recognize both the mental effects of stress, as well as the common physical side effects.[7] (See Common Effects of Stress on Mental Health and Physical Side Effects of Stress.)

Myth: Stress is not dangerous or life-altering.

Fact: Chronic stress, which causes anxiety, can impact a person's life expectancy. In one meta-analysis, researchers found that an estimated five million deaths each year are attributed to mood and anxiety disorders worldwide.[8] Another study that assessed mortality risk in people with anxiety disorders found that anxiety significantly increased mortality risk. In this cohort study with more than 30 million person-years of follow-up, researchers found the risk of death by natural and unnatural causes was significantly higher among individuals with anxiety disorders compared with the general population.[9]

Myth: Stress can cause disease.

Fact: Stress doesn't cause disease. Rather, it increases the risk of developing diseases such as cancer and irritable bowel syndrome. According to the National Cancer Institute, psychological stress can increase the risk of harmful and maladaptive coping mechanisms such as overeating, drinking alcohol or smoking, all of which increase the risk of cancer. And ulcers, which are often thought to be caused by stress, are actually caused by taking too much aspirin or nonsteroidal anti-inflammatory drugs to combat stomach upset that is often caused by stress. Ulcers can also lead to gastrointestinal disorders such as irritable bowel syndrome.[7]

Myth: Stress can be diagnosed.

Fact: Stress is subjective, so there is no standardized test, outside of laboratory research settings, to formally diagnose stress. Again, what feels very stressful for one person may not cause high levels of stress for another. Only the person experiencing stress can determine how severe it feels. However, questionnaires can be used to assess an individual's stress level and how it is affecting that person's lifestyle. If a stress-related disorder is suspected, a physician can evaluate for physical symptoms.

It's important to note that stress is not a psychiatric diagnosis, but it is closely linked to mental health. In fact, stress can cause mental health problems and exacerbate existing problems. In these cases, a mental health expert can address the psychological symptoms.[10]

Myth: Stress can't be prevented.

Fact: Actually, there are many strategies people can employ to help handle stress better, including:[11]

- Relaxation activities such as meditation, yoga, tai chi, breathing exercises and muscle relaxation
- Eating right, exercising and getting enough sleep
- Staying positive and practicing gratitude
- Accepting that not all situations can be controlled
- Learning to say no to additional responsibilities when too busy
- Staying connected with people who are calm and who can provide emotional support

Myth: People don't need to seek treatment for stress.

Fact: Since stress can lead to serious health problems, individuals who are suspected to be suffering from stress should seek treatment. Doctors don't typically prescribe medication to cope with stress; however, they do prescribe it to treat an underlying illness such as depression or an anxiety disorder.

The most successful treatments target the source of the stress rather than its side effects. These treatments focus on:[3]

- Identifying the signs of stress
- Getting plenty of sleep and exercise
- Practicing relaxation skills
- Setting goals and establishing priorities
- Spending time with others

Biofeedback has been studied for its effect on reducing stress with positive results. One study that sought to determine whether a biofeedback-based stress management tool (consisting of rhythmic breathing, actively self-generated positive emotions and a portable biofeedback device) reduces physician stress found it to be a simple and effective stress-reduction strategy. In the study, 40 staff physicians (23 men and 17 women) from various medical practices (one from primary care, 30 from a medical specialty and nine from a surgical specialty) were recruited by means of electronic mail, regular mail and posters placed in the physicians' lounge and throughout the hospital.

Physicians in the intervention group were instructed to use a biofeedback-based stress-management tool three times daily. Participants in both the control and intervention groups received twice-weekly support visits from the research team over 28 days, with the intervention group also receiving reinforcement in the use of the stress-management tool during these support visits. During the 28-day extension period, both the control and the intervention groups received the intervention, but without intensive support from the research team. Stress was measured with a scale developed to capture short-term changes in global perceptions of stress for physicians (maximum score 200).

Results showed the mean stress score declined significantly for the intervention group (change -14.7, standard deviation [SD] 23.8; $p = 0.013$) but not for the control group (change -2.2, SD 8.4; $p = 0.30$). The difference in mean score change between the groups was 12.5 ($p = 0.048$). The lower mean stress scores in the intervention group were maintained during the trial extension to day 56. And, the mean stress score for the control group changed significantly during the 28-day extension period (change -8.5, SD 7.6; $p < 0.001$).[12]

Integrative treatments can be extremely helpful for treating stress. These include:[13]

- *Meditation and mindfulness-based stress reduction (MBSR).* These therapies are proven to help reduce anxiety and depression. MBSR draws on the principles of meditation to help individuals become more aware of how negative thoughts impact physical feelings. Research shows the benefits of MBSR are reduced stress and worrying, improved memory and focus, fewer emotional ups and downs, greater resilience and improved relationships.
- *Cognitive behavioral therapy (CBT).* CBT is a type of talk therapy focused on pinpointing and questioning negative thoughts. Research shows CBT is more effective in reducing mental health symptoms than using medication alone.
- *Acupuncture.* This ancient Chinese practice involves using tiny needles to stimulate the nervous and immune systems. Research shows it helps support conventional treatment for a range of problems that include stress, chronic pain and digestive disorders.
- *Massage.* Studies show massage helps treat a variety of stress-related disorders, including anxiety and insomnia. And, while one massage is effective, a series of massage treatments is even more effective.

Dispelling the Myths Now

According to the American Institute of Stress, Americans are one of the most stressed out groups of people in the world, with the current stress level experienced by Americans 20 percentage points higher than the global average. And, stress levels are only increasing. It's well-established that stress can cause physiological and psychological health issues that may result in disease and shortened lifespan. Therefore, it's important to dispel any myths about stress and how it impacts individuals, but also how it can be managed and treated. ❖

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Lori Lewis, whose son Ryan died from an overdose of opioids, has become an advocate for opioid addiction awareness.

Opioid Addiction: *A Patient's Perspective*

By Trudie Mitschang

LORI LEWIS knows all too well that if a mother's love could cure addiction, her son Ryan would be alive today. He was just 23 years old when he died of a drug overdose on July 10, 2014. He was a gifted artist and musician whose descent into addiction began with a prescription for Vicodin.

Lori, who is a registered nurse, was prescribed Vicodin after the first of two back surgeries. "About a year after the first surgery, I began to have back pain again and decided to take the medication that was left over," explained Lori. "When I went in the medicine cabinet, the pills looked different, and I discovered the prescription had been replaced with Tylenol capsules. That's when I suspected something was wrong."

Lori and her husband called a family meeting with all four of their children, and their son Ryan eventually confessed that he had taken the Vicodin. As parents, they were naturally alarmed, but still unaware of how serious a potential opioid addiction could be. "The opioid epidemic hadn't fully hit, and we, along with many doctors and nurses, still thought they were safe," says Lori. Around the same time, I discovered Ryan had also taken some Adderall that had been prescribed for his brother's attention-deficit/hyperactivity disorder."

For the Lewis family, this was the beginning of a long battle with addiction that would eventually cost their son his life.

Over time, Lori says her once free-spirited son became increasingly moody and irritable, and they worried about his mental health. One day, Ryan's girlfriend called Lori at work to report that Ryan was talking about suicide. "I took him to the emergency room where a blood test revealed opioids and benzos, which are prescribed for anxiety," says Lori.

Over the next few months, Lori and her husband saw a number of other red flags that they now share with other families as a warning sign. Ryan was losing weight. He was moody and often had headaches, nausea and vomiting and cold sweats. Spoons in the home were disappearing. Valuables began disappearing, including a cell phone, jewelry, a coin collection and a camera. Ryan complained of severe muscle and bone aches and intense cramping in his limbs. He wore long-sleeved shirts and jeans even in hot weather. And, he lost many old friends and had many new friends.

At that time, Ryan was often sick in the morning but would recover in the afternoon. Lori says she knows now that these were symptoms of opioid withdrawal.

Over a two-year period, Ryan was admitted to residential treatment four times. During one stay, he finally admitted that his opioid addiction had shifted from pills to heroin. In a pursuit to break free from his addiction, Ryan continued to spend time in and out of treatment centers. After a third stay in residential treatment, it looked like he might have finally turned a corner by remaining drug-free for five months. Then one night, his girlfriend sent Lori a picture of Ryan asking if he looked normal. "He was nodding off on her sofa with his head arched back, mouth open and eyes half closed," says Lori. "That's when we picked him up and got him into treatment for the fourth and last time."

After another 28-day stay, Ryan was sent to recover in a sober house with a strict policy against medication-assisted treatment. That meant Ryan couldn't take Suboxone, a medication he desperately needed to reduce cravings and prevent relapses. "I believe it was that policy that led to the phone call we got three days later informing us that Ryan had died of an overdose in his room," says Lori.

Before that fatal overdose, Lori says Ryan survived two other overdoses. As a nurse, Lori knew that opioids cause drowsiness and can slow or even stop someone from breathing. Fortunately, she says, there is a medication that rapidly reverses an opioid overdose called naloxone (generic for Narcan). "It begins to work within two minutes. It's safe, easy to use and state laws make Narcan available without a prescription," explains Lori. "Research shows that every 227 doses of naloxone distributed saves one life."

Today, Lori serves as an advocate for opioid addiction awareness and uses every opportunity to tell her son's story and, hopefully, save a life. "Ryan's life has been cut short forever," laments Lori. "My hope is that we can save other lives with education and awareness, proper disposal of unused medication, greater access to naloxone and more compassionate, evidence-based treatment." ❖

Opioid Addiction:
An Expert's Perspective

ALICIA HOUSE has been working in the opioid use disorder field since 2017. Prior to her current role as executive director for the Steve Rummler HOPE Network (SRHN), she held positions at the organization in sober living, outreach, intake coordination and overdose prevention. Alicia has been on the Minnesota Opioid Epidemic Response Council since 2020 and is a current advocacy member for the FED UP! Coalition.

BSTQ: Tell us about SRHN.

Alicia: The mission of SRHN is to heighten awareness of the opioid crisis, address its impact on the physical and emotional burdens of addiction and chronic pain and improve the associated care processes. We envision a world in which individuals impacted by the opioid crisis have access to compassionate, evidence-based treatment, and can find support and acceptance in their communities. Since its inception in 2011, SRHN has been an important leader in addressing the opioid epidemic in Minnesota and across the nation. Our flagship program began in 2015 and operates today with two simple philosophies: No one should have to die of an overdose, and everyone deserves the chance for recovery. We provide naloxone (the opioid overdose reversal medication) training, education, organizational policies and fentanyl test strip (FTS) kits to the public at no cost. We also create educational content on topics such as stigma and harm reduction, pathways to recovery and opioid use disorder.

BSTQ: How does your overdose response training work?

Alicia: SRHN's training covers basic naloxone pharmacology, recognizing overdose symptoms and different administration types (intramuscular [IM] and intranasal/nasal applicator). We offer one-hour in-person and virtual training. After the training, participants receive a certificate and a free naloxone kit.

BSTQ: What is Naloxone Access Point (NAP)?

Alicia: NAP is a publicly accessible pick-up site that anyone can visit to pick up free IM naloxone and FTS kits. SRHN is currently partnered with 87 organizations and businesses across the state of Minnesota that help improve community access to lifesaving overdose prevention resources.

BSTQ: What role does education play in helping individuals and families recover?

Alicia: Without knowing what help exists, families are not able to advocate for individualized care. Instead, they may be told what they need without being in a position to question the approach, which may not uncover what may ultimately be needed and deserved for a successful outcome.

At SRHN, we develop educational content on topics ranging from substance use disorders, harm reduction, chronic pain and, of course, the opioid crisis.

BSTQ: Tell us about your advocacy work.

Alicia: SRHN advances public policies and legislation at the local, state and national levels that will improve care for those suffering from chronic pain, increase oversight of Big Pharma and shift the structural treatment of those with the disease of addiction. We succeeded in passing the 2014 Steve's Law, also known as Minnesota's Good Samaritan and Naloxone Law, which allows any layperson to carry and administer naloxone, as well as provides limited immunity from prosecution for possession of drugs or drug paraphernalia to those who seek medical assistance for someone experiencing a drug overdose if the items are found as a result of the person seeking help; the overdose victim is protected as well. We also wrote and passed the Opioid Epidemic Response Law in 2019, which raises funds from drug manufacturer and distributor fees related to the prescribing, manufacturing and distribution of opioids in the state, to help fight the opioid crisis in Minnesota.

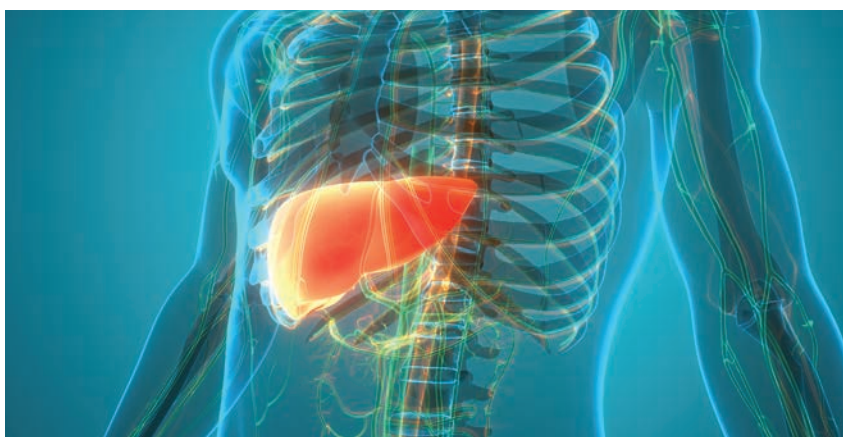
BSTQ: What do you wish healthcare professionals understood about the opioid crisis?

Alicia: Everyone's experience of this crisis is different. It is important that we understand the lens we see through is going to give us a unique picture of what this crisis is and how it is affecting our communities. Because of this, we cannot treat individual patients the same as everyone else. This means the level of care, medications, dosing, expectations, etc., need to be tailored to the individual. No one has as much knowledge and understanding of what is best for someone as the people going through the treatment. ❖

TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

Alpha-1 Antitrypsin Deficiency: A Wealth of New Treatments Now in Clinical Testing

By Keith Berman, MPH, MBA



ONE DAY IN 1962 while in his laboratory, the Swedish medical biochemist Carl-Bertil Laurell noticed an absence of the normally intense electrophoretic alpha-1 protein band in the plasma of two hospitalized patients suffering from emphysema with no known predisposing risk factors.[1] He determined that the missing protein band was alpha-1 antitrypsin (AAT), at that time a plasma protease inhibitor of uncertain significance. "A subnormal serum content of a1-antitrypsin may be a manifestation of an inherited predisposition to emphysema," he concluded.

While it is now known to have anti-inflammatory, immunomodulatory, anti-infective and tissue-repair properties, AAT performs a particularly important physiologic regulatory function: It neutralizes excess free elastase and proteinase 3 generated by activated lung neutrophils, thus preventing excessive degradation of lung elastin and collagen connective tissue.

Encoded by the SERPINA1 gene, the normal AAT "M" protease inhibitor (Pi) allele is synthesized by hepatocytes and secreted into the circulation. To date, however, more than 120 mutations of the SERPINA1 gene have been identified, the two most frequent being the "S" and "Z" allelic variants. The "Z" variant in particular encodes a highly defective AAT protein, which misfolds and aggregates as Z-AAT polymers that accumulate within the endoplasmic reticulum of hepatocytes, instead of being secreted into the circulation.

Individuals with the PiMS and PiMZ genotypes remain at very low risk of pulmonary disease, as they express sufficient functional serum AAT to counterbalance neutrophil elastase. Those with the PiSZ genotype and serum AAT levels below a certain threshold can develop chronic progressive lung disease. But most severely affected individuals have the PiZZ genotype, meaning they are homozygous for the PiZ allele. In these individuals, serum AAT levels are typically only about 15 percent of normal. Compounding this problem, the AAT-Z polymers that do manage to reach the circulation have only 10 to 20 percent of normal AAT inhibitory capacity.[2]

Unsurprisingly, individuals with the PiZZ genotype account for more than 95 percent of cases of clinically apparent AAT deficiency (AATD),[3] manifesting clinically as emphysema with or without chronic obstructive pulmonary disease (COPD). Chronic entrapment of hepatotoxic AAT-Z protein often additionally leads to the development of liver fibrosis and cirrhosis. Other less common sequelae of severe AATD include hepatocellular carcinoma, necrotizing panniculitis, granulomatosis with polyangiitis and bronchiectasis.

Altogether, the prevalence of AATD is estimated to be between one per 3,000 to 5,000 people, translating to roughly 70,000 to 100,000 affected individuals in the United States.[4] However, as many as 90 percent of these individuals remain undiagnosed, as this relatively rare cause of obstructive lung disease tends to be overlooked. It can take many years for an AATD diagnosis to finally be established by specific testing, meaning thousands of individuals with AATD and active, symptomatic lung disease are walking around undiagnosed and untreated.

Since the U.S. Food and Drug Administration (FDA) approval of the first product in 1987, lifelong augmentation and maintenance therapy with AAT concentrates* purified from plasma collected from healthy donors has

* Identified in their FDA-approved product labeling as apha1-protease inhibitor (human)

Table 1. Currently Available Human Alpha-1 Antitrypsin* Concentrates

Product	Manufacturer	Delivery Form	Approved
Aralast NP	Takeda	Lyophilized powder for solution	2002
Glassia	Takeda	Liquid	2010
Prolastin-C Liquid	Grifols	Liquid	1987
Zemaira	CSL Behring	Lyophilized powder for solution	2003

*Identified as alpha-1 proteinase inhibitor in labeling for all licensed products

remained the only available treatment for adult AATD patients with clinical evidence of emphysema (Table 1).

A few clinical studies, most recently the double-blind, randomized RAPID trial, have documented a significant reduction in the annual rate of CT-measured lung density loss at total lung capacity in study subjects who received the standard 60 mg/kg weekly AAT augmentation regimen compared to those assigned to placebo.[5] A subsequent meta-analysis of three randomized placebo-controlled trials confirmed that AAT augmentation therapy was able to slow the progression of emphysema when measured by CT density.[6]

Unfortunately, however, standard human AAT augmentation therapy for AATD is limited by a number of significant shortcomings:

- The requirement for weekly intravenous (IV) dosing may dissuade some patients from initiating or remaining compliant with the lifetime AAT augmentation therapy regimen.
- The limited supply of donor plasma could eventually preclude treatment for currently undiagnosed patients with severe disease, as well as those with less severe forms of AATD (i.e., PiMZ and PiSZ genotypes) and evident lung disease who may also benefit from augmentation therapy.
- The high cost of lifelong AAT augmentation therapy, recently estimated at about $82,000 annually,[7] can potentially create access barriers for some patients.
- AAT therapy addresses only AATD-associated lung disease; it does not treat or prevent serious liver disease or other extrapulmonary disease manifestations.

These shortcomings are currently the targets of a diverse range of new investigational therapies (Table 2), which can be broadly categorized as follows: 1) alternative human AAT delivery forms, 2) recombinant AAT products and 3) agents that interfere with hepatic production of abnormal AAT mutants.

Alternative AAT Delivery Routes

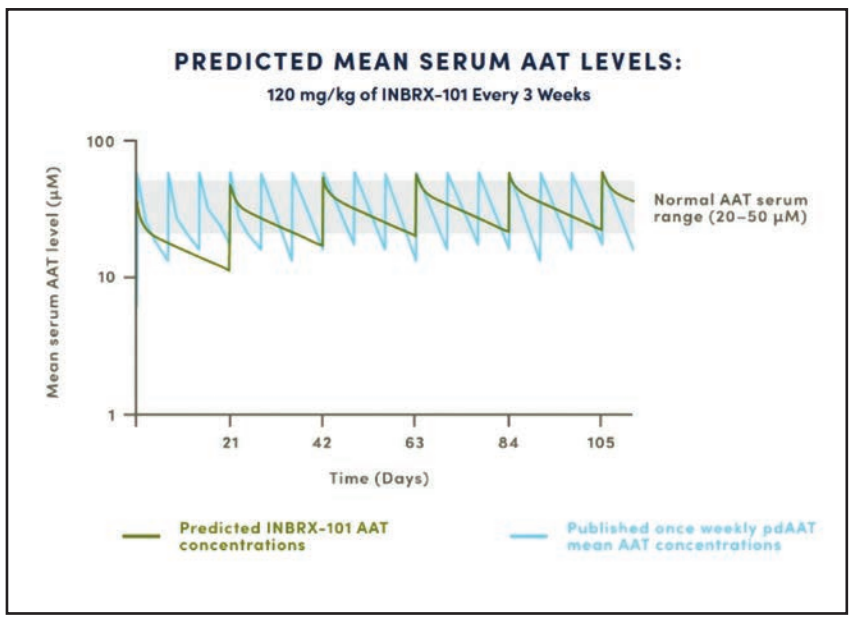
Grifols (AAT-SC 15%). A Phase I/II clinical trial initiated by Grifols in 2021 is currently evaluating the safety, tolerability and pharmacokinetics of two different subcutaneously administered doses of a concentrated plasma-derived AAT (pdAAT) formulation — 72 mg/kg and 144 mg/kg — against standard 60 mg/kg and doubled 120 mg/kg doses of its IV Prolastin-C Liquid AAT product.[8]

This small 16-subject trial is exploring both the feasibility of substituting more convenient subcutaneous delivery and the tolerability of a two-fold higher dose, with the attendant potential to further slow

Table 2. Leading Investigational Treatments for Alpha-1 Antitrypsin Deficiency

Product / *Developer*	Description	Target Organ	Development Stage
AAT-SC 15% *Grifols*	Subcutaneous human AAT	Lung	Phase I/II
AAT for inhalation *Kamada*	Nebulized inhaled human AAT	Lung	Phase III
INBRX-101; rhAAT-Fc *Inhibrx*	Recombinant human AAT, FC fusion protein	Lung	Phase II
Belcesiran *Dicerna Pharmaceuticals*	RNA interference [RNAi] drug targeting Z-AAT protein	Liver	Phase II
Fazirsiran *Arrowhead/Takeda*	RNA interference [RNAi] drug targeting Z-AAT protein	Liver	Phase II
Alvelestat *Mereo Biopharma*	Nebulized inhaled human AAT	Lung	Phase II
VX-634/VX-864 *Vertex Pharmaceuticals*	Small molecule AAT correctors	Lung; liver	Phase II

Figure. Overlay of Predicted Mean Serum AAT Levels with Inhibrx' INBRX-101 (rhAAT-Fc) Dosing Every 3 Weeks, and Published Mean Serum AAT Levels with Once-Weekly pdAAT Dosing



Source: Inhibrx, Inc.

the rate of chronic lung injury in severely affected AATD patients. Separately, Grifols is continuing to enroll subjects with severe AATD and emphysema in a Phase III trial evaluating standard 60 mg/kg weekly IV dosing of Prolastin-C against 120 mg/kg weekly IV dosing of an investigational modified process AAT product, dubbed Alpha-1 MP, with assessments of multiple pulmonary function and quality-of-life endpoints over a three-year period.[9]

Kamada (AAT for inhalation). An obvious conceptual appeal of direct delivery of AAT to the lung parenchyma by inhalation is avoidance of the need for IV sticks, but its potential efficacy through that delivery route is uncertain. Kamada, an Israeli biotechnology firm that developed the first licensed liquid human AAT formulation (Glassia), is currently enrolling a planned total of 220 adult AADT patients with moderate or severe measured airflow limitation at a single study site in the Netherlands.[10] Subjects are being randomized to receive 80 mg/day of human AAT formulated for inhalation through a nebulizer, or daily inhalation of a nebulized sodium chloride placebo solution. The primary endpoint is forced expiratory volume in one second (FEV1) after 104 weeks of treatment.

Recombinant AAT

Inhibrx (INBRX-101; rhAAT-Fc). Inhibrx has developed a novel extended half-life recombinant human AAT protein that incorporates the same immunoglobulin Fc domain fusion approach that has been successfully applied to prolong the half-lives of other licensed protein therapeutics.** INBRX-101 has been additionally engineered to maximize the protein's functional AAT activity in the lungs.

Findings from a completed multiple ascending dose Phase I study showed the expected accumulation of functional AAT levels and achievement of fully normal levels in severely deficient AATD patients after five to six consecutive doses. Inhibrx believes that the time interval between INBRX-101[11] dosing may be extended from the weekly frequency required with plasma-derived AAT (pdAAT) to as long as every three to four weeks, while maintaining circulating AAT levels in the normal range (Figure).

Inhibrx plans to initiate a Phase II clinical trial using functional AAT as a surrogate endpoint with the intent to submit for regulatory approval under FDA's accelerated approval program.

RNAi Drugs to Block Hepatotoxic Z-AAT Protein Production

Dicerna Pharmaceuticals (belcesiran; DCR-A1AT). Massachusetts-based Dicerna, a Novo Nordisk company, develops RNA interference (RNAi) drugs that are designed to silence the genes that produce defective or undesirable proteins. In a transgenic mouse model of AATD, subcutaneous injection of its RNAi drug dramatically reduced both expression and intrahepatic polymer load of the hepatotoxic Z-AAT protein, compared to control mice receiving a saline injection. Extended monthly dosing of belcesiran additionally prevented development of liver fibrosis and other liver pathology in these experimental PiZ mice. A dose-dependent knockdown in the circulating AAT protein level was similarly achieved using a targeted RNAi agent in nonhuman primates.[12]

** Including ELOCTATE antihemophilic factor (recombinant), Fc fusion protein; ALPROLIX coagulation factor IX (recombinant), Fc fusion protein

Belcesiran is currently being evaluated in the company's randomized, multidose, double-blind, placebo-controlled Phase II ESTRELLA trial to assess its safety, tolerability, pharmacokinetics and pharmacodynamics in participants with a diagnosis of PiZZ-type alpha-1 antitrypsin deficiency-associated liver disease (AATLD).[13]

Arrowhead Pharmaceuticals/Takeda (fazirsiran; ARO-AAT). Arrowhead has developed its own investigational RNAi therapeutic to reduce Z-AAT accumulation in the liver. In mid-2022, Arrowhead reported results from a Phase II clinical study involving 16 participants with AATLD who were homozygous for the PiZZ mutation, who received subcutaneous fazirsiran on day one and week four, and then every 12 weeks. All subjects had reduced accumulation of Z-AAT in the liver, with a median drop of 83 percent at week 24 or 48. The nadir in serum was a reduction of approximately 90 percent. Associated with these findings was a reduction in histologic globule burden, from a mean score of 7.4 (on a 0 to 9 scale) at baseline to 2.3 at week 24 or 48. Fibrosis progression was observed in seven of 15 patients, while progression was observed in just two of 15 patients.[14]

In January of this year, Arrowhead announced topline results from its Phase II SEQUOIA clinical study:[15] a median 94 percent reduction in serum mutant Z-AAT concentration at week 48 with the highest of three tested fazirsiran doses (200 mg), and a median 94 percent reduction in total liver Z-AAT at the postbaseline liver biopsy visit. PAS-D globule burden, a histological measure of Z-AAT accumulation, fell by 68 percent between baseline and the postbaseline liver biopsy visit. Half of patients at all dosage levels (25 mg, 100 mg and 200 mg) achieved a measurable improvement in fibrosis. In contrast, patients receiving placebo who had baseline fibrosis experienced no change in serum Z-AAT, a 26 percent increase in liver Z-AAT, and no improvement in PAS-D globule burden. Treatment-emergent adverse events were generally well-balanced between fazirsiran and placebo groups.

Arrowhead and Takeda signed a collaboration and licensing agreement in October 2020, under which they will continue to co-develop fazirsiran and, if approved, co-commercialize the product in the U.S.

Oral Neutrophil Elastase Inhibitors

Mereo BioPharma (MPH966; alvelestat). Alvelestat acts to inhibit the neutrophil elastase enzyme whose activity in healthy individuals is inhibited by normal endogenous AAT. Mereo believes that this orally administered drug has the potential to protect AATD patients from further lung damage. Recognizing it as a potential first-in-class oral neutrophil elastase inhibitor, FDA has granted alvelestat a fast track drug designation.

Results from the United Kingdom-based company's Phase II ASTRAEUS study of alvelestat in patients with severe AATD-associated emphysema demonstrated statistically significant changes relative to placebo in three primary biomarker endpoints associated with AATD-related lung disease, including up to 90 percent reduction in blood neutrophil elastase activity.[16]

In collaboration with the National Institutes of Health and investigators at the University of Alabama at Birmingham, Mereo is currently enrolling subjects with confirmed AAT in a Phase II randomized, double-blinded clinical trial in a total of 66 participants with confirmed AAT, who are being randomized to receive 120 mg of alvelestat or a placebo pill taken orally twice-daily for 12 weeks.[17] The primary endpoint is within-individual percentage change in blood markers for neutrophil elastase activity. A readout of preliminary findings from this study are anticipated in mid-2023.

Small Molecule AAT Correctors

Vertex Pharmaceuticals (VX-634 and VX-864). Vertex has developed a new class of oral AATD-targeted drug candidates that could potentially restore the elastase inhibitor function of abnormal AAT, as well as resolve its hepatotoxicity. These investigational small molecule "AAT correctors" are designed to promote proper folding of Z-AAT protein in individuals with the PiZZ genotype, correcting it to become functional AAT (fAAT) that can be expressed by hepatocytes into the bloodstream.

A completed 28-day Phase II study showed that VX-864 treatment reduced

> Inhibrx plans to initiate a Phase II clinical trial using functional AAT as a surrogate endpoint with the intent to submit for regulatory approval under FDA's accelerated approval program.

levels of Z-AAT polymer in the blood of AATD patients by an average of 90 percent from baseline, with modest increases in fAAT. In December 2022, Vertex initiated a second Phase II clinical trial to examine whether longer-term VX-864 administration also results in liver Z-AAT polymer clearance and, if so, whether this longer-term treatment might also result in larger increases in plasma fAAT levels.[18] A total of 20 participants will take VX-864 tablets orally every 12 hours for 48 weeks; the primary outcome measure is change in functional blood AAT levels from baseline.[19]

Additionally, Vertex is now evaluating the safety and tolerability of a new small molecule AAT corrector with significantly improved potency, dubbed VX-634, in more than 100 healthy volunteers.[20]

Implications for the Future

At present, physicians have only intravenous AAT augmentation therapy to try to limit the unrelenting progression of lung damage in severely affected patients with the PiZZ, PiSZ and PiNull genotypes. And they have nothing to address fibrotic or cirrhotic disease sequelae.

But should a number of the investigational agents now in clinical testing prove safe and effective, one can envision a scenario where physicians can employ therapeutics in combination to address the imbalance in lung neutrophil protease activity to prevent further destructive damage, and to block the accumulation of abnormal AAT in hepatocytes to protect the liver. This scenario should additionally provide greater impetus for physicians to order AATD testing on all individuals with COPD and unexplained chronic liver disease, as well as relatives of individuals identified with an abnormal gene for AAT, as currently recommended by the Scientific Advisory Committee of the Alpha-1 Foundation.[21]

It is now conceivable that physicians could soon be empowered to effectively manage and even prevent overt lung and liver disease in their patients with AATD through early detection and timely initiation of treatments they select from an expanded armamentarium. The clinical trial findings that become available over the next several years could prove to be transformational for the many thousands of individuals diagnosed — and yet to be diagnosed — with AATD. ❖

Arrowhead and Takeda signed a collaboration and licensing agreement in October 2020, under which they will continue to co-develop fazirsiran and, if approved, co-commercialize the product in the U.S.

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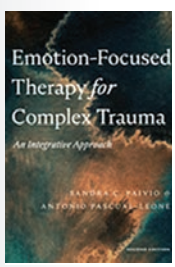
Emotion-Focused Therapy for Complex Trauma: An Integrative Approach, Second Edition

Authors: Sandra C. Paivio and Antonio Pascual-Leone

This fully updated second edition presents theory, research and practice guidelines for short-term, evidence-based individual treatment for adults experiencing the effects of complex relational trauma. The authors bring more than 25 years of research and clinical expertise to this evidence-based treatment model, which enables therapists to skillfully navigate the unique challenges facing these clients. Chapters present practical aspects of emotion-focused therapy for trauma alongside supporting research, allowing clinicians from different theoretical perspectives to either apply the complete package or integrate aspects of the model into their current practice.



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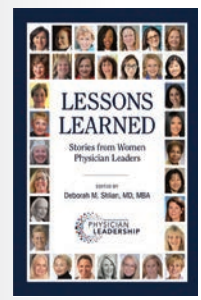


Lessons Learned: Stories from Women Physician Leaders

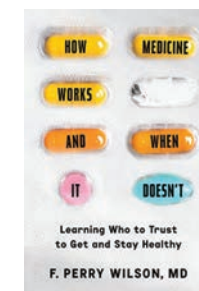
Author: Deborah M. Shlian, MD, MBA

In *Lessons Learned: Stories from Women Physician Leaders*, editor and author Deborah M. Shlian, MD, MBA, profiles 33 exceptional women physicians who have defied the odds. They share their personal and compelling stories — including obstacles and challenges faced in balancing work, family and personal life — as their career paths take them from clinical medicine to leadership within government, academia, hospitals, provider groups, managed care, pharma, consulting and entrepreneurial venture. The lessons they learned are relevant not only to women and are not applicable just to healthcare — they are universal.

www.amazon.com/Lessons-Learned-Stories-Physician-Leaders/dp/0996663258

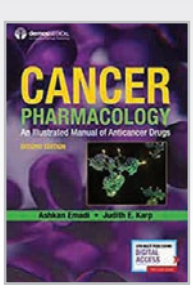
How Medicine Works and When It Doesn't: Learning Who to Trust to Get and Stay Healthy

Author: F. Perry Wilson, MD



Through stories from his own practice and historical case studies, F. Perry Wilson, MD, a physician and researcher from the Yale School of Medicine, explains how and why the doctor-patient relationship has eroded in recent years and illuminates how profit-driven companies — from Big Pharma to healthcare corporations — have corrupted what should have been medicine's golden age. By clarifying the realities of the medical field today, Dr. Wilson gives readers the tools they need to make informed decisions, from evaluating the validity of medical information online to helping caregivers advocate for their loved ones, both in the doctor's office and with the insurance company.

www.amazon.com/How-Medicine-Works-When-Doesnt/dp/1538723603



Cancer Pharmacology: An Illustrated Manual of Anticancer Drugs, 2nd Edition

Editors: Ashkan Emadi, MD, PhD, and Judith E. Karp, MD

This reference details the essential basic and clinical science of all approved, effective and life-prolonging drug therapies in oncology. Now with a greater emphasis on clinical context, application and management in each chapter, this significantly revised edition provides both early-career and seasoned clinicians with a practical, bench-to-bedside approach and patient-oriented guide. The book provides detailed coverage of the major advances in cancer pharmacology at the forefront of our standards of care for solid tumors and hematologic malignancies, in addition to the basic science that is directly necessary and applicable when at the patient's bedside.

www.amazon.com/Cancer-Pharmacology-Illustrated-Manual-Anticancer/dp/0826149324

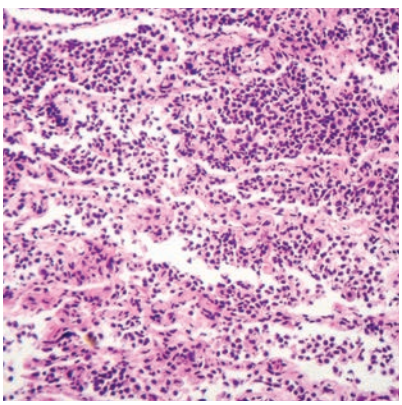
IVIG May Improve Survival in Patients with Acute Exacerbation of Fibrotic Idiopathic Interstitial Pneumonia

Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is a frequently fatal condition, particularly in patients with a lower percent-predicted forced vital capacity within 12 months before AE onset and/or a lower PaO2/FiO2 ratio at AE onset. Currently, there are no established treatments beyond a weak recommendation for treatment with high-dose corticosteroids. Investigators at Okayama University Hospital and KKR Takamatsu Hospital in Japan hypothesized that intravenous immune globulin (IVIG), which has both anti-inflammatory and anti-infective effects, may have a positive effect on AE of fibrotic idiopathic interstitial pneumonias (IIPs), including IPF.

They retrospectively analyzed 52 consecutive patients diagnosed with AE of fibrotic IIPs and treated with pulse corticosteroid (methylprednisolone 500 to 1000 mg/day for three days) between April 2018 and May 2021 at their two institutions. Thirteen of the 52 patients received IVIG (5 g/day for three to five days) concurrently with pulse corticosteroid therapy. The remaining 39 patients were assigned to the control group.

The survival rate on day 90 was significantly higher in the IVIG group than in the control group (76.9 percent versus 38.5 percent, p = 0.02). IVIG administration (odds ratio [OR], 0.11; 95 percent confidence interval [CI], 0.02-0.69; p = 0.02) and C-reactive protein (OR, 1.19; 95 percent CI, 1.06-1.22, p < 0.01) were independently associated with 90-day mortality.

Encouraged by this evidence that administration of IVIG may improve



90-day survival of patients with AE of fibrotic IIPs, in May 2022, the study investigators initiated a prospective, randomized clinical trial in hopes of confirming this treatment effect. ❖

Higo, H, Ichikawa, H, Nakamura, N, et al. Intravenous Immunoglobulin for Acute Exacerbation of Fibrotic Idiopathic Interstitial Pneumonias. *Sarcoidosis, Vasculitis and Diffuse Lung Diseases,* 2022 Dec 19;39(4):e2022038.

Post-AMI Infusion of Human Apolipoprotein A-1 (CSL112) Strongly Boosts Impaired Cholesterol Efflux Capacity

Infusion of CSL112, an investigational human plasma-derived apolipoprotein A-I (apoA-I) formulated with phosphatidylcholine (PC), rapidly and strongly elevated impaired cholesterol efflux capacity (CEC) following acute myocardial infarction (AMI), according to a 63-subject sub-study from the randomized, double-blind, saline placebo-controlled, dose ranging Phase IIb AEGIS-I study. CSL112 is intended to improve CEC and thereby reduce the incidence of early recurrent cardiovascular events following AMI.

AMI patients were stratified by renal function and randomized to four weekly two-hour infusions of low- and high-dose (2 g and 6 g) CSL112 or placebo. CSL112 infusions resulted in rapid, dose-dependent increases in baseline corrected apoA-I and PC, which peaked at the end of the two-hour infusion. Similarly, there was an immediate, strong, dose-dependent elevation in both total CEC and ABCA1-mediated CEC relative to baseline. Mild renal impairment did not affect the pharmacokinetics (PK) or pharmacodynamics (PD) of CSL112.

Additionally, following CSL112 administration, there were rapid, dose-dependent increases in plasma HDL-C levels, with a broad peak at two to six hours and gradual decline over approximately 48 hours (2 g infusion) or 96 hours (6 g infusion). There were no increases in the atherogenic lipids/lipoproteins non-HDL-C, LDL-C or apoB following infusion of CSL112. No dose-effects on inflammatory or cardio-metabolic biomarkers were observed.

These data demonstrate that four weekly infusions of CSL112 have a sustained impact on CEC, as well as support the selection of the 6 g dose for further development, the investigators concluded. ❖

Gibson, CM, Kazmi, SHA, Korjian, S, et al. CSL112 (Apolipoprotein A-I [Human]) Strongly Enhances Plasma ApoA-I and Cholesterol Efflux Capacity in Post-Acute Myocardial Infarction Patients: A PK/PK Substudy of the AEGIS-I Trial. *Journal of Cardiovascular Pharmacology and Therapeutics,* 2022 Jan-Dec; 27: 10742484221121507. Accessed at journals.sagepub.com/doi/10.1177/10742484221121507.

Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2023, through June 30, 2023

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$964.54	$949.07
	BIVIGAM	ADMA Biologics	J1556	$141.90	$139.62
	FLEBOGAMMA DIF	Grifols	J1572	$89.08	$87.65
	GAMMAGARD SD	Takeda	J1566	$146.34	$144.00
	GAMMAPLEX	BPL	J1557	$108.02	$106.28
	OCTAGAM	Octapharma	J1568	$83.64	$82.30
	PANZYGA	Octapharma/Pfizer	90283/J1599	$131.64	$129.53
	PRIVIGEN	CSL Behring	J1459	$94.38	$92.87
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$93.00	$91.51
	GAMMAKED	Kedrion	J1561	$95.41	$93.88
	GAMUNEX-C	Grifols	J1561	$95.41	$93.88
SCIG	CUTAQUIG	Octapharma	J1551	$141.46	$139.19
	CUVITRU	Takeda	J1555	$149.10	$146.71
	HIZENTRA	CSL Behring	J1559	$126.18	$124.16
	HYQVIA	Takeda	J1575	$158.71	$156.16
	XEMBIFY	Grifols	J1558	$136.23	$134.05

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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
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	0.5 g, 2.5 g, 5 g, 10 g, 20 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 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	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI	
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	1 g, 5 g, 10 g, 20 g
			SCIG: PI	
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
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, 4 g PFS
	HYQVIA Liquid, 10%	Takeda	PI	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

2022-2023 Influenza Vaccine

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	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90687/90688
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	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI	0.7 mL PFS 10-BX	65 years and older	90662

2023-2024 Influenza Vaccine

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.

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Benefits:

Choice
Multiple presentations from top manufacturers.

Commitment
Aligned with manufacturers' estimated shipping commitments.

Confidence
Dependable deliveries to meet your patients' needs.

Safety
Guaranteed Channel Integrity® ensures safe, reliable products for your patients.

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