SPRING 2019

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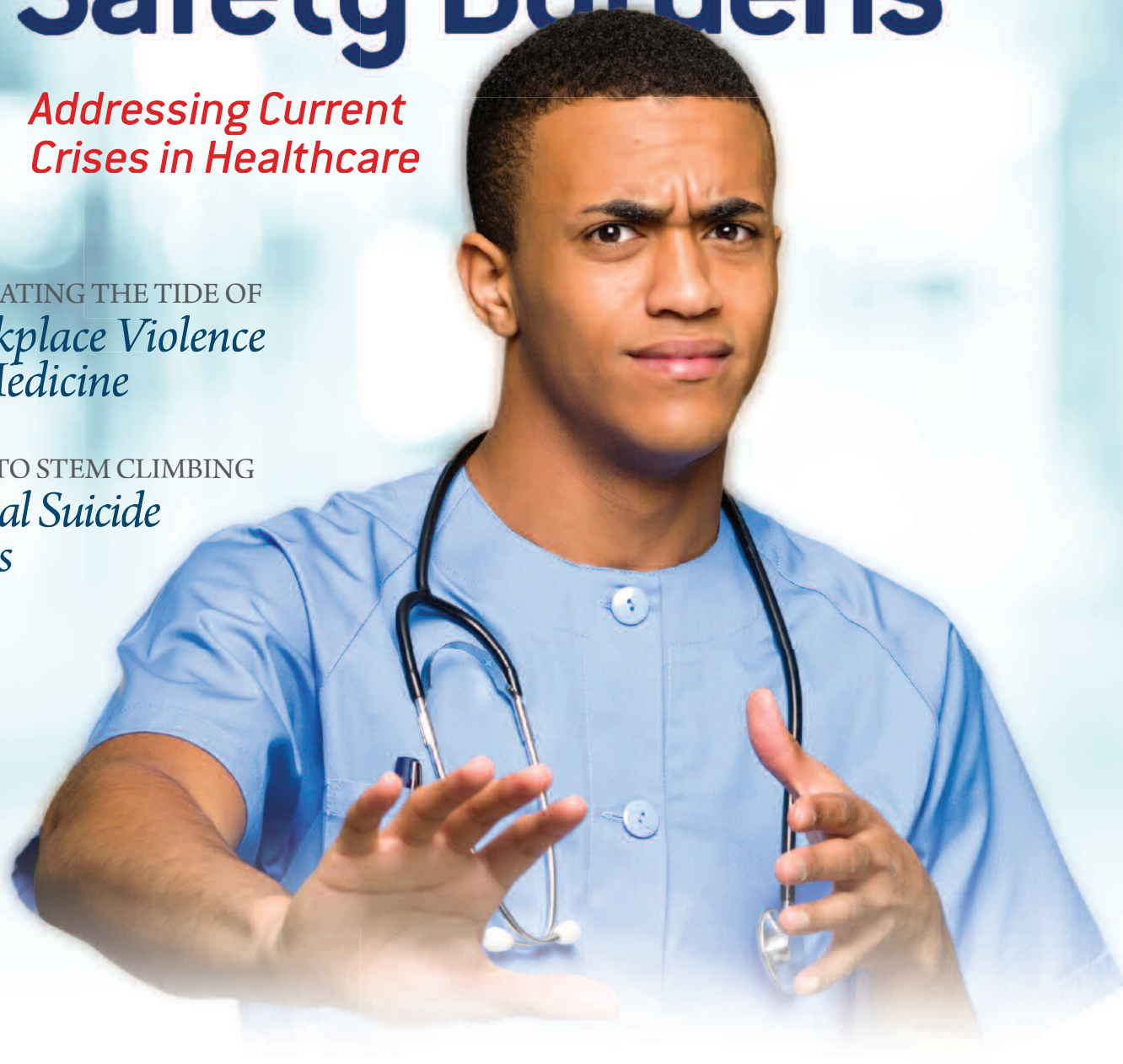
QUARTERLY

SPECIAL FOCUS:
SAFETY

Safety Burdens

Addressing Current Crises in Healthcare



COMBATING THE TIDE OF
Workplace Violence in Medicine

HOW TO STEM CLIMBING
Global Suicide Rates

IMPROVING MEANINGFUL
Clinical Trial Data Collection

Albumin as Drug Therapy for Decompensated Cirrhosis p.42

8 Critical Steps

Purchasing

At FFF, we only purchase products from the manufacturer–never from another distributor or source. This means the integrity of our products is never in question from tampering or mishandling.

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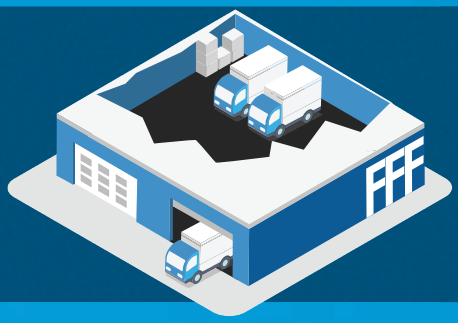

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Interactive Allocation

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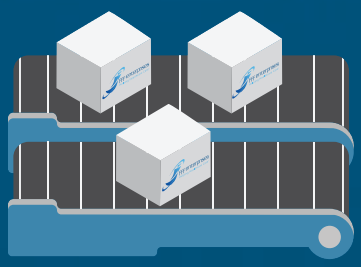

To Guaranteed Channel Integrity™

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Methods of Delivery

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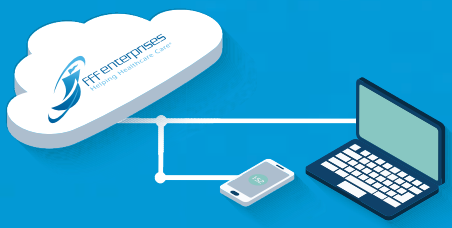

Verification

In compliance with 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.

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.

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

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Helping Healthcare Care®

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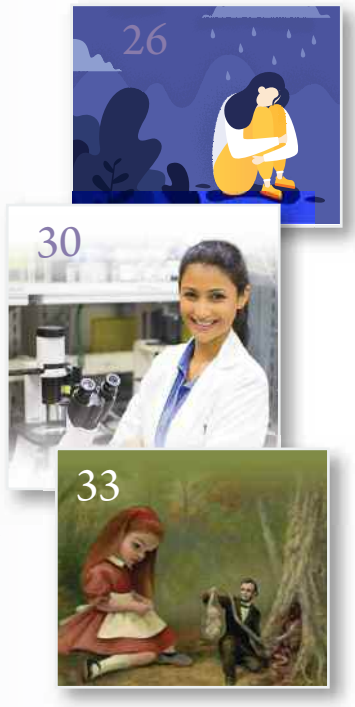
Features



Up Front

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About BioSupply Trends Quarterly

BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 44000 Winchester Road, Temecula, CA 92590

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

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Addressing Healthcare Worker and Patient Safety Issues

WHILE THE HEALTHCARE industry has made great strides over the years when it comes to safety for both patients and healthcare workers, there is always room for improvement. In this safety-themed issue, we address three troublesome safety issues, as well as one recent discovery that could save the lives of many in the near future.

Since a main guiding principle for healthcare workers is to take care of patients, it's easy to assume medical facilities are reasonably safe places. Yet, disturbingly, a growing number of workers report they are victims of violence from those for whom they are caring. And, it's likely these numbers are underreported since workers often don't report incidents because many feel their assailants aren't responsible for their actions due to their illness. As we discuss in our article "Addressing Workplace Violence in Healthcare Facilities" (p.18), this occupational hazard can have devastating consequences. Affected workers suffer physically and psychologically, and facilities are greatly impacted financially. In response, facility administrators are implementing violence prevention programs, and policymakers at the state and federal levels are taking legislative action.

Clinical trials are at the heart of ensuring medicines and medical devices are safe for patients, as well as advancing scientific discovery to better treat patients. But, history has shown transparency of clinical trial data has been lackluster at best, thus impeding scientific progress. As we report in our article "Improving Access to Clinical Trial Data" (p.30), the Institute of Medicine released a wide range of recommendations to instill a culture of greater data transparency among investigators and shareholders, while also protecting participant privacy. In addition, a private action tank is pushing a social contract titled Health Citizenship to improve data collection, sharing and transparency to speed scientific discovery. And, most recently in 2018, the U.S. Food and Drug Administration launched pilot programs to enhance transparency of clinical trial data and medical device software standards.

With some diseases, however, safety issues are unknown simply because of lack of study. This is the case for attention-deficit hyperactive disorder (ADHD) in reproductive-age women who are often prescribed ADHD medicines that could affect them and their unborn children. Indeed, as we report in our article "ADHD in Reproductive-Age Women" (p.38), ADHD prescription drug use among this population has increased a whopping 700 percent! This worrisome issue has led researchers to begin looking at the reasons behind this staggering increase, as well as what risks these medicines might pose.

Lastly, it has recently been discovered that human albumin, whose role has historically been thought of as merely a blood volume expander, may have more healing potential. In our article "Human Albumin as Drug Therapy for Decompensated Cirrhosis: A New Lifesaving Role for an Old Player?" (p.42), we review findings that began with treating cirrhosis and spontaneous bacterial peritonitis that have now led to new clinical trials, which may reveal this plasma product's new lifesaving role.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it 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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FDA Takes Steps for the Development of Non-Opioid Pain Medications

The U.S. Food and Drug Administration (FDA) is issuing several documents that should lead to smaller clinical trials, faster approvals and quicker launches of novel nonaddictive therapies that are alternatives to opioid pain medications. One of the documents provides drug companies information on what FDA is looking for in non-opioid medications for chronic pain. Another details how manufacturers can show their product reduces patients' exposure to opioids for acute pain. And, yet another updates drugmakers on how they should assess the risks of illicit use of their drugs. In addition, FDA is withdrawing its existing 2014 guidance to the drug industry on pain medications, which is overly broad, according to FDA Commissioner Scott Gottlieb, and is sometimes a barrier to new products and innovations. This move is FDA's latest effort to combat the opioid epidemic, which Gottlieb says is one of the agency's top priorities. ❖

McGinley L. FDA Pushes for Development of Non-Opioid Pain Medications. *The Washington Post*, Aug. 29, 2018. Accessed at www.washingtonpost.com/news/to-your-health/wp/2018/08/29/fda-pushes-for-development-of-non-opioid-pain-medications/?noredirect=on&utm_term=.f903997c1cfe.

CMS to Strengthen and Enhance Oversight and Transparency of Medicare Accrediting Organizations

In October, the Centers for Medicare and Medicaid Services (CMS) took steps to enhance and strengthen its oversight and quality transparency of accrediting organizations (AOs) in three ways: 1) the public posting of AO performance data, 2) a redesigned process for AO validation surveys and 3) the release of the annual report to Congress. Together, these efforts are designed to provide important insights to the public and assist AOs, providers and suppliers in ensuring patient health and safety.

To increase transparency for consumers, the agency will post on its CMS.gov website (at qcor.cms.gov/hosp_cop/HospitalCOPs.html) the latest quality-of-care deficiency findings following complaint surveys at facilities accredited by AOs; a list of providers determined by CMS to be out of compliance, with information included on the provider's AO; and overall performance data for AOs.

Historically, CMS has measured AOs' effectiveness by choosing a sample of facilities, performing state-conducted assessment services within 60 days following AO surveys and comparing results of the state surveys with the AO surveys. Now, CMS will test a more streamlined assessment by eliminating the second state-conducted validation survey and instead using direct observation during the original AO-run survey to evaluate AOs' ability to assess compliance with CMS's conditions of participation. CMS will also analyze and incorporate state complaint investigations of accredited facilities as part of the agency's strengthened validation program.

The most recent annual report to Congress, the "Review of Medicare's Program for Oversight of Accrediting Organizations and the Clinical Laboratory Improvement Validation Program Fiscal Year 2017," is posted on the CMS website. According to CMS, it will continue to publish this report online annually to demonstrate the impact of these changes on the oversight of AOs and to provide greater transparency to the public. ❖

CMS to Strengthen Oversight of Medicare's Accrediting Organizations. Centers for Medicare and Medicaid Services press release, Oct. 4, 2018. Accessed at www.cms.gov/newsroom/press-releases/cms-strengthen-oversight-medicares-accreditation-organizations.

CMS's New Oncology Care Model Aims to Provide Better Care for Chemotherapy Patients

The Centers for Medicare and Medicaid (CMS) has developed the Oncology Care Model (OCM) to provide higher quality and more highly coordinated oncology care at the same or lower cost to Medicare. Specifically, the goal of OCM is to utilize financial incentives to enable improved care coordination, appropriateness of care and access to care for beneficiaries undergoing chemotherapy. The CMS Innovation Center expects these improvements will result in better care and smarter spending. According to CMS, "Practitioners in OCM are expected to rely on the most current medical evidence and shared decision-making with beneficiaries to inform their recommendation about whether a beneficiary should receive chemotherapy treatment."

Fourteen commercial payers are participating in OCM, which includes a two-part payment system for these practices. These include a per-beneficiary Monthly Enhanced Oncology Services (MEOS) payment for the duration of the episode and the potential for a performance-based payment for episodes of chemotherapy care. The $160 MEOS payment assists practices in effectively managing and coordinating care for oncology patients during episodes of care, while the potential for performance-based payment incentivizes practices to lower the total cost of care and improve care for beneficiaries during treatment episodes.

In addition, the OCM model is working with electronic health records vendors to review data needs for OCM implementation and strategies to support practices in reporting data to the OCM Data Registry. ❖

CMS.gov. Oncology Care Model. Accessed at innovation.cms.gov/initiatives/Oncology-Care.

$293 Million Awarded by HHS to Expand Primary Healthcare Workforce

In response to a growing shortage of primary healthcare physicians, especially in rural underserved areas, the U.S. Department of Health and Human Services' (HHS) Health Resources and Services Administration (HRSA) has awarded $293 million in awards to primary healthcare clinicians and students through the National Health Service Corps (NHSC) and Nurse Corps programs. The awards will go to:

• The NHSC Scholarship Program ($47.1 million) to provide 222 new awards and seven continuation awards to students pursuing primary care training leading to a degree in medicine, dentistry or a degree as a nurse-midwife, physician assistant or nurse practitioner in exchange for providing primary healthcare services in areas of greatest need.

• The NHSC Loan Repayment Program ($142.1 million) to provide 3,262 new awards and 2,384 one-year continuation awards to fully trained, licensed primary care clinicians in exchange for providing primary healthcare services in an area of greatest need.

• The NHSC Students to Service Loan Repayment Program ($19.3 million) to provide 162 new awards that provide loan repayment assistance to medical and dental students in their last year of school in return for choosing primary care as a practice focus and working in rural and urban areas of greatest need.

• The NHSC State Loan Repayment Program ($12.6 million) to provide cost-sharing grants to 37 states and territories that operate their own loan repayment programs, funding 1,350 new and continuation awards.

• The Nurse Corps Scholarship Program ($25.1 million) to provide 215 new awards and four continuation awards to nursing students in exchange for a commitment to work at least two years in a facility with critical shortages.

• The Nurse Corps Loan Repayment Program ($44.4 million) to provide 544 new awards and 279 one-year continuation awards to nurses in exchange for a commitment to serve at a healthcare facility with a critical shortage of nurses or serve as nurse faculty at an accredited school of nursing.

• The Faculty Loan Repayment Program ($1.1 million) to provide 23 new awards to health profession educators in exchange for serving as a faculty member in an accredited and eligible health profession school.

• The Native Hawaiian Health Scholarship Program exit disclaimer icon ($900,000) to provide nine new awards and one continuation award to Native Hawaiian health profession students trained in those disciplines and specialties most needed to deliver quality, culturally competent, primary health services to Native Hawaiians in the state of Hawaii.

Currently, an estimated 13 million patients receive care from more than 12,500 NHSC and Nurse Corps clinicians. Another 1,725 primary care students are either in school or in residency preparing for future service with the Corps program. "These programs connect primary care providers with the rural, urban and tribal communities across the country that need them the most," said HRSA Administrator George Sigounas, MS, PhD. "In addition to providing essential medical and dental care, these clinicians are on the front lines helping to fight pressing public health issues like the growing opioid epidemic." ❖

HHS Awards $293 Million to Expand Primary Health Care Workforce. U.S. Department of Health and Human Services press release, Oct. 18, 2018. Accessed at www.hhs.gov/about/news/2018/10/18/hhs-awards-293-million-expand-primary-health-care-workforce.html.

Approaching New Payment Rules

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

ACCORDING TO AN annual survey of the American College of Healthcare Executives, financial challenges topped the 2018 list of the 10 most concerning issues for community hospital CEOs, with 57 percent of them voicing concern on high prices and insufficient reimbursement for medications.[1] The following summarizes the Centers for Medicare and Medicaid Services' (CMS) outpatient prospective payment system (OPPS) and physician fee service (PFS) impact on drugs, as well as outlines changes some payers are making in response.

OPPS and PFS Impacts

CMS continues its focus on a patient-driven healthcare system with reimbursement across the patient episodic care journey rather than on single encounters in healthcare facilities. Three major themes in the OPPS and PFS payment rules stand out: 1) simplifying electronic health records requirements, reporting and regulations, 2) cutting costs and save money by saving patients money and reducing operating costs and 3) addressing the opioid crisis. The PFS rule, specifically, proposes telehealth/virtual care reimbursement, which offers many new opportunities.

Site-neutral payment, under which hospital clinic visits are reimbursed at the same rate as physician offices and other ambulatory facilities, has caused a flurry of complaints and legal activity. With clinic visits the most common service billed under OPPS, a decreased payment rate when provided at off-campus provider-based departments at 40 percent of OPPS rates, regardless of whether the provider-based department was grandfathered under Section 603 of the Bipartisan Budget Act of 2015, is anticipated to save $760 million. At the same time, as the average co-payment drops from $23 per visit to $9 per visit, patients save $150 million. And, while sequestration remains in effect and 2 percent is deducted from every CMS payment to facilities, these don't reduce co-payments. Therefore, as facilities search for every opportunity to stabilize revenue and cut costs, pharmacies must understand drug payment rules and what steps to take to ensure payment. Additionally, making practice changes such as working with specialty pharmacy white bagging and negotiating with private insurers is essential.

Paying for Medicare Part B Drugs Under OPPS

Medicare Part B drugs, usually injectables, are administered in outpatient settings pursuant to physicians' orders. CMS pays for Part B drugs in five different ways divided into two categories: 1) separately payable with line-item reimbursement, and 2) not separately payable without line-item reimbursement because they're paid as part of a bundle/package. Regardless of where a drug falls in these two categories, it's essential to bill for each and every drug. CMS uses this documented claims information to set rates for future years and to compile data pools for analytic purposes. Any missing or erroneous data skews the accuracy of the pools and leads to faulty pathway development or decision-making.

Separately payable drugs include: 1) new drugs not yet assigned a unique healthcare common procedure coding system (HCPCS) code, 2) new pass-through drugs, biologicals and radiopharmaceuticals (status indicator [SI] G) and 3) specified covered outpatient drugs (SI K). Not separately payable drugs include: 4) lower-cost packaged products costing less than $125 per day (up from $120 per day in 2018) and 5) products used in policy packaged services, regardless of cost.

Payment for all packaged drugs, biologicals and radiopharmaceuticals is included in the services and procedures with which they are reported. These include all diagnostic radiopharmaceuticals; contrast agents; anesthesia drugs; implantable biologicals that are surgically inserted or implanted into the body through a surgical incision or natural orifice; drugs, biologicals and radiopharmaceuticals that function as supplies when used in a diagnostic test or procedure; and drugs and biologicals that function as supplies or implantable devices in a surgical procedure.

OPPS 2019 Payment for Unbundled Drugs

Transitional pass-through status for some drugs will expire in the quarter as close to three full years as possible after they were first covered by pass-through payment. The rule lists 60 drugs with new/continuing pass-through status (SI G) and 23 that lose pass-through payment status and move from SI G to SI K (separately payable) or SI N (items and services packaged into ambulatory payment classification [APC] rates).

In 2019, new drugs and biologicals will be paid at wholesaler acquisition cost (WAC) plus 3 percent (not WAC plus 6 percent) before average sales price (ASP) is available. If WAC is not available, CMS will pay 95 percent of average wholesale price (AWP). Once ASP is established, the rate reverts to ASP plus 6 percent. Provisions for reducing transitional pass-through payments for policy-packaged drugs, biologicals and radiopharmaceuticals to offset costs packaged into APC groups are being developed for diagnostics and skin substitutes and will be published by CMS as decisions are made.

Drugs, biologicals and therapeutic radiopharmaceuticals. These will continue to be paid at ASP plus 6 percent under the 2013 statutory default payment policy. However, while radiopharmaceutical manufacturers are not required to submit ASP, when they

do so voluntarily, CMS uses it for a patient-ready dose. Otherwise, CMS bases payment on mean unit cost from its claims data.

Non-opioid pain management drugs. CMS is unpackaging and paying separately for the cost of non-opioid pain management drugs functioning as surgical supplies when used in the ambulatory surgery center (ASC) setting. Also, CMS will make an equitable payment adjustment in the form of an add-on payment for APCs that use an appropriate non-opioid pain management drug, device or service.

Biosimilar products. There are no proposed changes to the 2018 CMS revised payment policy for biosimilar products that established separate coding and a separate payment rate, even if they have the same biological reference product as another biosimilar product. All biosimilar biological products are eligible for pass-through status, not just the first biosimilar for a reference product. Biosimilar products purchased under the 340B drug pricing program are also subject to payment cuts.

Recommended Action Steps Using Addenda A and B

Addenda A and B are snapshots of HCPCS codes and their status indicators, APC groups and OPPS payment rates in effect at the beginning of each quarter. Updates to Addenda A and B are posted quarterly to the OPPS website.[2] To access the pharmacy products, sort the Excel table on the SI column and keep only the SI G, K and N line items. Then:

1) Ensure all drugs with SI G, K and N are billed regardless of whether they are separately payable to avoid them being stripped out before a claim is submitted.

2) Check the new/continuing pass-through products to identify any HCPCS code changes, then incorporate those into the pharmacy drug master and charge description master files. In addition, determine the correct file build for new pass-through drugs, and add waste billing, if applicable.

3) Prepare for changes in the list of waste billing drugs, and determine which of those on the current list have moved from K to N status, making them no longer eligible for waste billing.

What Changes Other Payers Are Making in 2019

Medicare Part C, also known as Medicare Advantage (MA), engages private health insurance plans to provide managed care to 20 million (one-third of all) beneficiaries. This year, these plans can negotiate Part B and Part D drug prices and implement step therapy, which can only be applied to new prescriptions for patients not actively receiving a given medication. MA plans are required to pass savings on to beneficiaries through rewards given as part of drug management care coordination that must be equivalent to greater than half the amount saved on average per participant and could be in the form of lower premiums.

Insurers also have many requirements related to drugs and their payment and, therefore, are big proponents of managed care. More than 48 million Americans, or approximately 80 percent of Medicaid patients, are enrolled in managed care. Since each state maintains its own Medicaid program, each will have unique complexities in its managed-care environment. Common tools used by managed care to control drug costs include restricted formularies, prior authorization, designated distributors such as specialty pharmacies, step therapy and utilization review, among others. And, each of these tools tends to go against the grain of traditional healthcare site practices.

Embracing a New School Approach

For billing to go smoothly and accurately, someone needs to be able to manage all aspects of specialty pharmacy drugs from beginning to end. Considerations for this assignment should be given to an oncology pharmacy navigator, immunotherapy navigator, specialty pharmacy navigator or even the entire outpatient/ambulatory clinical team. This functional oversight includes obtaining and maintaining authorizations, reviewing insurance benefits, verifying insurance is active for date of service, ensuring chemotherapy/immunotherapy/specialty drug orders flow to the verification team, sending authorized order reminders to inform infusion charge nurses to schedule patients for treatment and generating reports of prior authorizations due to expire so new ones can be obtained. These tasks will require maintaining relationships with insurance, specialty pharmacy companies and 340B representatives, dealing with patient assistance co-pays, conducting foundation research, and tracking and managing physician responsibilities for prescriptions.

There are supply chain implications as well, with payer-mandated drug acquisitions and white bagging. Old-school thinking is refusing to follow the payer requests and buying product knowing there won't be any reimbursement. New-school thinking embraces new concepts to accommodate patients and avoid non-reimbursable costs. This is especially important for facilities that offer specialty drugs, incorporate biosimilars and pride themselves on being progressive. ❖

BONNIE KIRSCHENBAUM, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

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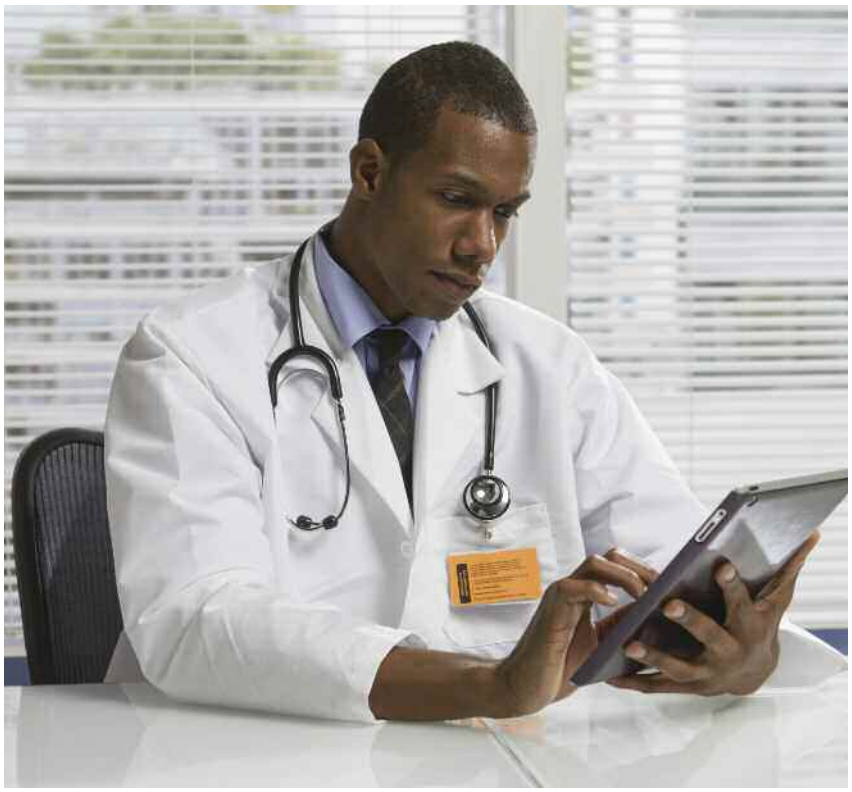
2. Centers for Medicare and Medicaid Services. Addendum A and Addendum B Updates. Accessed at www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates.html.

Adopting a Social Media Strategy

By Ronale Tucker Rhodes, MS



SOCIAL MEDIA platforms play an important role in society, including disseminating news from local and global sources, providing education and entertainment, and allowing for the easy exchange of information. For healthcare providers specifically, these platforms offer a unique opportunity to connect with current and prospective patients and share credible medical information to improve quality of care. In fact, social media use by healthcare facilities has been on the rise during the past decade, with 53 percent of physician practices reporting they have a Facebook page and utilization of social media by hospitals rising from 79 percent in 2012 to 91 percent in 2013.[1] What's more, in a recent study, 41 percent of people said social media would affect their choice of a specific doctor, hospital or medical facility, and 60 percent of doctors said social media improves the quality of care delivered to patients.[2] It makes sense, then, for providers to take part in the social media arena. But, to ensure their participation provides the most benefit, it also makes good business sense to implement a social media strategy.

Benefits of Social Media

Social media as we know it today did not really establish itself until the early 2000s. Therefore, the benefits of these platforms for the healthcare industry are not yet fully known. However, what is known is what these platforms can provide:[3]

- *Medical advice.* Consumers flock to social media to engage with others who have the same medical conditions, which offers healthcare practitioners an opportunity to provide accountable medical advice.
- *More tailored information.* Google has become a main source to find information for consumers to diagnose themselves. Healthcare organizations can take advantage of this by educating the general public and their patients on medical conditions. They can also point consumers to more credible sites such as Google Scholar. In addition, interaction with consumers can be a two-way street: Practitioners can expand their healthcare knowledge by listening to patients and communicating with other medical professionals.
- *Social support.* Studies suggest patients' adherence and general health improve when receiving social support, and social media platforms are the perfect outlet for physicians to reach out to patients.
- *Data dissemination.* Social media can provide timely forecasts of disease incidence such as influenza (flu). These trends can help researchers, epidemiologists and healthcare practitioners quantify changes in disease awareness and sentiments toward treatment and preventive care.

Putting Social Media to Work

There are many ways healthcare organizations can employ social media:

1) *Share information with consumers to help keep them healthy.* For instance, they can provide general information about flu shots and tips to avoid colds; share news about outbreaks or health hazards; provide updates on new technologies; introduce new doctors in the practice; answer questions about various topics; deliver generic pre- and postoperative care

information; and offer any updates that relate to the practice.[4] Mayo Clinic set the example for this by establishing its Mayo Clinic Center for Social Media with a goal of using social media to improve health and well-being for people and to build relationships between patients and professionals. Through this effort, it gained more than 700,000 Twitter followers, more than 500,000 Facebook fans, a significant presence on Google+ and Pinterest, and almost 3,000 videos on its YouTube Channel.[5]

2) *Evaluate competitors.* Professionals can adopt other organizations' successful social media involvement to enhance their own and increase patient satisfaction.[4]

3) *Gather feedback from patients to improve quality of care.* By interacting with patients on social media, practitioners can better understand how patients are reacting to medicines and how they feel about new techniques being used in the industry. They can also evaluate whether they need to offer additional services.[4]

4) *Train medical personnel.* Training can be made more enjoyable and interactive by encouraging new hires to use certain hashtags on Twitter or to join other groups to ask questions and receive answers. These sites also provide educational presenters with immediate feedback on training sessions.[4]

5) *Provide updates on procedures in real time.* Healthcare providers can deliver up-to-date information during procedures to fellow doctors, medical students or others.[4] For instance, in 2014, Sunnybrook Hospital in Toronto, Ontario, Canada, live-tweeted a bypass surgery to raise awareness about heart disease and demystify the operating room. Throughout the surgery, the communications team shared photos, videos and information from inside the operating room, as well as fielded questions from tweeters who were following. From that successful event, the hospital gained 5,000 Twitter followers in just a few hours and received international media coverage.[5]

6) *Provide information to consumers in times of crisis.* Hospitals and other organizations can deliver real-time updates on facility capacity, operation status or emergency room access. They can also share information provided by organizations such as the Red Cross and the Centers for Disease Control and Prevention.[4]

7) *Help practitioners collaborate with one another.* Social media can be used to help health professionals find and connect with others both inside and outside their network to share knowledge or research. For instance, Texas Health, a network of 25 hospitals that employs 5,500 physicians, created an enterprise social network to help physicians communicate and work with one another to overcome challenges posed by the work environment such as electronic health records requirements.[6]

Employing Best Practices

To maximize a social media strategy, as well as engage in an industry-appropriate manner, best practices cannot be overlooked. These include:

• *Setting measurable goals.* This means defining ways in which social media will help the organization that can be tracked and measured. Some common goals include getting the public to know the organization's name, with a positive perception of the business; driving traffic to the organization's social media page or website; engaging with potential customers by answering questions or helping existing customers with products or services; and interacting with fans/followers by giving them reasons to mention the brand and give referrals.[7]

• *Choosing the right social media networks.* Use the organization's target customers and their online behaviors to determine which networks will work best for their products and services.[7]

• *Branding profile pages.* The organization's identity should be uniform across all channels by using a logo and tagline, consistent imagery, a company description, and the proper tone and voice.[5]

• *Editing and reviewing.* A mandatory review process should be in place to avoid publishing inaccurate information.[5]

• *Educating employees.* All employees should have a thorough understanding of social media policies. They need to know when they should and should not engage, and what information they are permitted to share.[5]

• *Knowing when to take the conversation offline.* Employees should avoid discussing sensitive or personal issues with patients online, and be redirected to the appropriate channels to address these issues.[5]

Avoiding HIPAA Violations

Healthcare facilities must implement strict guidelines for what employees are allowed to post on social media sites. These include:

• Distribute clear social networking policies to employees.

• Avoid any discussion of patients, even in general terms.

• Speak generally about conditions and treatments.

• Prominently post policies and procedures on all social media platforms.

• Do not practice medicine online by responding to patients offline. ❖

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Vaccines

Severe Flu Increases Risks for Pregnant Women and Their Babies

A new study shows pregnant women who are hospitalized in the intensive care unit (ICU) with influenza (flu) are four times more likely to deliver babies prematurely and four-and-a-half times more likely to have a baby of low birth weight. In the study, researchers compared 490 pregnant women with the flu, 64 of whom were so ill they were admitted to a hospital ICU, and 1,451 who did not have the flu. They found babies of the most seriously ill women were eight times more likely to have low Apgar scores, a measure of a baby's color, heart rate, reflexes, muscle tone and breathing in the minutes after birth. According to Sonja Rasmussen, MD, of the University of Florida College of Medicine, it's not clear what affected these newborns, but it's suspected that "when moms are in the ICU, they often need help breathing, they need a ventilator to breathe for them, and it may be that there is some period of time [when] they aren't breathing well enough to get adequate oxygen to the baby." In addition, she says it's possible nutrition plays a role. "When you're having trouble breathing, you have trouble eating, and it may be that Mom wasn't getting good nutrition during her time in the ICU," Dr. Rasmussen explains. In pregnant women with the flu who were able to stay home (and even those admitted to the hospital but not admitted to the ICU), there was no significant increase in risk for adverse health outcomes for their babies.

Dr. Rasmussen says the findings underscore the importance of pregnant women receiving the influenza vaccine and getting prompt treatment with antiviral medications. Prior to the 2009 pandemic, only approximately 20 percent to 30 percent of pregnant women got the flu vaccine. After that, doctors and health professionals strongly urged vaccination, and the rate increased to approximately 50 percent. ❖

Neighmond P. Severe Flu Raises Risk of Birth Problems for Pregnant Women, Babies. NPR, Jan. 10, 2018. Accessed at www.npr.org/sections/health-shots/2019/01/10/683927732/severe-flu-raises-risk-of-birth-problems-for-pregnant-women-babies.

Vaccines

Common Misconceptions Are the Cause for Almost Half of U.S. Adults Skipping the Flu Shot

Despite repeated warnings about the dangers of not getting an influenza (flu) shot and last year's record number of flu-related deaths, more than 40 percent of Americans haven't been vaccinated against the flu and aren't planning to be due to misconceptions, according to a new survey. The survey of 1,202 adults conducted between Nov. 14 and 19 by the National Opinion Research Center (NORC) at the University of Chicago found 43 percent of adults had received the flu shot and 14 percent were planning to get the flu shot, but 41 percent said they don't plan to get vaccinated and approximately 2 percent were undecided or did not respond. The highest vaccination rate (62 percent) was for adults older than 60 years, the group at highest risk for flu-related complications, which leaves one in four adults older than

60 years not planning to get vaccinated. Adults younger than 45 years were the least likely to report being vaccinated. And, among adults with children younger than 18 years living at home, 39 percent said they do not vaccinate their children.

The top reasons for not vaccinating against the flu were concern about side effects (36 percent), concern about getting the flu from the vaccine (31 percent) and the belief the flu vaccine doesn't work (31 percent). "Unfortunately, many people are still not getting flu shots due to broader misconceptions about the value of receiving a flu shot and concerns about the safety and efficacy of the vaccines," said Caitlin Oppenheimer, MPH, senior vice president of public health research at NORC. In addition to misconceptions, approximately two-thirds of survey respondents were unaware of the high hospitalization and death rates from the flu last year. ❖

Brooks M. Almost Half of U.S. Adults to Skip Flu Shot. WebMD, Dec. 10, 2018. Accessed at www.webmd.com/cold-and-flu/news/20181210/almost-half-of-us-adults-to-skip-flu-shot#1.

Medicines

Tdap Booster Vaccine Receives Expanded FDA Indication

Sanofi Pasteur's Adacel Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) absorbed vaccine has been granted expanded indication by the U.S. Food and Drug Administration (FDA) to include repeat vaccinations for tetanus, diphtheria and pertussis. With this expanded indication, Adacel is the first and only Tdap vaccine approved for repeated dose in people ages 10 years to 64 years, eight years or more after their first vaccination, in the U.S. It is also currently the only Tdap vaccine available in a syringe made without natural rubber latex, in the event of a patient allergy.

The expanded indication was based on a clinical trial that involved 1,300-plus adults ages 18 years to 64 years that compared the vaccine to a tetanus-diphtheria (Td) vaccine eight years to 12 years after a previous dose of Adacel. Trial results showed a second dose of the investigative vaccine in adults was associated with no significant difference in adverse events compared to the Td vaccine group. Among the 999 Tdap vaccine patients, 87.7 percent reported at least one injection-site reaction, compared to 88 percent of the Td vaccine recipients.

"In the United States, people who received their first Tdap vaccine dose as an adolescent are now approaching the age at which they are recommended to receive a decennial Td vaccine booster," investigators wrote. "Some providers might find it convenient or necessary (e.g., because of the availability of vaccine or during an outbreak) to give such a booster as Tdap." However, the investigators noted that "although the results provide reassurance about the safety and tolerability of and immunogenicity conferred by repeat Tdap booster doses, advisory committees still need to determine the optimal interval for booster doses by using data provided by routine pertussis surveillance and outbreak evaluations." ❖

Kunzmann K. FDA Approves Tdap Booster Vaccination. *MD Magazine*, Jan. 14, 2019. Accessed at www.mdmag.com/medical-news/fda-tdap-booster-vaccine-adults.

Research

Study Says Glaucoma May Be an Autoimmune Disease

A study conducted by the Massachusetts Institute of Technology (MIT) and the Massachusetts Eye and Ear has found glaucoma may be an autoimmune disorder. In the study of mice, researchers looked for immune cells in the retinas of mice and found T cells, which is unusual because T cells are normally blocked from entering the retina by a layer of cells called the blood-retina barrier to suppress inflammation in the eye. The researchers also found when intraocular pressure goes up, T cells are somehow able to get through this barrier and into the retina. One of the biggest risk factors for glaucoma is elevated eye pressure, which occurs as people age and the ducts that allow fluid to drain from the eye become blocked. The study showed the body's own T cells are responsible for the progressive retinal degeneration seen in glaucoma, and the T cells appear to be primed to attack retinal neurons as the result of previous interactions with bacteria that normally live in the body.

According to Jianzhu Chen, an MIT professor of biology, a member of MIT's Koch Institute for Integrative Cancer Research and one of the senior authors of the study, "This opens a new approach to prevent and treat glaucoma." The study appeared in *Nature Communications* on August 10. ❖

Trafton A. Study Suggests Glaucoma May Be an Autoimmune Disease. Massachusetts Institute of Technology press release, Aug. 10, 2018. Accessed at news.mit.edu/2018/glaucoma-autoimmune-disease-0810.

Medicines

FDA Approves Drug to Treat Acute Myeloid Leukemia

Xospata (gilteritinib) has been approved by the U.S. Food and Drug Administration to treat adult patients with relapsed or refractory acute myeloid leukemia (AML) with a certain genetic mutation. The drug is specifically indicated for a FTL3 genetic mutation as detected by an agency-approved test. FDA also approved an expanded indication for a companion diagnostic to include its use with the leukemia drug. Approval is based on a clinical trial of 138 patients with relapsed or refractory AML and the FLT 3 mutation, 21 percent of whom achieved complete remission, and 31 percent of the remaining patients requiring transfusions at the beginning of treatment who became transfusion-free for at least 56 days. ❖

FDA Approves Acute Myeloid Leukemia Drug. U.S. Food and Drug Administration press release, Dec. 6, 2018. Accessed at www.fdanews.com/articles/189417-fda-approves-acute-myeloid-leukemia-drug?utm_campaign=Drug%20Daily%20Bulletin&utm_source=hs_email&utm_medium=email&utm_content=68097763&_hsenc=p2ANqtz-9RU80TrFNacS5Y2auEDUSAWq3_fA2WZDtK-3Ar-lse0kvNXEk94JQydc9lxl1LARhsYzAE1VJwLXlVR35Cz1mTuNs4OA&_hsmi=68097763.

Research

Human Vaccines Project Launches Study of How the Immune System Responds to the Flu

With a goal of understanding the immune system to develop longer-lasting protection against influenza (flu), researchers will conduct a comprehensive evaluation of the human immune system's response to flu. Participants in the study will be healthy men and women who will receive a standard influenza vaccine from whom scientists will take a range of measurements to analyze individual response to the vaccine. In addition to measuring the antibody response to the flu, the study will also look at gene regulation, the influence of the microbiome and other factors such as gender. Researchers will also take samples after vaccination of participants' lymph nodes and bone marrow where key immune cells reside. "By sampling the blood frequently and getting samples from lymph nodes and the bone marrow, we can provide one of the most comprehensive studies of the immune response to influenza that scientists have ever been able to undertake," says Wayne Koff, CEO and president of the Human Vaccines Project. "Such work will accelerate the development of more effective influenza vaccines and may lead to the development of a universal influenza vaccine that provides durable protection against influenza even as it changes from year to year. The study will also help elucidate mechanisms of the human immune system that are universal to how people fight disease."

The study is part of the nonprofit Human Vaccines Project's global consortium of researchers to systematically decode the human immune system to create better prevention, diagnostics and treatments for a range of diseases. Sequiris will provide the vaccine and Vanderbilt University Medical Center will lead the study with scientists from the University of British Columbia, Telethon Kids Institute in Australia, University of California, San Diego, J. Craig Venter Institute, the Scripps Research Institute and La Jolla Institute providing expertise and analysis. ❖

New Study to Decode What Makes People Immune to Influenza. Human Vaccines Project press release, Nov. 1, 2018. Accessed at www.eurekalert.org/pub_releases/2018-11/hvp-nst103118.php.

Medicines

Romiplostim Approved to Treat Pediatric Patients with Immune Thrombocytopenia

The U.S. Food and Drug Administration has approved Amgen's romiplostim to treat pediatric patients ages 1 year and older with immune thrombocytopenia (ITP) for a minimum of six months and who have had an insufficient response to corticosteroids, immune globulin or splenectomy.

Approval was based on two double-blind placebo-controlled clinical trials in pediatric patients 1 year and older with ITP for at least six months. In one study, patients whose disease was refractory or relapsed after at least one prior ITP therapy were randomized to receive romiplostim or placebo. Durable platelet response (at least six weekly platelet counts greater than or equal to 50 × 10^9/L during weeks 18 through 25 of treatment) was achieved in 22 patients (52 percent) who received romiplostim and two (10 percent) on the placebo arm. Overall platelet response, defined as a durable or a transient platelet response, was achieved in 30 (71 percent) and four (20 percent) patients, respectively. Patients who received romiplostim had platelet counts greater than or equal to 50 x 10^9/L for a median of 12 weeks, compared to one week in patients who received placebo. The results for all three endpoints were statistically significant, with p-values all less than 0.05.

In the other study, patients diagnosed with ITP at least six months prior to enrollment were randomized to receive romiplostim or placebo. Fifteen patients who received romiplostim achieved a platelet count of greater than or equal to 50 x 10^9/L for two consecutive weeks and an increase in platelet count of greater than or equal to 20 × 10^9/L above baseline for two consecutive weeks during the treatment period. No patient receiving placebo achieved either endpoint.

In pediatric patients, the most common adverse reactions included contusion, upper respiratory tract infection and oropharyngeal pain. ❖

FDA Approves Romiplostim for Pediatric Patients with Immune Thrombocytopenia. U.S. Food and Drug Administration press release, Dec. 14, 2018. Accessed at www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628525.htm.

Research

Study Finds Nasal Flu Vaccine Less Effective Than the Flu Shot

In a recent meta-analysis of pooled individual patient-level data, researchers found reduced effectiveness of the quadrivalent live-attenuated influenza vaccine (LAIV4) against influenza A/H1N1pdm09 compared with inactivated influenza vaccine (IIV) in children and adolescents.

The meta-analysis looked at data from five U.S. studies from the 2013–2014 flu season through the 2015–2016 flu season to compare the vaccine effectiveness of LAIV4 and IIV against medically attended, laboratory-confirmed influenza among patients ages 2 years to 17 years by influenza season, subtype, age group and prior vaccination status. The vaccine effectiveness of IIV or LAIV4 was calculated as 100%×(1–odds ratio), comparing the odds of vaccination among patients who were influenza-positive to patients who were influenza-negative from adjusted logistic regression models. Relative effectiveness was defined as the odds of influenza comparing LAIV4 and IIV recipients.

Of 17,173 patients ages 2 years to 17 years, 4,579 received IIV, 1,979 received LAIV4 and 10,615 were unvaccinated. Against influenza A/H1N1pdm09, vaccine effectiveness was 67 percent for IIV and 20 percent for LAIV4. Results were similar when stratified by vaccination in the previous season. LAIV4 recipients had significantly higher odds of influenza A/H1N1pdm09 compared with IIV recipients. LAIV4 and IIV had similar effectiveness against influenza A/H3N2 and B. According to the researchers, overall findings were consistent when stratified by influenza season and age group.

The Advisory Committee on Immunization Practices provided an interim recommendation against LAIV4 use during the 2016-2017 and 2017-2018 seasons. However, AstraZeneca, manufacturer of LAIV4, implemented an improved strain selection process for the vaccine in the 2017-2018 flu season. Data showed improved viral shedding and immunogenicity in young children. And, Public Health England (PHE) published provisional end-of-season adjusted vaccine effectiveness estimates from the 2017-2018 season, which demonstrated LAIV4 provided statistically significant vaccine effectiveness against A/H1N1 strains during the 2017-2018 season in children 2 years to 17 years of age. ❖

Chung JR, Flannery B, Ambros CS, et al. Live Attenuated and Inactivated Influenza Vaccine Effectiveness. *Pediatrics*, February 2019, Volume 143, Issue 2. Accessed at pediatrics.aappublications.org/content/143/2/e20182094.

Rosenthal M. Is Nasal Flu Vaccine as Effective as Flu Shot? *Pharmacy Practice News*, Feb. 11, 2019. Accessed at www.pharmacypracticenews.com/Web-Only/Article/02-19/Nasal-Flu-Vaccine-Less-Effective-Than-Flu-Shot-/54122?sub=B4B2F5FD2CBFB371D36E5FCBAF39E4F635E2E73F1E972A49633E767CC862&enl=true&dgid=--DGID--&order=3&date=20190211&click=title.

Legislation

Majority of Vaccination Bills Propose Increasing Exemptions, But Most Enacted Limit Exemptions

A content analysis of proposed and enacted legislation between 2011 and 2017 that would directly affect states' immunization exemption laws identified 175 bills related to vaccination policies, 53 percent of which would increase access to vaccine exemption, with the remaining limiting exemption laws. Yet, although more anti-vaccination legislation was introduced during the study period, bills that limited vaccine exemptions were significantly more likely to be enacted. For example, 12 of the 13 bills signed into law (92 percent) limited access to vaccine exemptions. The study also found Republican legislators were more likely to promote bills that increased people's access to vaccine exemptions. The four states that had at least 10 proposed bills that would increase access to vaccine exemptions during the study period included New Jersey (32), New York (28), West Virginia (15) and Mississippi (12). Currently, all states allow medical exemptions to vaccination; however, all but three states — West Virginia, Mississippi and California — allow vaccine exemptions for religious or possibly even ideological reasons.

"Public health and medical societies can be influences on legislators, so this study should act as an alarm that the majority of bills in state legislatures are anti-vaccination," said Neal D. Goldstein, PhD, MBI, assistant research professor of epidemiology and biostatistics at the Drexel University Dornsife School of Public Health. "Even though the ones that make it to law are pro-vaccination, the fact that these anti-vaccination bills are even introduced is concerning. Organizations like the AAP [American Academy of Pediatrics] have a specific role to play in ensuring that evidence-based bills are supported, and nonevidence-based bills are dismissed." ❖

Goldstein ND, et al. 53% of State Immunization Bills Propose to Increase Access to Exemptions. *American Journal of Public Health*, 2018; doi: 10.2105. Accessed at www.healio.com/pediatrics/vaccine-preventable-diseases/news/online/%7B1558c854-22e9-4282-bd3b-d6184b7eee9d%7D/53-of-state-bills-propose-to-increase-access-to-vaccine-exemptions.

Medicines

FDA Approves Hepatitis A and Measles Exposure Drug

The U.S. Food and Drug Administration (FDA) has approved Grifols' GamaSTAN to treat people exposed to measles and the hepatitis A viruses. GamaSTAN is the only immune globulin (IG) product available in the United States to protect against these viruses after exposure. "Vaccination, while a valuable option for hepatitis A and measles postexposure prophylaxis, may take several weeks to take effect as your immune system works to build the antibodies it needs to fight these viruses," said Stephen Scholand, MD, an infectious disease specialist at MidState Medical Center. "Immune globulins such as GamaSTAN have been a valuable treatment option for many decades because they offer immediate and rapid protection with antibodies that fight infection."

The Centers for Disease Control and Prevention (CDC) recommends IG for hepatitis A virus (HAV) postexposure treatment for people over 40 years. In addition, CDC recommends IGs should be used for children age 12 months and younger, immunocompromised persons, persons with chronic liver disease and those who are allergic to the vaccine or a vaccine component. "When administered within two weeks after exposure to HAV, immune globulin is 80 percent to 90 percent effective in preventing hepatitis A infection," said a CDC spokesperson.

GamaSTAN is also approved for rubella and varicella postexposure treatment.

However, it is not indicated for routine prevention or treatment of viral hepatitis type B, rubella, poliomyelitis, mumps or varicella. ❖

Jefferson RS. FDA Approves New Drug for Hepatitis A and Measles Exposure. *Forbes*, Sept. 12, 2018. Accessed at www.forbes.com/sites/robinseatonjefferson/2018/09/12/fda-approves-new-drug-for-hepatitis-a-and-measles-exposure/#303358a3a410.

Medicines

First Therapy Approved to Treat Rare Blood Clotting Disorder

In February, the U.S. Food and Drug Administration (FDA) approved Cablivi (caplacizumab-yhdp) injection, the first therapy specifically indicated, in combination with plasma exchange and immunosuppressive therapy, for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), a rare and life-threatening disorder that causes blood clotting.

Approval was based on a clinical trial of 145 patients who were randomized to receive either Cablivi or a placebo. Patients in both groups received the current standard of care of plasma exchange and immunosuppressive therapy. Results of the trial demonstrated platelet counts improved faster among patients treated with Cablivi compared to placebo. Treatment with Cablivi also resulted in a lower total number of patients with either aTTP-related death and recurrence of aTTP during the treatment period, or at least one treatment-emergent major thrombotic event (where blood clots form inside a blood vessel and may then break free to travel throughout the body). The proportion of patients with a recurrence of aTTP in the overall study period (the drug treatment period plus a 28-day follow-up period after discontinuation of drug treatment) was lower in the Cablivi group (13 percent) compared to the placebo group (38 percent), a finding that was statistically significant. Common side effects of Cablivi were bleeding of the nose or gums and headache.

"Patients with aTTP endure hours of treatment with daily plasma exchange, which requires being attached to a machine that takes blood out of the body and mixes it with donated plasma and then returns it to the body. Even after days or weeks of this treatment, as well as taking drugs that suppress the immune system, many patients will have a recurrence of aTTP," said Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "Cablivi is the first targeted treatment that inhibits the formation of blood clots. It provides a new treatment option for patients that may reduce recurrences." ❖

FDA Approves First Therapy for the Treatment of Adult Patients with a Rare Blood Clotting Disorder. U.S. Food and Drug Administration press release, Feb. 6, 2019. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630851.htm.

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Addressing Workplace Violence in Healthcare Facilities

With a significant rise in workplace violence in the healthcare industry, measures are being taken to address and prevent it.

By Abbie Cornett

WHEN CONSIDERING entering the healthcare profession, most people may not realize its dangers. But, in fact, working in the healthcare industry in the United States can be extremely perilous, with practitioners reporting being routinely physically or verbally assaulted by the people they are trying to help. Lisa Tenney of the Maryland Emergency Nurses Association is a prime example. "I have been bitten, kicked, punched, pushed, shoved, scratched and pushed," said Tenney. "I have been bullied and called very ugly names. I've had my life, the life of my unborn child and of my other family members threatened, requiring security escort to my car."[1] The majority of assaults are committed by patients, but violent threats can come from many different sources. Family members, disgruntled employees and drug seekers all pose a potential threat to safety. As such, action is needed to both address and prevent this serious issue.

Scope of the Problem

According to the U.S. Bureau of Labor Statistics (BLS) and Occupational Health and Safety Administration (OSHA), workplace violence in healthcare is four times higher than in private industry, and those numbers are growing (Figure 1). The most recently reported statistics by BLS show "intentional injury" by another person rose from 6.4 incidents per 10,000 hospital workers in 2016 (the most recent year of data).[2]

More alarmingly, research shows violence in healthcare settings is frequently either underreported or not reported at all. It is estimated less than half of all incidents are recorded.[3] The reason: Reporting is voluntary, so many victims don't report incidents. Indeed, victims often believe their assailants are not responsible for their actions since their mental state has been altered due to their condition.[1]

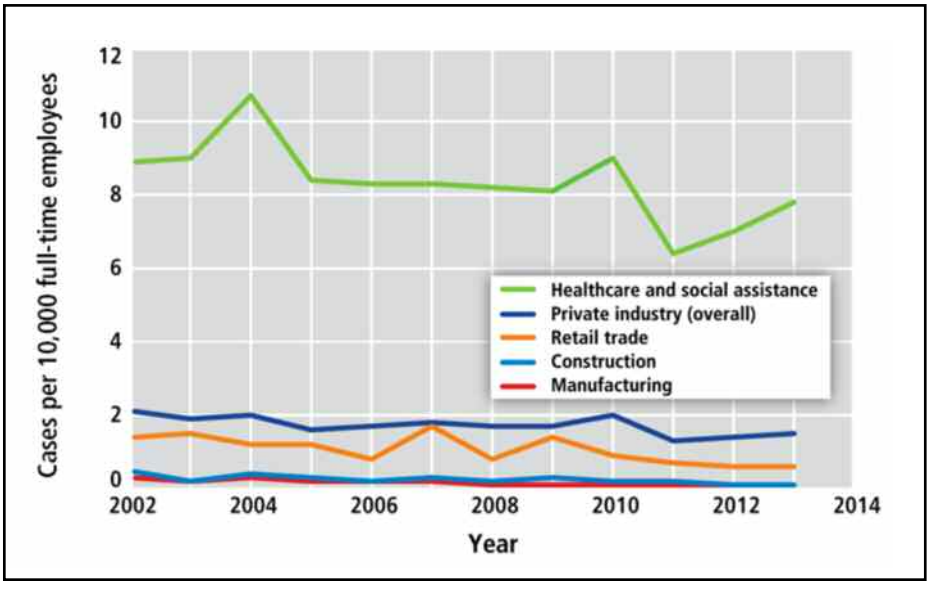
Who Is at Risk?

Workplace violence is a problem that affects everyone, from those who work with patients, to the patients, family members and visitors. While everyone is vulnerable, nurses and nursing assistants bear the brunt of assaults because they usually have the most patient contact. In addition, incidents of assault increase for professionals who work in higher-risk settings such as emergency departments, inpatient mental health facilities, homecare and long-term residential care facilities.

A study conducted on emergency department violence by the Emergency Nurses Association found 55.6 percent of nurses reported they had experienced physical violence, verbal violence or both.[4] And, the American College of Emergency Physicians released the results of its survey of 3,500 emergency physicians in October 2018 that called attention to the scope of violence against emergency room physicians: Nearly half (47 percent) reported having been physically assaulted while at work, with 60 percent saying those assaults occurred in the last year.[2]

According to the U.S. Bureau of Labor Statistics and Occupational Health and Safety Administration, workplace violence in healthcare is four times higher than in private industry, and those numbers are growing.

Figure 1. Violent Injuries Resulting in Days Away from Work, by Industry, 2002-2013[5]



The Root of the Problem

Why rates of violence are so high in healthcare settings is not easy to answer. Like first responders, healthcare professionals come into direct contact with a wide range of people, many of whom are under stress due to pain, illness or circumstances beyond their control.

Many incidents of violence, particularly those that occur in emergency rooms, can be traced to a number of critical unresolved social and healthcare issues, including diminishing resources for behavioral health, increasing opioid addiction, domestic violence and patients in police custody. In addition, factors that increase risk to emergency care providers include 24-hour access, unrestricted visitor access, overcrowding, long waiting periods and access to drugs.

Consequences of Violence

While violence against healthcare providers can be viewed as an occupational hazard, it can have real and devastating consequences for victims. Frequently, providers feel they are equipped to cope with violence because of their training. But, this is rarely the case. Healthcare workers suffer from many of the same physical and psychological consequences as any other victims, including physical injury, permanent disability or death, missed days of work and limited time to recover from injuries, as well as longer-term physiological and psychological consequences that include feelings of anger, fear, depression, guilt and symptoms suggestive of posttraumatic stress disorder such as increased startle response, changes in sleep patterns, increased body tension and generalized body soreness.[5]

Besides the human toll of violence, there is a significant financial impact on the nation's hospitals and long-term care centers.

Besides the human toll of violence, there is a significant financial impact on the nation's hospitals and long-term care centers. If an employee is injured and requires medical treatment or misses work, workers' compensation insurance typically covers the cost. If the hospital is self-insured, it will have to bear the full cost, which can be significant. For example, one hospital system had 30 nurses who required treatment for violent injuries in a particular year, which came to a total cost of $94,156 ($78,924 for treatment and $15,232 for lost wages).[6]

Workplace Violence Defined

The National Institute for Occupational Safety and Health defines workplace violence as "violent acts (including physical assaults and threats of assaults) directed toward persons at work or on duty.[13] The U.S. Department of Labor defines workplace violence as any action (verbal, written or physical aggression) intended to control or cause, or is capable of causing, death or serious bodily injury to oneself or others, or damage to property. Workplace violence includes abusive behavior toward authority, intimidating or harassing behavior and threats.[14]

Action Recommendations for Reducing Workplace Violence[15]

- Develop and enforce comprehensive policies and procedures against workplace violence.
- Evaluate objective measures of violence to identify risks and risk levels.
- Train staff to recognize the warning signs of violent behavior and to respond proactively.
- Establish a comprehensive workplace violence prevention program.
- Encourage all employees and other staff to report incidents of violence or any perceived threats of violence.
- Ensure appropriate follow-up to violent events, including communication, post-incident support and investigation.
- Ensure the violence prevention program addresses the possibility of gun violence, including active shooters.

In addition, injuries and stress can lead to fatigue and burnout that can result in people leaving the profession at a time when they are desperately needed. More importantly, caregiver burnout is a potential threat to quality of care and patient safety. It can result in poorer interactions with patients, resulting in sub-standard care, medical errors, poorer patient outcomes and higher rates of readmission.[7]

Responding to Violence

In response to the rising number of assaults, healthcare executives and providers, as well as policymakers, have taken action in myriad ways. Nine states (California, Connecticut, Illinois, Maine, Maryland, New York, New Jersey, Oregon and Washington) have enacted legislation mandating healthcare

facilities implement workplace violence prevention programs.[8] These laws vary considerably in substance and scope. For instance, New Jersey's law encompasses the healthcare sector, but Maine's includes only hospitals.[3] California's legislation requires healthcare employers to identify specific risk factors for each unit throughout a facility, and to establish procedures to correct any workplace violence hazards, including providing adequate staffing to protect nurses, other workers, patients, families and visitors. In fact, California's regulations are so stringent that Cal/OSHA is considering expanding its workplace violence regulations, which affect only healthcare facilities, to cover employers in all industries.[9]

At the federal level, Congressman Joe Courtney (D-Conn.) introduced H.R. 7141, the Workplace Violence Prevention for Health Care and Social Services Workers Act. The bill compels OSHA to complete "stalled" healthcare workplace violence safety standards, and seeks to "create an enforceable standard to ensure that employers are taking these risks seriously, and creating safe workplaces that their employees deserve."[10] Key elements of the bill include requiring a safety plan so there is a clear protocol in place when patients become violent, requiring follow-up and investigation of any incidents of violence, and protecting employees who call 911 against any professional punishment or retaliation.

Preventive Violence Measures

Many instances of workplace violence can be minimized or eliminated by implementing violence prevention programs that teach workers to perform a hazard evaluation and conduct proper training for staff. Following are six critical steps to help prevent workplace violence:[11]

1) Adopting a zero-tolerance policy toward workplace violence that covers all workers, patients, clients, visitors, contractors and anyone else who may come in contact with workers of the facility;[12]

2) Conducting a threat assessment to areas of risk such as parking garages or places where staff can be isolated or trapped;

3) Educating and training staff to identify people who are exhibiting behaviors that may incite the potential for violence (training should also include how staff members should respond to threats and active shooter situations, bomb threats and hostage scenarios);

4) Adopting mandatory reporting of all incidents and ensuring employees suffer no punitive actions as a result of reporting an incident;

5) Not using obscure language such as code words like code blue or code red to identify emergency situations so everyone is able to understand the situation; and

6) Establishing working relationships with local law enforcement.

A good resource for information on how to evaluate and prepare a facility can be found at www.osha.gov/SLTC/workplaceviolence.

A High-Priority Issue

Until recently, not much attention has been focused on the safety of healthcare professionals. While many in the field feel the threat of violence is part of the job, it is not. Injuries inflicted by patients or family members not only pose a threat to workers, but they result in significant costs for facilities and decreased quality of care for patients. Prevention of injuries from violence and verbal assaults should be given the highest priority to ensure caregivers are physically and mentally able to provide patients with the highest level of care. ❖

Many instances of workplace violence can be minimized or eliminated by implementing violence prevention programs that teach workers to perform a hazard evaluation and conduct proper training for staff.

ABBIE CORNETT is the patient advocate for *IG Living* magazine.

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NovoSeven® RT is the #1 prescribed bypassing agent used in hospitals[1]

Addressing bleeds, whenever they occur

A well-established safety profile

- Low rate of thrombotic events based on clinical trials and registry data[2]
  - 0.2% in CHwI bleeds, 4% in AH patients, <0.2% in GT bleeds

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- CHAwI or CHBwI, AH, GT, and CFVIId

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With NovoSeven® RT, the experience continues

- >30 years of clinical experience[3,a]

For CHAwI patients taking emicizumab, MASAC recommends that[4,b]

- rFVIIa be used to treat acute bleeds
- Use of aPCC be avoided if possible
- rFVIIa be given to patients who will undergo major procedures

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CHwI=congenital hemophilia with inhibitors; CHAwI=congenital hemophilia A with inhibitors; CHBwI=congenital hemophilia B with inhibitors; AH=acquired hemophilia; GT=Glanzmann's thrombasthenia; CFVIId=congenital factor VII deficiency; MASAC=Medical and Scientific Advisory Council; rFVIIa=recombinant activated factor VII; aPCC=activated prothrombin complex concentrate.

[a] 1988: compassionate use initiated in the United States; 1999: FDA approval received for CHwI.[2,5]

[b] Please read the full MASAC recommendations on treating bleeding episodes and surgery in patients with CHwI.

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Indications and Usage

NovoSeven® RT (coagulation Factor VIIa, recombinant) is a coagulation factor indicated for:

- Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and perioperative management in adults with acquired hemophilia

Important Safety Information

WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

Warnings and Precautions

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance
- Patients with congenital hemophilia receiving concomitant treatment with aPCCs (activated prothrombin complex concentrates), older patients particularly with acquired hemophilia and receiving other hemostatic agents, and patients with a history of cardiac and vascular disease may have an increased risk of developing thrombotic events
- Hypersensitivity reactions, including anaphylaxis, can occur with NovoSeven® RT. Patients with a known hypersensitivity to mouse, hamster, or bovine proteins may be at a higher risk of hypersensitivity reactions. Discontinue infusion and administer appropriate treatment when hypersensitivity reactions occur
- Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity (FVII:C). If FVII:C fails to reach the expected level, or PT is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed
- Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis

Adverse Reactions

- The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® RT in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia

Drug Interactions

- Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII

Please see Brief Summary of Prescribing Information on the following pages.

References: 1. Data on file as of 2018. Novo Nordisk Inc; Plainsboro, NJ. **2.** NovoSeven® RT [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2019. **3.** Hedner U. History of rFVIIa therapy. *Thromb Res*. 2010;125:(suppl 1)S4-S6. **4.** National Hemophilia Foundation. MASAC recommendation on the use and management of emicizumab-kxwh (Hemlibra®) for hemophilia A with and without inhibitors. MASAC Document #255. https://www.hemophilia.org/sites/default/files/document/files/255Emicizumab.pdf. Accessed February 27, 2019. **5.** Neufeld EJ, Négrier C, Arkhammar P, et al. Safety update on the use of recombinant activated factor VII in approved indications. *Blood Rev*. 2015;29(suppl1) S34-S41.

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

NOVOSEVEN® RT
Coagulation Factor VIIa (Recombinant)

Rx only

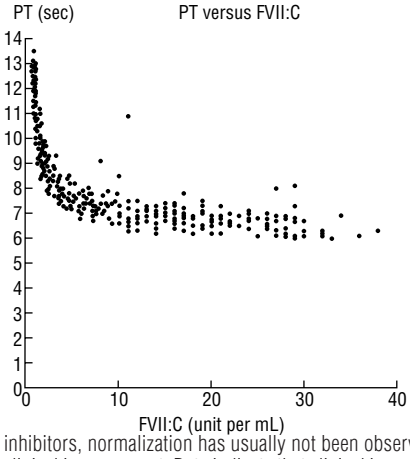
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: THROMBOSIS: Serious arterial and venous thrombotic events following administration of NOVOSEVEN® RT have been reported. *[See Warnings and Precautions]* Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NOVOSEVEN® RT. *[See Warnings and Precautions]* Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. *[See Warnings and Precautions]*

INDICATIONS AND USAGE: NOVOSEVEN® RT, Coagulation Factor VIIa (Recombinant), is indicated for: Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets; Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia.

CONTRAINDICATIONS: None known.

WARNINGS AND PRECAUTIONS: Thrombosis: Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance. Patients with congenital hemophilia receiving concomitant treatment with aPCCs (activated prothrombin complex concentrates), older patients particularly with acquired hemophilia and receiving other hemostatic agents, or patients with a history of cardiac, vascular disease or predisposed to thrombotic events may have an increased risk of developing thrombotic events *[See Adverse Reactions and Drug Interactions]*. Monitor patients who receive NOVOSEVEN® RT for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of NOVOSEVEN® RT or stop the treatment, depending on the patient's condition. **Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis, can occur with NOVOSEVEN® RT. Patients with a known hypersensitivity to mouse, hamster, or bovine proteins may be at a higher risk of hypersensitivity reactions. Discontinue infusion and administer appropriate treatment when hypersensitivity reactions occur. **Antibody Formation in Factor VII Deficient Patients:** Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NOVOSEVEN® RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. **Laboratory Tests:** Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NOVOSEVEN® has been shown to produce the following characteristics: PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 units per mL. For FVII:C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NOVOSEVEN® RT administration is unknown.



INR: NOVOSEVEN® has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NOVOSEVEN® on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized. aPTT: While administration of NOVOSEVEN® shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds. FVIIa:C: FVIIa:C levels were measured two hours after NOVOSEVEN® administration of 35 micrograms per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

ADVERSE REACTIONS: The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NOVOSEVEN® in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia. **Clinical Trials Experience:** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice. Adverse reactions outlined below have been reported from clinical trials and data collected in registries. Hemophilia A or B Patients with Inhibitors: In two studies for hemophilia A or B patients with inhibitors treated for bleeding episodes (N=298), adverse reactions were reported in ≥2% of the patients that were treated with NOVOSEVEN® for 1,939 bleeding episodes (see Table 3 below).

Table 3: Adverse Reactions Reported in ≥2% of the 298 Patients with Hemophilia A or B with Inhibitors

Body System Reactions	**# of adverse reactions** (n=1,939 treatments)	**# of patients** (n=298 patients)
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Fibrinogen plasma decreased	10	5
Cardiovascular		
Hypertension	9	6

Serious adverse reactions included thrombosis, pain, thrombophlebitis deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and abnormal hepatic function. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome. In two clinical trials evaluating safety and efficacy of NOVOSEVEN® administration in the perioperative setting in hemophilia A or B patients with inhibitors (N=51), the following serious adverse reactions were reported: acute post-operative hemarthrosis (n=1), internal jugular thrombosis adverse reaction (n=1), decreased therapeutic response (n=4). *Immunogenicity:* There have been no confirmed reports of inhibitory antibodies against NOVOSEVEN® or FVII in patients with congenital hemophilia A or B with alloantibodies. The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NOVOSEVEN® RT with the incidence of antibodies to other products may be misleading. Congenital Factor VII Deficiency: Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that 75 patients with Factor VII deficiency had received NOVOSEVEN®: 70 patients for 124 bleeding episodes, surgeries, or prophylaxis; 5 patients in the pharmacokinetics trial. The following adverse reactions were reported: intracranial hypertension (n=1), IgG antibody against rFVIIa and FVII (n=1), localized phlebitis (n=1). *Immunogenicity:* In 75 patients with factor FVII deficiency treated with NOVOSEVEN® RT, one patient developed IgG antibody against rFVIIa and FVII. Patients with factor VII deficiency treated with NOVOSEVEN® RT should be monitored for factor VII antibodies. The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NOVOSEVEN® RT with the incidence of antibodies to other products may be misleading. Acquired Hemophilia: Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NOVOSEVEN® for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 patients experienced 8 serious adverse reactions. Serious adverse reactions included shock (n=1), cerebrovascular accident (n=1) and thromboembolic events (n=6) which included cerebral artery occlusion, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions had a fatal outcome. Glanzmann's Thrombasthenia: Data collected from the Glanzmann's Thrombasthenia Registry (GTR) and the HTRS registry showed that 140 patients with Glanzmann's thrombasthenia received NOVOSEVEN® RT for 518 bleeding episodes, surgeries or traumatic injuries. The following adverse reactions were reported: deep vein thrombosis (n=1), headache (n=2), fever (n=2), nausea (n=1), and dyspnea (n=1). **Post marketing Experience:** Adverse reactions reported during post marketing period were similar in nature to those observed during clinical trials and include reports of thromboembolic adverse events.

DRUG INTERACTIONS: Avoid simultaneous use of activated prothrombin complex concentrates. Do not mix NOVOSEVEN® RT with infusion solutions. Thrombosis may occur if NOVOSEVEN® RT is administered concomitantly with Coagulation Factor XIII. *[See Warnings and Precautions]*

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: There are no adequate and well-controlled studies using NOVOSEVEN® RT in pregnant women to determine whether there is a drug-associated risk. Treatment of rats and rabbits with NOVOSEVEN® in reproduction studies has been associated with mortality at doses up to 6 mg per kg body weight and 5 mg per kg body weight respectively. At 6 mg per kg body weight in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg body weight, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg per kg body weight of NOVOSEVEN® gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NOVOSEVEN®. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. **Lactation:** Risk Summary: There is no information regarding the presence of NOVOSEVEN® RT in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NOVOSEVEN® RT and any potential adverse effects on the breastfed infant from NOVOSEVEN® RT or from the underlying maternal condition. **Pediatric Use:** Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age. Hemophilia A or B with Inhibitors: During the investigational phase of product development NOVOSEVEN® was used in 16 children aged 0 to <2 years for 151 bleeding episodes, 27 children aged 2 to <6 years for 140 bleeding episodes, 43 children aged 6 to <12 for 375 bleeding episodes and 30 children aged 12 to 16 years for 446 bleeding episodes. In a double-blind, randomized comparison trial of two dose levels of NOVOSEVEN® in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors 20 children aged 0 to <12 and 8 children aged 12 to 16 were treated with NOVOSEVEN® in doses of 35 or 70 micrograms per kg dose. Treatment was assessed as effective (definite relief of pain/tenderness as reported by the patient and/or a measurable decrease of the size of the hemorrhage and/or arrest of bleeding within 8 hours [rated as excellent = 51%], within 8-14 hours [rated as effective = 18%] or after 14 hours [rated as partially effective = 25%]) in 94% of the patients. NOVOSEVEN® was used in two trials in surgery. In a dose comparison 22 children aged 0 to 16 years were treated with NOVOSEVEN®. Effective intraoperative hemostasis (defined as bleeding that had stopped completely or had decreased substantially [rated as effective = 86%] or bleeding that was reduced but continued [rated as partially effective = 9%]) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 10/12 (83%) in the 35 mcg/kg dose group at 48 hours; effective hemostasis was achieved in 10/10 (100%) in the 90 mcg/kg dose group and 9/12 (75%) in the 35 mcg/kg dose group at 5 days. In the surgery trial comparing bolus (BI) and continuous infusion (CI) 6 children aged 10 to 15 years participated, 3 in each group. Both regimens were 100% effective (defined as bleeding has stopped completely, or decreased substantially) intra-operatively, through the first 24 hours and at day 5. At the end of the study period (Postoperative day 10 or discontinuation of therapy) hemostasis in two patients in the BI group was rated effective and hemostasis in one patient was rated as ineffective (defined as bleeding is the same or has worsened). Hemostasis in all three patients in the CI group was rated as effective. Adverse drug reactions in pediatric patients were similar to those previously reported in clinical trials with NOVOSEVEN®, including one thrombotic event in a 4 year old with internal jugular vein thrombosis after port-a-cath placement which resolved. Congenital Factor VII deficiency: In published literature, compassionate use trials and registries on use of NOVOSEVEN® in congenital Factor VII deficiency, NOVOSEVEN® was used in 24 children aged 0 to <12 years and 7 children aged 12 to 16 years for 38 bleeding episodes, 16 surgeries and 8 prophylaxis regimens. Treatment was effective in 95% of bleeding episodes (5% not rated) and 100% of surgeries. No thrombotic events were reported. A seven-month old exposed to NOVOSEVEN® and various plasma products developed antibodies against FVII and rFVIIa [*see Adverse Reactions and Overdosage*]. Glanzmann's Thrombasthenia: In the Glanzmann's Thrombasthenia Registry, NOVOSEVEN® was used in 43 children aged 0 to 12 years for 157 bleeding episodes and in 15 children aged 0 to 12 years for 19 surgical procedures. NOVOSEVEN® was also used in 8 children aged >12 to 16 years for 17 bleeding episodes and in 3 children aged >12 to 16 years for 3 surgical procedures. Efficacy of regimens including NOVOSEVEN® was evaluated by independent adjudicators as 93.6% and 100% for bleeding episodes in children aged 0 to 12 years and >12 to 16 years, respectively. Efficacy in surgical procedures was evaluated as 100% for all surgical procedures in children aged 0 to 16 years. No adverse reactions were reported in Glanzmann's thrombasthenia children. **Geriatric Use:** Clinical studies of NOVOSEVEN® RT in congenital factor deficiencies and Glanzmann's thrombasthenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

OVERDOSAGE: Dose limiting toxicities of NOVOSEVEN® RT have not been investigated in clinical trials. The following are examples of accidental overdose. One newborn female with congenital factor VII deficiency was administered an overdose of NOVOSEVEN® (single dose: 800 micrograms per kg body weight). Following additional administration of NOVOSEVEN® and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. One Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms per kg body weight (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke). One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days. There were no reported complications in either case.

More detailed information is available upon request.

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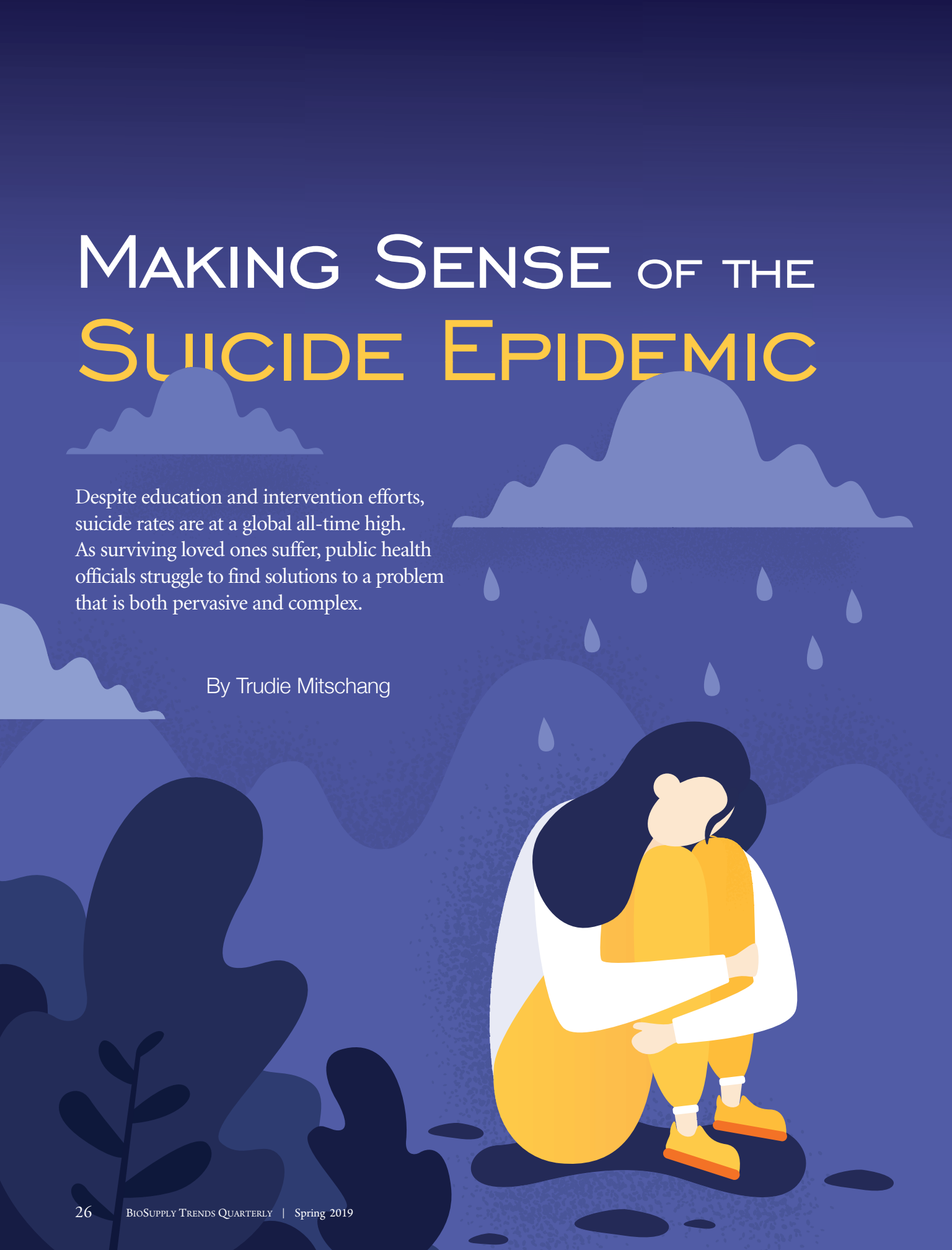
NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Making Sense of the Suicide Epidemic

Despite education and intervention efforts, suicide rates are at a global all-time high. As surviving loved ones suffer, public health officials struggle to find solutions to a problem that is both pervasive and complex.

By Trudie Mitschang



FROM ACTOR ROBIN Williams and designer Kate Spade to celebrity chef Anthony Bourdain, high-profile suicides have dominated the headlines in recent years. These internationally publicized deaths put renewed focus on a tragedy that affects individuals of all ages, races, economic backgrounds and walks of life, often leaving friends and family members grappling with one anguished question: Why?

As researchers, educators and mental health professionals work to find answers, one fact is clear: Suicide is not just a problem in the United States; data indicate it's become a global epidemic, especially among young people.[1]

Consider the following:

• Suicide is the second-leading cause of death globally for 15- to 29-year-olds.

• An alarming 78 percent of suicides occur in low- to middle-income countries.

• The Japanese, despite being a very high-income country and having a population less than half the size of the United States, has the same number of suicides annually.[2]

Suicide and Mental Health

According to the Centers for Disease Control and Prevention (CDC), the link between suicide and mental disorders — in particular, depression and alcohol abuse — is well-established, particularly in high-income countries like the U.S.

Professor Julie Cerel, president of the American Association of Suicidology, notes that access to better reporting standards could account for the global uptick in suicides, but she also points out that a lack of adequate funding for mental health research and preventive care is equally to blame. She highlights that as of 2018, only 10 states mandate suicide prevention training for health professionals.[1] "Our mental health systems are just really struggling across the country," she explains. "In terms of training mental health professionals, we're not doing a great job."

A recent CDC report highlights the complexity of suicide.[3] While a mental health condition may be a contributing factor for many people, the report states "many factors contribute to suicide among those with and without known mental health conditions." A relationship problem was the top factor contributing to suicide, followed by a personal crisis in the past or upcoming two weeks and problematic substance use. CDC reports about half of people who die by suicide do not have a known mental health condition. However, many of them may have been dealing with mental health challenges that had not been diagnosed or known to those around them.

When it comes to known risk factors, the American Psychiatric Association identifies the following:[4]

• Previous suicide attempt(s)

• A history of suicide in the family

• Substance misuse

• Mood disorders (depression, bipolar disorder)

• Access to lethal means (e.g., keeping firearms in the home)

• Losses and other events (for example, the breakup of a relationship or a death, academic failures, legal difficulties, financial difficulties, bullying)

• History of trauma or abuse

• Chronic physical illness, including chronic pain

• Exposure to the suicidal behavior of others

In some cases, a recent stressor or sudden catastrophic event or failure can leave people feeling desperate, unable to see a way out, and becomes a "tipping point" toward suicide.

Dealing with the Stigma

As with any form of mental illness, one of the biggest barriers to preventing suicide is stigma, which prevents at-risk individuals from seeking help. Additionally, while many people have the mistaken notion that talking about suicide causes it to happen more frequently, statistics do not support this notion — all the more reason mental health professionals advocate for a shift in thinking that will remove the stigma surrounding both suicide and mental illness. "Since we can't see a mental illness in the same way we can see a broken bone or cancer cells, there is this belief that these illnesses are not 'real,' or at the very least are not 'medical' illnesses," says Alexa Moody, founder and executive director of Please Live, a nonprofit dedicated to raising awareness of mental illness and preventing suicide. "This simply isn't true. You can actually see the differences on brain scans."[5]

While a mental health condition may be a contributing factor for many people, the report states "many factors contribute to suicide among those with and without known mental health conditions."

For example, a diagnosis of clinical depression is marked by imbalanced chemicals in the brain that lead to feelings of

unhappiness or a lack of fulfillment. "When these chemicals are off-balance, those emotions are difficult or sometimes impossible to achieve, so you take medicine to correct the chemical imbalance," Moody says. "It's the same as someone who is a diabetic; their body is not producing the correct amounts of insulin, so they take medication to correct that imbalance."

As with any form of mental illness, one of the biggest barriers to preventing suicide is stigma, which prevents at-risk individuals from seeking help.

That mental illness isn't legitimate is just one myth in this field. Another, Moody says, is that talking about suicide will "plant the idea" in someone's head. "This misconception is commonly shared by adults, school administrators, parents and community providers," she says, adding that a refusal to talk about it ends up making the suicidal person feel alone and misunderstood, potentially making suicidal thoughts worse. On the other hand, with early intervention, many people report not having suicidal thoughts again. "We must address suicide and mental illness, and address it frankly and factually, for people to feel comfortable to get the help they need."

As a mental illness survivor herself, Moody has a message of hope for others who may be suffering: With proper treatment, most people can and will get better. "Wellness and recovery are possible," she explains, "and you don't have to live with depression, anxiety or suicidal thoughts for the rest of your life."[5]

The Fatal Link Between Suicide and Guns

When looking at the disparity between suicide and attempted suicide rates, research shows that whether attempters live or die depends in large part on the ready availability of highly lethal means, especially firearms. National data indicate that while guns are not the most popular means of taking one's life, they are the most deadly. Statistics show 85 percent of attempts with a gun are fatal, compared with 69 percent for hanging and 2 percent for self-poisoning.[6]

A study by the Harvard School of Public Health (HSPH) of all 50 U.S. states reveals a powerful link between rates of firearm ownership and suicides. Based on a survey of American households conducted in 2002, HSPH Assistant Professor of Health Policy and Management Matthew Miller, Research Associate Deborah Azrael, and colleagues at the School's Injury Control Research Center (ICRC) found that in states where guns were prevalent (as in Wyoming, where 63 percent of households reported owning guns), rates of suicide were higher. The inverse was also true: Where gun ownership was less common, suicide rates were also lower.[6]

The simple fact is few can survive a self-inflicted gunshot wound. In response to these concerns, ICRC's Catherine Barber launched Means Matter, a campaign that asks the public to help prevent suicide deaths by adopting practices and policies that keep guns out of the hands of vulnerable adults and children. Barber, who co-directed the National Violent Injury Statistics System, has also developed free, self-paced, online workshops to help public officials, mental health service providers and community groups put together suicide prevention programs and policies.

Current CDC Suicide Statistics[3]

- Suicide is the 10th-leading cause of death in the U.S. for all ages.
- There is one death by suicide in the U.S. every 12 minutes.
- Depression affects 20 percent to 25 percent of Americans ages 18 or older in a given year.
- Suicide takes the lives of more than 44,965 Americans annually.
- The highest suicide rates in the U.S. are among whites, American Indians and Alaska Natives.
- An estimated quarter million people each year become suicide survivors.
- Suicide among males is four times higher than among females. Male deaths represent 79 percent of all U.S. suicides.
- Firearms are the most commonly used method of suicide among males.
- Females are more likely than males to have had suicidal thoughts.
- Poisoning is the most common method of suicide for females.

Because suicide decisions are often made impulsively, access to firearms can mean the difference between life and death. An investigation by the New Hampshire medical examiner's office showed nearly one in 10 suicides by firearms from 2007 to 2009 involved a weapon that was purchased or rented the preceding week — often within just a few hours.[6] Guns, then, take what is often an ambivalent decision and turn it into an irrevocable one.

But what about the argument that people who are stopped from killing themselves today just find another way to complete the act later? Some undoubtedly will, but studies show the majority of survivors do not. The period of greatest vulnerability seems to be in the first year after an attempt, a time when treatment for those who try to end their life is critically important.

Spotlight on Education and Prevention

The American Foundation for Suicide Prevention (AFSP) offers a variety of programs designed to raise awareness about suicide. Headquartered in New York, the organization was founded in 1987 with a mission to "give those affected by suicide a nationwide community empowered by research, education and advocacy to take action against this leading cause of death." AFSP has local chapters in all 50 states with programs and events nationwide. Among its many initiatives, AFSP launched Out of the Darkness Community Walks to give people the courage to open up about their own struggle or loss, and the platform to eradicate the shame associated with suicide and mental illness. The organization also spearheads student-specific campus walks at colleges and high schools, and 16-mile overnight walks in cities across the country.[7]

The American Psychological Association (APA) is another organization that has been actively working to shift public policy to address suicide risk. Its efforts have focused on increasing access to care, including screening for depression, suicide and other mental health concerns; ensuring insurance coverage for prevention; increasing the number of trained healthcare professionals, including psychologists and other mental health professionals, and effective peer services; and increasing acute treatment resources by expanding Medicaid coverage for short-term acute inpatient stays.[8]

On April 21, 2018, APA joined organizations such as The Trevor Project, The Jed Foundation and the American Association of Suicidology in co-sponsoring the American Foundation for Suicide Prevention's first annual Rally to Prevent Suicide. More than 500 individuals participated in the event on the steps of the Capitol, urging members of Congress to prioritize suicide research and community behavioral health clinic funding, as well as pass H.R. 2345, the National Suicide Hotline Improvement Act, which would create a three-digit emergency number for individuals experiencing a mental health crisis. "Suicide, like so many tragedies, is the direct result of despair, and there is only one cure for despair — hope," said APA member Joel A. Dvoskin, PhD, ABPP. "It is my hope that our political parties can join together in a bipartisan effort to give people in the most acute despair some measure of hope for a better life — by improving the services that are provided."

Suicide is a complex public health crisis with no easy solutions.

What the Future Holds

Suicide is a complex public health crisis with no easy solutions. In a recent report titled National Strategy for Suicide Prevention Implementation,[9] three federal departments outlined their alliance aimed at suicide prevention efforts. According to the report, the U.S. Department of Defense, U.S. Department of Health and Human Services and the U.S. Department of Veterans Affairs have partnered in a significant collaborative effort with goals and objectives that include integrating and coordinating suicide prevention activities across multiple sectors and settings; establishing effective, sustainable and collaborative suicide prevention programming at the state/territorial, tribal and local levels; and sustaining and strengthening collaborations across federal agencies to advance suicide prevention. The initiative also hopes to increase knowledge of the warning signs for suicide and connect individuals in crisis with assistance and care.[9]

In a summary statement, former U.S. Surgeon General Regina Benjamin said, "Reducing the number of suicides requires the engagement and commitment of people in many sectors in and outside of government, including public health, mental health, healthcare, the Armed Forces, business, entertainment, media and education." ❖

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Improving Access to **Clinical Trial Data**

To advance scientific discovery and improve patient outcomes, new programs being introduced to increase transparency in data collection and patient engagement are on the rise.

By Amy Scanlin, MS

THE CONCERN ABOUT transparency is all around us, from claims made about the foods we eat to how a person's data is shared among entities. Similarly, transparency is also a concern with the growing data sharing movement among clinical trial shareholders, including sponsors, clinicians, participants and other interested parties who may be able to utilize the information earlier and more easily to further scientific understandings and initiatives in healthcare. Specifically, when sharing data during the clinical trial process, protecting patient privacy and confidential information about the drug or device being evaluated must be balanced with concerns about a lack of transparency and timely reporting that plagues the ability to effect change, thus stifling innovation.

Data can be used as a mechanism for progress when it is appropriately gathered, analyzed, reported and, in turn, reallocated to benefit future studies, saving time and dollars and reducing duplication of efforts, thus speeding the pace of research. On the other hand, there are valid concerns about how much and what type of data is shared, as well as how sharing might negatively impact confidentiality of critical information and privacy. Significant issues are on the line as the community works together to find pathways forward, respectful of the interests of all parties, to benefit the greater good.

So, how do we get there from here? Is the problem with data transparency determined purely from the investigators' standpoint? Is a siloed data sharing infrastructure unable to facilitate innovation? Or, more inclusively, is there a collective concern, whereby improvements in any of these limitations will lead to forward steps resulting in greater progress? From manufacturers to investigators, patients and those administering study oversight and review, better collaboration will fit the puzzle pieces together and foster proactive and positive change.

FDAAA and ClinicalTrials.gov

The registration of study trials and subsequent data reporting enable the U.S. Food and Drug Administration (FDA) to oversee the safety of study design protocols and outcomes. When studies are not registered, however, FDA loses that ability, and patients, providers, fellow investigators and other interested parties are left with an incomplete picture of the trials, as well as their effects on patient populations.

As a matter of record, the 2007 FDA Amendments Act (FDAAA) mandates sponsors of applicable clinical trials register and report summary results at the congressionally authorized clinicaltrials.gov registry created to provide information about publicly and privately supported clinical trials on the National Institutes of Health's (NIH) database. As part of that mandate, FDAAA also requires sponsors to report trial results within one year after the completion of data collection for the prespecified primary outcome or within one year after the date of early termination, unless there are legally acceptable reasons for the delay.

Unfortunately, reviews and comparisons of trials listed on clinicaltrials.gov have found compliance with these mandates has been historically poor regardless of the funding source, trial phase and whether the trial is under FDA oversight. Interestingly, one study identified trials funded by industry tended to have greater reporting results than those funded by NIH or other sources. And, earlier phase trials tend to report fewer results compared to Phase IV trials, with the presumption earlier trials are more proof-of-concept and may contain more proprietary information. However, even within a five-year period, only 80 percent of industry-funded studies reported their results, compared to 50 percent for NIH-funded studies and 42 percent of trials funded by academic or other sources. In addition, studies conducted without FDA oversight were also less likely to report on time.[1]

Recommendations for Change

In 2015, in an attempt to improve the entire process and encourage shareholder participation, the Institute of Medicine (IOM) released a report titled "Sharing Clinical Trial Data — Maximizing Benefits, Minimizing Risk," which included a wide range of recommendations for addressing the problems of three types of study data:[1]

- Metadata (or data about the data, including protocols),
- Raw data (data collected from participants that has been "cleaned, abstracted, coded and transcribed to become the analyzable data") and
- Analysis data (such as summaries, lay summaries, etc.).[2]

The report recommends a culture of greater data transparency by all parties to improve the bottom line. With greater transparency, data sharing would become an expected part of a study trial process in which funders contribute to the development of an infrastructure that allows for data sharing in accordance with specified grant terms and per regulations. In addition, it recommends funders consider past data sharing as part of their future considerations for funding requests and, as part of that funding, include enforcement requirements for data sharing as part of grant terms.

The IOM also recommended regulatory authorities around the world work toward harmonizing clinical study report templates that avoid revealing stockholder and participant confidential information. By doing this, future clinical trials could be designed with the expectation of data sharing among stakeholders and use of common data elements as part of the study design unless there is a compelling reason not to do so.

The release of study data would then provide an opportunity for those involved in clinical trials to publish their results prior to allowing access to secondary investigators in a manner in which commercial interests of sponsors working to gain regulatory approval is protected. It is the IOM's recommendation that any adverse event summaries, summary level results and lay summaries be provided to trial participants and be publicly available no later than 12 months after study completion. In addition, IOM recommends the full data package be shared no later than 18 months after study completion (barring any pending regulatory applications).[2]

The registration of study trials and subsequent data reporting enable the U.S. Food and Drug Administration to oversee the safety of study design protocols and outcomes.

When deciding to release data, privacy considerations for protecting patient data cannot be understated. Patients must understand not only the study protocols for the trial they are considering, but how and what data might be shared and what protections for that data are in place. For instance, there are many ways to protect data confidentiality, including de-identification, data use agreements and independent review panels.

Change via Social Contracts

Building upon the IOM 2015 report in support of clinical trial data sharing, FasterCures (an action tank that works to speed and improve the medical research system) suggests a social contract with implied rights and responsibilities for each stakeholder. Dubbed Health Citizenship, "The path to better health and the advancement of science," says FasterCures, "begin[s] and end[s] with engaged patients."[3]

FDA Commissioner Scott Gottlieb issued a statement in January 2018 on the agency's new steps to enhance the transparency of clinical trial information to support innovation and scientific inquiry related to new drugs.

According to FasterCures, lackluster data reporting, including registration of study trials, is a lost opportunity for cascading positive impacts on the costs of research and the speed of scientific discovery. Reporting both positive and adverse outcomes in a timely manner equates to improved efficiencies in attempts to reproduce results, as well as reduces redundancies in costs and time while saving precious research dollars. It goes without saying, there is no larger benefit when negative results go unreported because it eliminates the ability of providers and patients to benefit from the research.

It is the hope of many thought leaders that as data collection, sharing and transparency continue to evolve, including first-person sourcing such as wearable devices and the mining of de-identified electronic health records, the barriers currently posed with traditional methods of research and regulatory requirements are reanalyzed fostering a forward trajectory and increasing the speed of progress.

Heeding the Call

FDA is mandated by the FDAAA to maintain a website that provides safety information, including safety alerts, warning letters and links to clinical trial information. In addition, it has begun to incorporate broader transparency policies designed to bridge the gap of some discrepancies between the comprehensive information within its possession and other incomplete information released to the public,[4] which could have negative outcomes for public health.

FDA Commissioner Scott Gottlieb issued a statement in January 2018 on the agency's new steps to enhance the transparency of clinical trial information to support innovation and scientific inquiry related to new drugs. This includes a pilot program to repackage information released in clinical study reports (CSRs) so the information is easier to access on the agency's drug approval database drugs@FDA. It is FDA's view that releasing more premarket and postmarket clinical trial data will enable greater extraction of detailed clinical evidence supporting FDA's approval decisions. CSRs contain bottom-line detailed scientific summaries, including the clinical trial's methods, efficacy and safety results. As part of the pilot, FDA will release, as applicable, the study report body, including protocols and amendments, as well as the statistical analysis plan for each of the participating product's pivotal studies, while protecting patient privacy, trade secrets and confidential commercial information contained in the CSRs.

In addition, FDA's Digital Health Software Precertification Pilot Program is evaluating nine companies designing medical device software against quality and excellence standards, including product quality, patient safety, clinical responsibility, cybersecurity responsibility and proactive culture. The agency will then work with the developers to collect and interpret real-world information about their medical device software to assess the product's safety and effectiveness and to address any emerging risks.[5]

Practical and Pragmatic Steps Forward

As the opportunity for meaningful data collection accelerates, study sponsors, clinicians and their patients all play an active role in ensuring change progresses in a thoughtful manner. However the details of these initiatives play out, efforts for improving transparency and encouraging active participation for all parties will contribute to moving healthcare forward toward improved patient outcomes. ❖

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Infectious Mononucleosis: The Best-Recognized Epstein-Barr Virus Infection

Typically treated with supportive care, this common human infection usually resolves in weeks with some symptoms persisting for months.

By E. Richard Stiehm, MD

An EBV Vignette

Sally, a 6-year-old girl, was bitten by a mosquito. Within 24 hours, she developed a fever followed by complaints that the trees looked too close, the birds were the size of her kitty and the leaves on the tree were blue! Her temperature was 101.5 Fahrenheit, but a physical exam and spinal tap were also normal. Routine laboratory studies were negative except for an elevated IgE of 1,120 IU/ml. An EEG showed an epileptic focus in the left occipital area. Tests for Epstein-Barr virus showed the IgM-VCA was positive as was a mononucleosis spot test, both suggesting a primary EBV infection. Sally improved after five days of oral steroid treatment, and her visual hallucinations gradually disappeared.

Diagnosis: This girl presented with an unusual manifestation of infectious mononucleosis, the "Alice in Wonderland" syndrome (metamorphopsia) (Figure 1). It is thought to be a viral-induced transient central nervous system vasculitis.[1]

Figure 1. Alice-in-Wonderland Syndrome.

EPSTEIN-BARR VIRUS (EBV) disease is the most common chronic infection in humans, affecting nearly all older adults sometime in their lifetime.[2] The best recognized EBV infection is infectious mononucleosis (IM), an acute febrile disease often seen in seronegative college students engaged in deep kissing, thus its familiar moniker "kissing disease" (Figure 2).[3] Salivary secretion of the virus may persist for three or four months after recovery from IM, permitting its widespread dissemination on college campuses.

Early primary EBV infections are common in young children living in the tropics or in lower socioeconomic conditions.[2] Such infections are generally mild or asymptomatic but lead to seroconversion with durable immunity to another primary EBV infection. Thus, IM is uncommon in these populations, and also in African-Americans.[4,5]

EBV is a herpes virus (human herpes virus-4) whose only natural reservoir is humans.

IM is only mildly contagious, as it is spread by oral secretions, not by respiratory droplets. It can also be transmitted by blood transfusion, organ transplants or, rarely, by maternal-fetal transmission.[2]

Figure 2. The Tonsils, Lymph Nodes and Large Lymphocytes of IM, the Kissing Disease

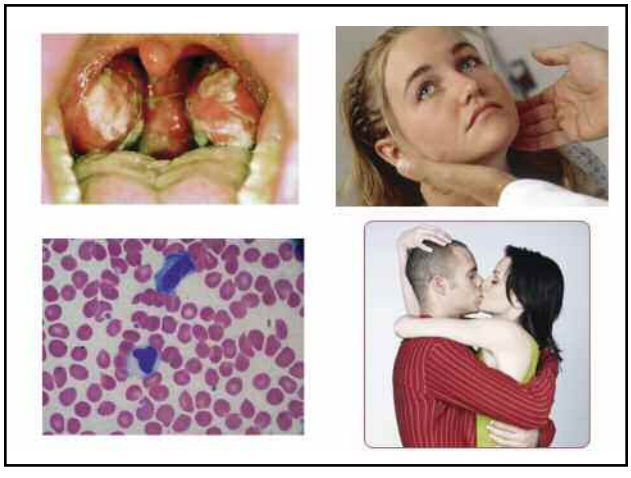
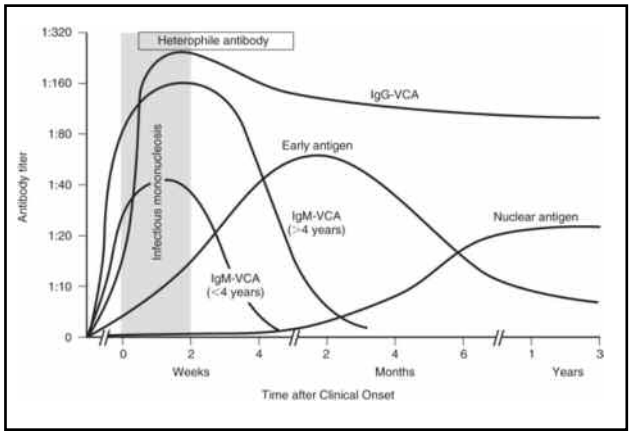


Figure 3. Evolution of Antibodies to EBV Antigens in Infectious Mononucleosis



Source: Jensen HB, Ench Y, and Sumaya CV. Epstein-Barr Virus, in Rose NR, de Macario ED, Folds JD et al., editors, *Manual of Clinical Laboratory Immunology 5th Edition,* Washington, D.C., American Society for Microbiology 1997: 634-43.

EBV and Its CD21 Receptor

EBV is a herpes virus (human herpes virus-4) whose only natural reservoir is humans.[2] The EBV receptor is the CD21 protein on the surface of B lymphocytes. Once EBV infection occurs, the virus remains forever in a latent state in B memory cells, resulting in lifetime seropositivity to the virus. Antibodies to the virus are directed at the viral capsid antigen (VCA), the nuclear antigen (EBNA) and the early antigen (EA), which appear in a characteristic sequence after an acute EBV infection (Figure 3).

B cells harboring the latent virus can become activated at any age to proliferate and release virus, usually following another illness, medications or stress. These secondary infections can be mild or severe and cause a myriad of illnesses.

The EBV CD21 receptor is also present on some nasopharyngeal epithelial cells. EBV entering the mouth attaches to these short-lived cells that proliferate and excrete virus into the saliva and infect local B cells that disseminate the virus throughout the body. They also stimulate the production of EBV-specific antibodies and CD8 cytotoxic T cells, the latter of which control the acute infection. Virus remains in the body forever as a latent infection in some memory B cells.

The ability of EBV to infect and immortalize B cells allows for the in vitro production of a permanent B cell line. These cells can be frozen, thawed and expanded to provide an unlimited source of a patient's DNA for genetic tests.

Delineation of Infectious Mononucleosis

In 1887, Emil Pfeiffer, MD, of Wiesbaden, Germany, described a short-term febrile illness characterized by fever, sore throat and cervical adenopathy that sometimes occurred in

families. He called this glandular fever.[6] In 1920, Thomas Peck Sprunt, MD, and Frank Alexander Evans, MD, at Johns Hopkins Hospital in Baltimore identified a similar syndrome among close contacts and noted the presence of large atypical lymphocytes in the blood smear and coined it IM.[7]

Then, in 1924, John R. Paul, MD, and W.W. Bunnell, MD, at the Yale School of Medicine observed in the serum of IM patients agglutinated (stuck together to form a mass) sheep erythrocytes, labeling these heterophile antibodies.[8] These antibodies persist for several weeks after an IM infection. This antibody became the standard diagnostic tool to diagnose the disease with an 85 percent to 90 percent specificity and sensitivity.[9] It was later improved upon by a preabsorption step with guinea pig kidney cells and the use of horse erythrocytes instead of sheep erythrocytes, and is now known as the monospot test, which is used today.[10]

Discovery of Epstein-Barr Virus

Despite its identification, the cause of IM remained a mystery that began to be unraveled in tropical Africa. In 1938, Denis Burkitt, MD, an English missionary doctor working in Uganda, noted several young children with prominent jaw tumors that on biopsy resembled a lymphoma (Figure 4).[11] He thought this was an infection possibly spread by the malaria mosquito. This fatal illness became known as Burkitt's lymphoma.

Twenty-six years later in 1964, Michael Epstein, CBE, FRS, FMedSci, and Yvonne Barr, PhD, of the United Kingdom were able to grow cells from a surgically removed Burkitt tumor.[12] Using the electron microscope, they identified a viral particle resembling a herpes virus,[13] which became known as the Epstein-Barr virus (EBV).

In 1966, Gertrude Henle, PhD, and Werner Henle, PhD, a husband and wife team of virologists in Philadelphia, developed an indirect immunofluorescent antibody test for EBV.[14] They showed this antibody was present in patients with Burkitt's lymphoma, but was also present in many normal individuals. It was also present in the blood of a laboratory worker who was recovering from IM. By good fortune, the worker had donated a blood sample before contracting IM, and this blood had no EBV antibodies. This suggested EBV was the cause of IM.[15]

Subsequent studies on many other IM patients validated this conclusion, solving the medical mysteries started in Germany in 1887 that continued in Uganda in 1938. A complete history of IM is available.[16]

Clinical Features

IM is particularly common among college students, 18 years to 24 years old.[3] EBV is transmitted by close oral contact with someone secreting the virus in the saliva; viral secretion may continue for several months after an initial EBV infection.[2]

After an incubation period of two weeks to four weeks, the cardinal features of fever, pharyngitis and lymphadenopathy occur. Fatigue and myalgia are also common and may persist for several weeks after other symptoms subside.[17,18] Persistent fatigue is more common in females and those with prior mood disorders.

EBV is transmitted by close oral contact with someone secreting the virus in the saliva; viral secretion may continue for several months after an initial EBV infection.

Sore throat is common, usually associated with enlarged tonsils with a gray or white exudate mimicking a streptococcal infection (Figure 2). Palatal petechiae or hemorrhagic streaks may also be noted. Posterior cervical lymphadenopathy appears early, and the nodes are symmetric and tender. Lymphadenopathy in other areas of the body may occur, unlike the adenopathy of bacterial pharyngitis. Occasionally, lymphadenopathy is so severe that airway obstruction or a peritonsillar abscess may develop.

Splenic enlargement occurs in about half of the patients, usually lasting for three weeks. Splenic rupture is uncommon, but strenuous physical activity, especially contact sports, should be avoided until the illness has subsided and the spleen is no longer enlarged.

Maculopapular or urticarial rashes are not uncommon. They are often provoked by antibiotics, usually ampicillin or amoxicillin but sometimes by azithromycin, levofloxacin, and cephalosporins. The mechanism is not known, but it does not appear to be a true drug allergy since it does not recur with a repeat dose after the patient is well.

Neurologic syndromes associated with IM include Guillain-Barré syndrome, cranial nerve palsies, peripheral neuropathy, aseptic meningitis, encephalitis and the Alice-in-Wonderland syndrome described in the vignette.[1]

Less common manifestations may affect many other organ systems as presented in Table 1. Differential diagnosis includes

streptococcal infections, acute cytomegalovirus or HIV infection, toxoplasmosis, lymphoma or hypersensitivity to a drug, particularly anticonvulsants or antibiotics.

Laboratory Features

Blood abnormalities include a leukocytosis due to an absolute lymphocytosis (e.g., greater than 4,500 cells/µl). Many of the lymphocytes are enlarged and atypical; these are CD8 cytotoxic cells directed against EBV-positive B lymphocytes.

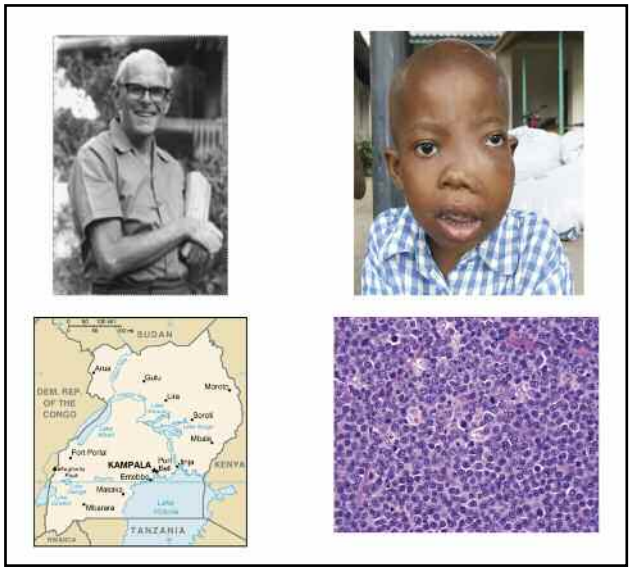
Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) are often elevated, as are immune globulin levels, principally IgM. Autoimmune antibodies may be present such as the direct Coombs test, rheumatoid factor and antinuclear antibody (ANA). Liver function tests are often elevated, indicating liver involvement.

The heterophile antibody or the monospot test is usually positive as are antibodies to viral antigens, including viral capsid antigen (VCA), nuclear antigen (EBNA) and early antigen (EA). These antibodies appear at different stages of the infection (Figure 3). Acute infection is associated with the appearance of IM antibodies to VCA (IgM-VCA) followed shortly by IgG-VCA and EA antibodies. Past infection is indicated by IgG-VCA without IgM-VCA antibodies.[2]

Table 1. Complications of Infectious Mononucleosis

- Cardiac: Myocarditis, pericarditis, arrythmias
- Dermatologic: Ampicillin and other antibiotic-induced rash, oral hairy leukoplakia, hypersensitivity to mosquito bites
- Hematologic: Hemolytic anemia, thrombocytopenia, leukopenia, aplastic anemia
- Hepatic: Hepatitis, Reye's syndrome
- Immunologic: Decreased cellular immunity, lymphoproliferative syndrome, Burkitt's lymphoma and non-Hodgkin's lymphoma
- Neuropsychiatric: Encephalitis, Guillain-Barré syndrome, Bell's palsy, psychosis, optic neuritis, transverse myelitis, Alice-in-Wonderland syndrome
- Renal: Glomerulonephritis, interstitial nephritis
- Respiratory: Upper-airway obstruction, interstitial pneumonitis, pneumonia
- Splenic: Rupture, spontaneous or posttraumatic

Figure 4. Jaw Tumors in Ugandan Children (described by Denis Burkitt, MD), Which Often Have a Distinct Starry Night Appearance on Microscopy



The presence of EBV in the blood as indicated by a polymerase chain reaction (PCR) test is indicative of current active EBV infection; its quantitation can be used to determine the severity and course of the disease.

Management

Isolation of patients is not necessary even though they may secrete virus in the saliva for several weeks.

Treatment of IM is usually supportive: rest, analgesics, adequate fluid and nutrition. Antivirals are of no proven value, even in severe cases. Corticosteroids are sometimes indicated if there is an associated hemolytic anemia, severe hepatitis or strikingly enlarged lymphadenopathy with respiratory or swallowing compromise.

Splenomegaly may be present in 50 percent of cases and subject to rupture. Therefore, strenuous exercise or contact sports should be avoided during the acute illness and until the spleen is no longer enlarged.

Patients can return to school or work as soon as they feel well. They are not contagious to everyday contacts, just to their kissing and sexual partners.

No vaccine is available.

Prognosis

Most patients eventually recover uneventfully and develop durable immunity to the virus. Acute symptoms resolve in two weeks to three weeks, but persistent fatigue may persist

for several months. Chronic fatigue may be prolonged, particularly among women and those with a prior history of a mood disorder.

Treatment of IM is usually supportive: rest, analgesics, adequate fluid and nutrition.

Reactivation of the virus from its latent state may occur years after primary infection. This may occur as a result of another illness or the use of a drug that suppresses cellular immunity. These disorders are multiple and a topic of another article.

Occasionally, the acute infection is followed by a chronic EBV infection with persistent viremia.[19] This is a serious disease with a guarded prognosis. By contrast, persistent seropositivity without viremia is common and not a cause of chronic disease, including chronic fatigue syndrome. ❖

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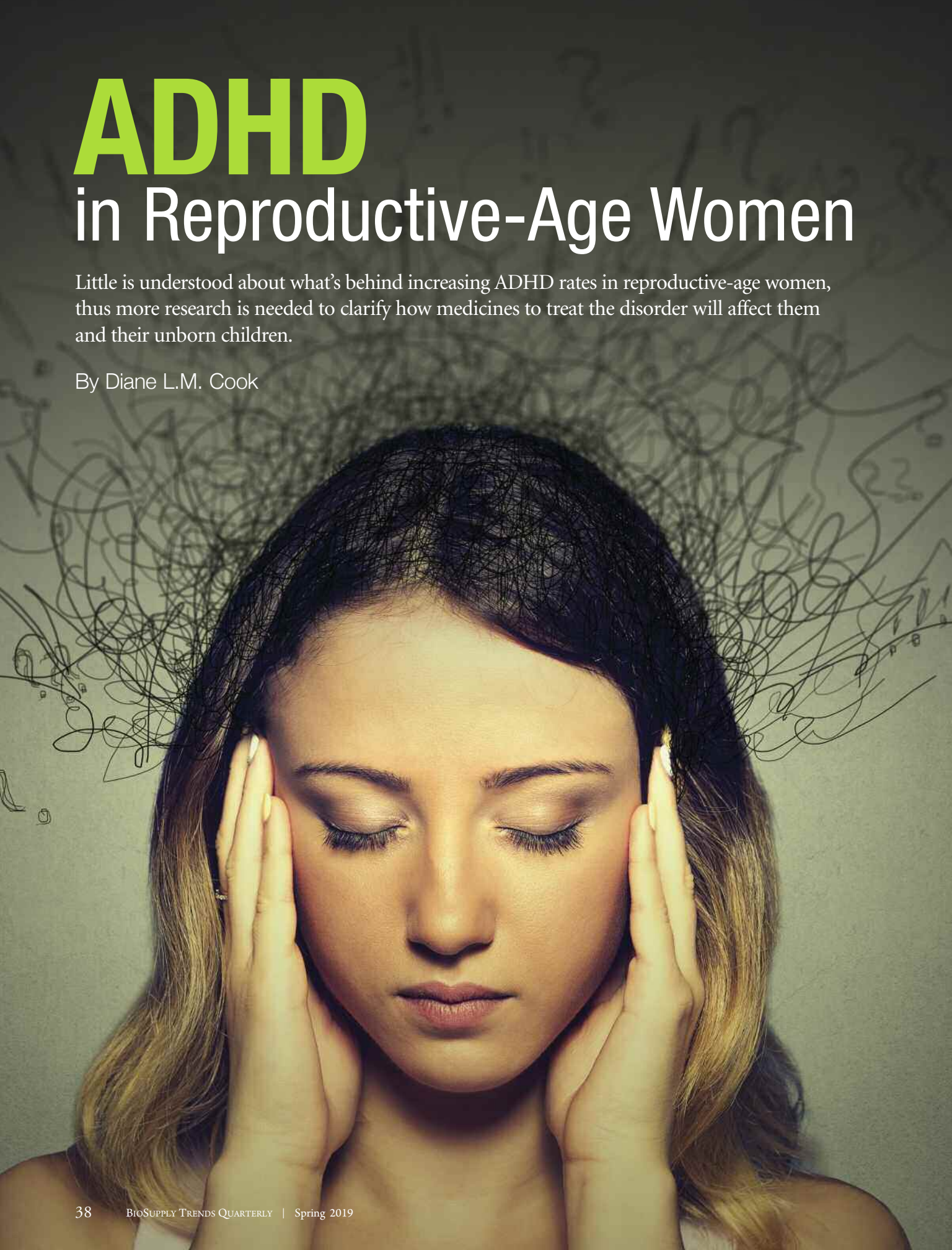
ADHD in Reproductive-Age Women

Little is understood about what's behind increasing ADHD rates in reproductive-age women, thus more research is needed to clarify how medicines to treat the disorder will affect them and their unborn children.

By Diane L.M. Cook



MOST RESEARCH conducted on attention-deficit hyperactive disorder (ADHD) has primarily focused on male children. Yet, a recent study shows ADHD prescription use among reproductive-age women has increased 700 percent.[1] In addition, it is unknown why ADHD rates are increasing among this age group, but another recent study shows sex hormones might play a role in the presentation of symptoms, diagnosis and treatment.[2] As such, much more investigation is needed to understand how ADHD presents in these women and how ADHD medication affects them and the developing fetus.

What Is ADHD?

ADHD is a neurodevelopmental disorder characterized by a persistent pattern of inattention and/or hyperactivity and impulsivity that interferes with a person's functioning or development.[3] It begins in childhood and often continues throughout adolescence and into adulthood. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* lists three ADHD presentation types: predominantly inattentive presentation (PIP, includes nine symptoms), predominantly hyperactive-impulsive presentation (PHIP, includes nine symptoms) or combined (a total of 18 symptoms). Symptoms can be mild, moderate or severe. And, since ADHD symptoms can change over time, adults might fit different presentations in adulthood than in childhood.[4]

For an adult to be diagnosed with ADHD, several PIP or PHIP symptoms had to be present prior to 12 years old; manifestations have to be present in more than one setting such as home, school or work; and there must be evidence symptoms interfere with the person's functioning in these settings.[4]

ADHD Statistics

According to *DSM-5*, population surveys suggest ADHD occurs in most cultures in about 5 percent of children and about 2.5 percent of adults, and a substantial proportion of children remain relatively impaired into adulthood. Differences in ADHD prevalence rates across regions appear attributable mainly to different diagnostic and methodological practices. The disorder is more frequent in males than females in the general population, with a ratio of approximately two to one in children and 1.6 to one in adults. In addition, females are more likely than males to present primarily with inattentive features.[4]

The National Resource Center on ADHD says the disorder can coexist with other psychotic or mental disorders. For adults with ADHD, more than 80 percent have at least one other disorder, more than 50 percent have two other disorders and more than 33 percent have at least three other disorders. These disorders include depression, anxiety, oppositional defiant disorder, conduct disorder and alcohol and drug use disorders. Many of these disorders' symptoms mimic ADHD symptoms and can be mistaken for ADHD.[3]

ADHD Treatment for Adults

Adults diagnosed with ADHD can be treated with behavioral interventions, medication or a combination of the two. Stimulants such as methylphenidate HC1 (Ritalin, Concerta and generics) and amphetamine mixed salts (Adderall, Adderall XR and generics) are the most common types of medication used. Other medications include lisdexamfetamine dimesylate (Vyvanse), dextroamphetamine (Dexedrine and generics) and atomoxetine (Strattera). These medications are prescribed for both ADHD-diagnosed females who are and are not pregnant.[5]

The Relationship Between Pregnancy and ADHD in Reproductive-Age Women

In 2014, Ronit Haimov-Kochman, MD, a physician in the IVF Unit at the Department of Obstetrics and Gynecology at the Hadassah Hebrew University Medical Center in Mount Scopus, Jerusalem, conducted a meta-analysis of previous studies that examined why ADHD in girls may be consistently underidentified and underdiagnosed. Titled Cognitive Functions of Regularly Cycling Women May Differ Throughout the Month, Depending on Sex Hormone Status; A Possible Explanation to Conflicting Results of Studies of ADHD in Females, her study demonstrated, "there is a growing body of literature showing that sex hormones have the ability to regulate intracellular signaling systems that are thought to be abnormal in ADHD. Thus, it is conceivable to believe that this functional interaction between sex hormones and molecules involved with synaptic plasticity and neurotransmitter systems may be associated with some of the clinical characteristics of women with ADHD.

Much more research is needed to understand how ADHD presents in these women and how ADHD medication affects them and the developing fetus.

"The studies of ADHD in females suggest confusing and nonconsistent conclusions. None of these studies examined the possible relationship between phase of the menstrual cycle, sex hormone levels and ADHD symptoms. The menstrual cycle should, therefore, be taken into consideration in future studies in the neurocognitive field since it offers a unique opportunity to

understand whether and how subtle fluctuations of sex hormones and specific combinations of sex hormones influence neuronal circuits implicated in the cognitive relation of emotional processing. The investigation of biological models involving the role of estrogen, progesterone and other sex steroids has the potential to generate new and improved diagnostic and treatment strategies that could change the course of cognitive-behavioral disorders such as ADHD."[2]

Possible Explanations for Increasing Prescription Drug Use Among Reproductive-Age Women

According to Kayla Anderson, PhD, an epidemiologist at the Center for Disease Control and Prevention's (CDC) National Center on Birth Defects and Developmental Disabilities, "Two CDC studies have recently reported that ADHD medication use is increasing among reproductive-age and pregnant women. Based on our data, we were not able to look at why there are increasing rates of ADHD medicine prescriptions among these women. However, there are at least two possible explanations, which need additional research, for why this increase might be occurring. First, in recent decades, there have been substantial increases in the percentage of children diagnosed with and treated for ADHD. As these children age into adulthood, they may continue having ADHD symptoms and continue taking their medication as treatment for this chronic, lifespan condition. And, second, there is increasing awareness that ADHD affects people of all ages, not just children, and that ADHD symptoms may show themselves differently for adults than children. This may mean that more adults are being diagnosed with and treated for ADHD.

"Two CDC studies have recently reported that ADHD medication use is increasing among reproductive-age and pregnant women."

In "ADHD Medication Prescription Claims Among Privately Insured Women Aged 15-44 Years — United States, 2003-2015," CDC used the Truven Health MarketScan Commercial Database to estimate the percentage of reproductive-age women with private employer-sponsored insurance who filled prescriptions for ADHD medications each year. It found, overall, the percentage who filled at least one ADHD prescription increased 344 percent. However, prescriptions filled by women age 25 years to 29 years increased a whopping 700 percent. In 2015, the most frequently filled medications were mixed amphetamine salts (60.8 percent), lisdexamfetamine (26.7 percent) and methylphenidate (18.1 percent). Among women who filled any ADHD prescriptions, the number of prescriptions filled per year rose from an average of 5.5 in 2003 to 7.2 in 2015.[1]

Potential Risks of ADHD Medicines in Reproductive-Age Women

In 2015, researchers at the Slone Epidemiology Center at Boston University wrote a letter to the editor of *Pharmacoepidemiology & Drug Safety* titled "Increasing Use of ADHD Medications in Pregnancy." The letter was a summary of data from the center's Birth Defects Study (BDS), which examined the prevalence of ADHD medications used among pregnant women from interviews conducted between 1998 and 2014. The study found 1) medication use is increasing among pregnant women, 2) the increase is entirely accounted for by increased use of Adderall and Adderall XR and 3) there is little information on possible risks to the fetus from such exposure.

According to the researchers, ADHD is one of the most common conditions of childhood and is typically treated with medication. Once initiated, medication often becomes chronic therapy, and approximately 30 percent of patients are estimated to continue pharmacologic treatment into adulthood. As a result, these drugs are likely to be used by pregnant women, raising concerns about possible fetal exposure. In addition, a recent publication noted premarket safety and efficacy studies for ADHD medications in children focused only on the short-term safety and efficacy of these medications, and no premarketing studies have focused on pregnant women and their offspring.

"Our observation … raises particular concern because pregnant women constitute a special population for whom exposure carries a potential risk not only to the woman herself, but also to the fetus she is carrying," said the researchers. "The few human studies that have explored possible effects of these drugs on the fetus included only small numbers of subjects or were primarily focused on methylphenidate, while our experience indicates that amphetamine mixed salts are by far the most common (and most rapidly increasing) ADHD medication used by pregnant women in the United States. With exposure prevalence now approximately 1 percent, these drugs rank among the most commonly used prescription medications in pregnancy, and it is also possible that use will increase further as more women whose exposure began in childhood enter childbearing age."[6]

Previous research has linked ADHD medication use during pregnancy with an increased risk for poor pregnancy outcomes, including spontaneous abortion, although research is limited. And, whether ADHD medications increase risk of birth defects is largely unknown, with only one published study.[1]

CDC's Treating for Two Initiative

The CDC's National Center on Birth Defects and Developmental Disabilities is working to improve the health of women and babies through its Treating for Two: Safer Medicine Use in Pregnancy initiative. The aim of the initiative is to address medication safety by conducting research before and during pregnancy to help women and their healthcare providers make evidence-based decisions regarding the risks and benefits of pharmacologic and behavioral treatment options for common conditions, including ADHD.

Treating for Two is CDC's prescription for this problem. Its mission is to provide evidence-based guidance on safer medication use during pregnancy and provide communication products to support shared decision-making among women and healthcare professionals.[7] "Treating for Two works to understand trends in medicine use, including ADHD medications, among pregnant women and women of reproductive age, and to provide women and healthcare providers with information about the safety or risk of using specific medicines during pregnancy," said Dr. Anderson. "This information will enable women and their doctors to make informed decisions about treating health conditions during pregnancy."

In 2018, as part of its work related to Treating for Two, CDC used data from the National Birth Defects Prevention Study, a U.S. population-based case-control study conducted between 1998 and 2011 that examined risk factors for major structural birth defects, as well as the use of ADHD medications among pregnant women. The study found "early pregnancy ADHD medication use was more commonly reported by mothers of infants/fetuses with gastroschisis, omphalocele and transverse limb deficiency."[8]

The Need for More Research

CDC says it is unknown if reproductive-age women, specifically women who are pregnant, present with increased symptoms of ADHD compared with nonpregnant women. "There is little information available about how frequently pregnant women report having ADHD diagnoses and regarding how ADHD symptoms may or may not change during pregnancy," said Dr. Anderson.

"Until the role of sex hormones in the female human brain is understood, it is important to take into account critical variables such as menstrual cycle phase, hormonal status (for example, postpartum, perimenopause, menopause) and external hormonal use (for example, combined oral contraception, hormonal replacement therapy at menopause)," said Dr. Haimov-Kochman. "The menstrual cycle offers a unique opportunity to study whether and how subtle fluctuations of sex hormones and specific combinations of sex hormones influence neuronal circuits implicated in the cognitive regulation of emotional processing. This may lead to better understanding of the sex hormone impact on women's brain in health, as well as in ADHD, and may resolve the inconsistency of the findings in women with ADHD."[2]

"Given that nearly half of U.S. pregnancies are unintended, and early pregnancy is a critical period for fetal development, examining trends in ADHD medication prescriptions among reproductive-age women is important to quantify the population at risk for potential exposure," explained Dr. Anderson. "Our group at CDC studies health outcomes, such as birth defects, related to medication use during pregnancy. There is currently very little information about the safety and risk of taking ADHD medications before and during pregnancy and related pregnancy, birth and infant outcomes, including birth defects. At this time, there is not enough data to determine the profile of risk or safety of taking ADHD medications during pregnancy. More research is urgently needed to understand the safety of ADHD medications before and during pregnancy."[1] ❖

CDC says it is unknown if reproductive-age women, specifically women who are pregnant, present with increased symptoms of ADHD compared with nonpregnant women.

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Human Albumin as Drug Therapy for Decompensated Cirrhosis: *A New Lifesaving Role for an Old Player?*

By Keith Berman, MPH, MBA

"The mechanism behind current usage of albumin is that of volume expansion. However, many hepatologists believe albumin has other medicinal properties."

— The ATTIRE Trial Investigators[22]

WHEN AN ACTOR is widely known for playing just one kind of part, we say he or she is "type-cast." Since it was first purified and administered to severely burned and bleeding U.S. soldiers during World War II, the clinical role for human albumin has unquestionably been type-cast as well. As albumin comprises roughly half of total plasma protein content and accounts for 75 percent of plasma oncotic pressure, it was quite natural to assume maintenance of circulating plasma volume is the primary role of this relatively small 66 kilodalton protein.

And so it is that, for more than seven decades, albumin has been relegated to a supporting role as a simple plasma volume expander whose oncotic properties are needed in clinical situations where use or continued use of crystalloids is contraindicated. But, recent in vitro and small animal studies, and now surprising new findings from clinical studies evaluating 20 percent albumin in patients with decompensated cirrhosis, point to therapeutic mechanisms beyond simple maintenance of circulating blood volume. A growing body of evidence suggests known pharmacologic properties of human albumin may contribute to reducing the risk of a range of cirrhosis complications, including bacterial sepsis, irreversible renal injury and death.

Study Findings Spur Interest in Albumin Functionality

Interest in the physiologic role of circulating albumin began in earnest after publication of a landmark 1999 clinical study evaluating exogenous albumin as a blood volume expander for cirrhotic patients with spontaneous bacterial peritonitis (SBP), with the goal of minimizing renal impairment thought to be due to an infection-mediated drop in effective arterial volume.[1] Spanish investigators randomized 126 patients to receive an intravenous antibiotic (cefotaxime) or antibiotic plus 1.5 gram/kg albumin administered at the time of diagnosis, followed by 1 gram/kg on day three of hospitalization. Both treatment groups experienced similarly high infection resolution rates (94 percent and 98 percent). But, the rate of nonreversible renal impairment (hepatorenal syndrome) was three-fold higher in the cefotaxime-only group than the cefotaxime-plus-albumin group (33 percent vs. 10 percent,

p=0.001), as was in-hospital mortality (29 percent vs. 10 percent, p=0.01).

This single study transformed the management of cirrhosis with SBP; albumin administration at diagnosis and on day three is now the standard of care in qualifying patients.[2] While prevention of circulatory dysfunction was considered the most likely explanation for how just two doses of exogenous albumin so sharply reduced rates both of hepatorenal syndrome and in-hospital mortality, the investigators noted "the possibility that the beneficial effects of albumin involve mechanisms other than those related to plasma expansion cannot be ruled out."

Protein chemistry research over the last two decades has vastly expanded our understanding of the physiologic actions of human albumin. Largely through its extraordinary ligand-binding properties, albumin mediates a diverse range of important functions. In particular, albumin:

- Accounts for most of the antioxidant capacity of human serum via scavenging and limiting production of reactive oxygen species (ROS), binding inactivating mediators of oxidant damage (e.g., Cu2+ and Fe3+) and binding and delivering antioxidant molecules;[3]
- Detoxifies circulating liver metabolites, including bilirubin, and transporting them to disposal sites, including the liver for eventual excretion in bile;[4]
- Binds and transports fatty acids essential for energy metabolism and membrane synthesis;[5]
- Serves as the primary reservoir for nitric oxide (NO), which acts as a mediator of vasodilation, platelet aggregation and superoxide production and removal; and
- Stimulates proliferation and maintains integrity and function of proximal renal tubular cells.[6]

Albumin, Prostaglandin E2 and Infection Risk

But a decade ago, United Kingdom (UK) and German collaborators showed albumin functionality declines* with increasing liver disease severity, likely due to accumulation of toxins, drugs and other ligands or to permanent derangements of the protein itself. Further, worsening albumin function was found to be associated with increased mortality.[7] The study authors speculated the diminished ability of circulating albumin to prevent oxidative stress damage might account for further decompensation. This might well turn out to be a contributing factor, but more recent work definitively points to another connection between impaired albumin functionality and mortality: increased risk of severe bacterial infection.

> "Protein chemistry research over the last two decades has vastly expanded our understanding of the physiologic actions of human albumin."

Patients with decompensated cirrhosis are highly prone to bacterial infection, which is either present or acquired during 25 percent to 30 percent of hospitalizations.[8] Bacterial infection is also a major cause of decompensation and hospitalization in persons with cirrhosis. These infections tend to progress to sepsis or severe sepsis, resulting in a four-fold increase in the probability of death relative to noncirrhotic hospitalized patients with infection.[9] Of cirrhosis patients who develop both infection and organ dysfunction, between 60 percent and 95 percent will die.[10]

In a 2014 report, a team of UK investigators observed circulating levels of a cyclooxygenase (COX)-derived lipid mediator called prostaglandin E2 (PGE_2) are highly elevated in patients with decompensated cirrhosis — more than seven times as high as in healthy volunteers.[11] PGE_2 has broad immunosuppressive effects that increase susceptibility to bacterial infection through several pathways, including blunting of antimicrobial helper T cell activity, interference with immune cell trafficking into tissue compartments and suppression of phagocytosis.[12,13] In both in vitro and in vivo models, they discovered plasma from decompensated cirrhosis patients suppressed pro-inflammatory cytokine secretion and bacterial killing in a PGE_2-dependent manner; these effects were not seen with plasma from patients with stable cirrhosis who had lower circulating PGE_2 levels.

Why is this important? Human albumin normally acts as a "sink" that avidly binds PGE_2 and catalyzes its inactivation. But endogenous serum albumin levels are low in acutely decompensated cirrhosis patients due to impaired albumin synthetic function. On top of this, albumin's PGE_2

** Assessed by measuring affinity of albumin fatty acid binding sites.*

binding capacity is markedly impaired in decompensated patients.[14,15]

As predicted, administration of commercial human albumin solution prepared from healthy donors to these patients reduced their plasma PGE_2 level and reversed the immunosuppressive properties of their plasma on repeat testing.

In this one seminal study, the UK investigators made three important discoveries:

1) Sharply elevated PGE_2 is the underlying cause of the immunosuppression that accounts for increased infection risk in patients with decompensated cirrhosis;

2) The elevated PGE_2 in these patients results from the characteristic combination of hypoalbuminemia and impaired albumin binding function; and

3) Infusion of exogenous commercial albumin solution reduces PGE_2 levels and reverses its immunosuppressive activity.

In a new 2018 report,[16] members of this same research team showed that, in patients with acute decompensation and acute-on-chronic liver failure, administration of 20 percent commercial human albumin to raise the serum albumin level to above 3 g/dL was again able to reverse plasma-mediated immunosuppression through binding and inactivation of PGE_2. They proposed that albumin, administered to target a serum albumin greater than 3 g/dL, be repurposed as "an immune-restorative drug" in hospitalized patients with decompensated cirrhosis. The immediate goal would be to augment treatment of infection and prevent nosocomial infection, with the potential to reduce mortality, ICU admissions, hospital stays and antibiotic use.

Long-Term Albumin Use for Cirrhosis with Ascites

Meanwhile, two other European research teams independently advanced clinical trials intended to learn whether human albumin therapy administered on a long-term basis could influence the grim prognosis for cirrhotic patients who develop ascites; about 15 percent of these individuals die within one year, and nearly 50 percent succumb within five years.[17]

Thirty-three Italian hospitals participating in the investigator-initiated ANSWER study randomized 440 patients with cirrhosis and uncomplicated ascites to receive either standard medical treatment (SMT) comprising anti-aldosteronic drugs and furosemide, or SMT plus 40 grams of human albumin twice weekly for two weeks, followed by 40 grams weekly for up to 18 months.[18]

By Kaplan-Meier estimates, overall 18-month survival was significantly higher in the SMT plus albumin group than in the SMT group (77 percent vs. 66 percent; p=0.028), translating into a 38 percent reduction in the mortality hazard ratio (0.62, 95 percent CI 0.40-0.95). Stated in real-world terms, treating just seven patients with albumin would be expected to prevent one death at 18-month follow-up.[19] With an incremental cost of less than $25,000 per quality-adjusted life year (QALY), long-term albumin treatment appeared to be cost-effective as well.

In their report published last June, the ANSWER study investigators concluded "long-term human albumin administration prolongs overall survival and might act as a disease-modifying treatment in patients with decompensated cirrhosis." This is the first prospective trial to document a clear survival benefit of routine long-term albumin infusions in patients with cirrhosis and ascites.

Just three months later in a separate single-center trial in Italy, investigators nonrandomly assigned 70 consecutively enrolled patients with cirrhosis and ascites refractory to standard of care (SOC) plus long-term albumin treatment (20 grams twice weekly), or SOC alone.[20] The expected two-year survival in this more severely ill population, whose ascites fail to resolve with low-sodium diet and diuretic drugs, is just 30 percent.[21] Patients received SOC when large-volume paracentesis was needed, and all patients were dosed with 6 grams to 8 grams of albumin per liter of ascites removed.

The cumulative incidence of 24-month mortality was significantly lower in the group treated with albumin and SMT than SOC alone (41.6 percent vs. 65.5 percent; p=0.032). Remarkably, compared to patients in the SOC group, patients with long-term albumin administration had far lower rates of emergent hospitalization for complications of cirrhosis, including hepatorenal syndrome, hepatic encephalopathy, tense ascites, SBP and non-SBP infections (Table 1). The study authors concluded that, in patients with

Table 1. Long-Term Albumin + SOC* in Cirrhosis/Refractory Ascites vs. SOC Alone: Probability of Emergent Hospitalization Due to Complications Over a 24-Month Follow-Up Period

Cirrhosis Complication	Albumin + SOC	SOC Alone	*P*
Hepatorenal syndrome	22.5%	57.7%	0.084
Hepatic encephalopathy	26.9%	64.5%	0.016
Tense ascites	37.1%	71.0%	0.002
Spontaneous bacterial peritonitis (SBP)	7.9%	50.6%	0.004
Non-SBP infection	27.2%	88.6%	0.001

**SOC = standard of care*

cirrhosis and refractory ascites, long-term treatment with human albumin "significantly improved survival and reduced inpatient hospitalization."

Now in Progress: Definitive Clinical Trials

While results of these two "pragmatic" clinical studies strongly suggest long-term administration of albumin to patients with decompensated cirrhosis can improve survival and reduce serious complications requiring hospitalization, these studies were not designed to provide a definitive answer. Most clinicians will require no less before they are willing to consider albumin as a therapeutic modality to be routinely administered, like a drug, on an extended or long-term basis.

Several Phase III clinical trials now in progress should conclusively answer whether in-hospital or long-term human albumin therapy can meaningfully improve the prognosis for patients with decompensated cirrhosis or acute-on-chronic liver failure (Table 2):

> "Patients with decompensated cirrhosis are highly prone to bacterial infection, which is either present or acquired during 25 percent to 30 percent of hospitalizations."

• The ATTIRE (Albumin To prevenT Infection in chronic liveR failurE) study is randomizing patients admitted to the hospital with decompensated cirrhosis and a serum albumin level of less than 35 grams/L to receive standard medical care or daily 20 percent human albumin infusions to raise and maintain levels above 30 grams/L. The composite primary endpoint at hospital discharge is 1) presence of new infection, 2) renal dysfunction and 3) mortality.[22]

• The PRECIOSA (Prevention of Mortality with Long-Term Administration of Human Albumin in Subjects with Decompensated Cirrhosis) study is testing whether long-term administration of 20 percent human albumin can reduce mortality in patients with ascites following discharge from the hospital.[23]

• The APACHE (Acute-on-Chronic Liver Failure Plasma Exchange) study is evaluating plasma exchange with 5 percent human albumin replacement to learn whether it can

Table 2. Phase III Clinical Trials Currently Evaluating Human Albumin Therapy for Decompensated Cirrhosis and Acute-on-Chronic Liver Failure

Study Name (Sponsor)	Study Population	Study Design	Primary/Secondary Endpoints	Projected Completion
ATTIRE (University College London)	Decompensated cirrhosis (Decompensation includes jaundice, ascites, hepatic encephalopathy, variceal bleeding, coagulopathy and/or hepatorenal syndrome)	Multicenter, open-label trial randomizing 866 hospitalized patients to receive daily 20% human albumin (up to 14 days) to target a serum albumin ≥35 g/L or usual standard of care treatment	Composite primary endpoint at hospital discharge: presence of new infection, renal dysfunction and mortality. Mortality at 28 days and 3 and 6 months post-discharge	December 2019
PRECIOSA (Grifols)	Subjects discharged after hospitalization for acute decompensation of liver cirrhosis with ascites (or with prior history of ascites requiring diuretic therapy)	Multicenter, parallel-group, open-label study randomizing 410 patients to receive standard medical treatment (SMT) or SMT + 20% human albumin at a dose of 1.5 g/kg body weight (maximum 100 g) every 10 ±2 days up to a maximum of 12 months	Time to liver transplantation or death through 1 year Total number of paracenteses through 1 year Incidence of refractory ascites through 1 year	October 2021
APACHE (Grifols)	Cirrhosis and acute-on-chronic liver failure	Multicenter, parallel-group, open-label study randomizing 380 hospitalized patients to receive SMT or SMT + 5% albumin plasma exchange for a minimum of 7 days, up to 17 days.	Time to death through day 90 Time to transplant or death through day 90 Time to death through day 28	December 2021

prolong short-term survival in patients with acute-on-chronic liver failure at very high risk of in-hospital mortality.[24]

Additionally, the Phase II HEAL (Hepatic Encephalopathy and Albumin) study is currently assessing whether up to five weekly infusions of 1.5 gram/kg of 25 percent human albumin can reduce cognitive impairment in patients with hepatic encephalopathy, a highly prevalent complication of cirrhosis that is both an independent risk factor for mortality and the leading cause of cirrhosis-related hospital readmissions.[25]

As with the other studies evaluating albumin for decompensated cirrhosis or liver failure, the therapeutic principle is entirely unrelated to albumin's oncotic function. Inflammation, endotoxemia, oxidative stress and endothelial dysfunction all play an important role in the pathogenesis of hepatic encephalopathy. The capacity of already depressed levels of circulating albumin to bind and remove the metabolites that cause these problems is impaired in advanced cirrhosis. Infusions of normal human albumin purified from plasma of healthy donors serve to restore critical antioxidant and other functions that endogenous albumin is unable to provide.

A New Starring Role for Human Albumin?

For three-quarters of a century, hospital pharmacies and blood banks have dispensed concentrated 25 percent human albumin solutions for very short-term use to essentially restore circulating volume or fluid balance between the intravascular and extravascular compartments. Twenty years after the surprising discovery that albumin can dramatically reduce renal impairment and death in patients with cirrhosis and SBP, two new clinical studies provide similar evidence of these benefits — and more — with administration of concentrated albumin in patients with cirrhosis and uncomplicated or refractory ascites.[18,20] Still other new findings suggest albumin-mediated immune-restorative and possibly other ligand binding-related functionalities may be at play.[16]

> "Several Phase III clinical trials now in progress should conclusively answer whether in-hospital or long-term human albumin therapy can meaningfully improve the prognosis for patients with decompensated cirrhosis or acute-on-chronic liver failure."

With at least three pivotal studies now in progress in critically ill cirrhosis patients, we will soon know whether medical science had simply overlooked some extraordinary pharmacologic talents of a plasma product it had long ago type-cast as a humble blood volume expander. A new second act for human albumin — arguably the single most versatile performer in the human proteome — may just be opening. ❖

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When Michael Singer was diagnosed with breast cancer at 50 years old, he was embarrassed. But, he soon learned his voice could make a difference for the 1 percent of men affected by this disease.

Male Breast Cancer: *A Patient's Perspective*

By Trudie Mitschang

IT IS ESTIMATED 2,550 men in the United States are diagnosed with breast cancer annually. Michael Singer never imagined he'd become, at age 50, one of the statistics.

BSTQ: What is your survival story?

Michael: This December, I will be a nine-year breast cancer survivor. I was diagnosed with ductal carcinoma in situ when I was 50 years old.

BSTQ: What were your symptoms?

Michael: I had a small lump like a pencil eraser under my left nipple. It wasn't rock hard, but it felt pliable. My nipple also felt sensitive. I had the lump under my nipple for several months. I was hoping it would just go away. I was at a checkup with my doctor, but I was too embarrassed to mention it. Later, the doctor's office called with concerns about my blood work. When I went back, I mentioned the lump, and my doctor was alarmed. He knew my family history and that I had lost my sister to metastatic breast cancer two years prior.

BSTQ: How were you diagnosed?

Michael: I was referred to a surgeon who tried a needle biopsy, followed by a surgical biopsy that led to the diagnosis of ductal carcinoma in situ. I had a mastectomy of my left breast several days later. I was diagnosed as stage 2B.

BSTQ: How did you handle the news emotionally?

Michael: I was embarrassed at first. I did not talk about my cancer. I thought I was a freak. I never heard of men getting breast cancer. I couldn't even say breast cancer; I told people I had chest cancer! After seeing a young man on the Katie Couric show with actor Richard Roundtree, I had an epiphany: Why am I embarrassed when these guys are on national TV talking about it? After that, I opened up. My friends and family were very supportive, and my wife encouraged me to get out there and share my story. My friends lovingly called me "Uni Nip." We laughed, and I accepted it totally and got into patient advocacy.

BSTQ: Tell us about your advocacy work.

Michael: I became a member of the Male Breast Cancer Coalition, a not-for-profit group that promotes education and awareness of male breast cancer. I first spoke at a community meeting about my cancer, and I met my locally elected State Assemblyman Michael Benedetto. He worked with me and sponsored a New York State Proclamation signed by Governor Cuomo that declared the third week of October as Male Breast Cancer Awareness Week in New York. I have been presented the proclamation at several events over the past few years. Since then, many states have yet to come on board, but we have been working with patients in all 50 states to make this a reality.

BSTQ: Tell us about your work with research organizations.

Michael: I have had the opportunity twice to serve as a consumer reviewer to evaluate research applications submitted to the Breast Cancer Research Program sponsored by the Department of Defense. I found this experience extremely rewarding, and it made me feel like I could make a difference. It was rewarding and emotional to interact with scientists and patient advocates dedicated to improving life for those of us living with this disease.

I also discovered the National Breast Cancer Coalition's advocacy training known as Project Lead Initiative. This educational program teaches advocates about public policy and the role they can play in breast cancer research. The training also covers the basics of molecular biology, genetics, clinical trials and epidemiology, which is the study of diseases in populations. This training empowered me to educate the public about male breast cancer.

BSTQ: What advice would you give to other men with this diagnosis?

Michael: Your voice is important. As an advocate for men with breast cancer, you represent a very small population in the breast cancer community. You are the voice of the 1 percent of breast cancer patients who are men. Be the voice of men who are no longer with us and the voice of men who are embarrassed to speak up. ❖

Dr. Oliver Bogler, a cancer scientist who was diagnosed with male breast cancer, is advocating for more research to better understand the disease in men and how to treat it.

Male Breast Cancer: *A Scientist's Perspective*

A CANCER scientist, Oliver Bogler, PhD, never expected to become a target of the disease himself. As fate would have it, Dr. Bogler was diagnosed with stage 3 breast cancer at 46 years old, and he embarked on a journey as a cancer patient and clinical trial participant. Today, Dr. Bogler is in remission and taking the drug tamoxifen to try to prevent recurrence. He blogs about the topic at Entering a World of Pink, a male breast cancer blog (malebreastcancerblog.org).

BSTQ: How has becoming a survivor impacted your perspective on the disease?

Dr. Bogler: This experience has given me multiple perspectives as I strive every day to make a difference in the battle against cancer. I am now advocating for more research on male breast cancer, serving as a reviewer on grants for breast cancer from the patient perspective, and I have also served as a volunteer to support men newly facing this diagnosis.

BSTQ: What's the prognosis for men with breast cancer?

Dr. Bogler: In the absence of any large cohort analyses of men, we rely heavily on data from women to help us understand what the future holds for each of us on this journey. However, some papers do look at this question with retrospective studies, which can be very informative, even if based on relatively small numbers. For example, a 2014 analysis of metastatic male breast cancer supported the use of current guidelines for female breast cancer in the treatment of men and suggested similar outcomes can be achieved. The key to understanding the prognosis for female breast cancer (all cancer, really) is classification into subtypes based on clinically meaningful characteristics. For instance, a 2015 study showed that molecular subtype is key for understanding outcomes for men with breast cancer, just like women.

BSTQ: Are molecular studies on male breast cancer different from female breast cancers?

Dr. Bogler: We are seeing an increase in studies that look at the molecular characteristics of male breast cancer. Having an inventory of the mutations and alterations in any cancer is important in this dawning age of "precision medicine," in which the goal is to make therapy choices based on such information. This molecular data will also be useful in determining what differences exist between the male and female versions of the disease.

BSTQ: What are the suspected causes of male breast cancer?

Dr. Bogler: Most sporadic cancer is probably caused by a combination of factors coming together: mutations in key genes, environmental factors driving the cancer forward and perhaps a more favorable genetic milieu in some of us. Few papers address the causes, but in some instances, things can be ruled out. A study in 2017 showed the precursor lesion for most male breast cancer is ductal carcinoma in situ, just as it is in women. A 2015 paper looked at whether external hormones could contribute to breast cancer risk, using data from transgender veterans, but no effect was seen in relatively brief exposures to hormones used in gender reassignment therapy. Interestingly, a study that measured endogenous levels of estrogens in male breast cancer patients showed elevated E2, the most common and potent form, was associated with increased risk. The difference between these studies may be the duration of the elevated hormone experience or may indicate there's more to the elevation of the endogenous hormones than just E2.

BSTQ: Are there factors that seem influenced by ethnic or racial groups?

Dr. Bogler: In some cancers, there are notable variations across different ethnic/racial groups or environments. Studies are now comparing male breast cancers from different parts of the world. For example, studies in Chinese men have shown that, overall, the picture is the same. However, closer to home, a recent analysis showed African American men with male breast cancer fare worse in the U.S. than their white counterparts, even when accounting for socioeconomics and insurance.

BSTQ: Are there any promising findings related to hormone therapy for men?

Dr. Bogler: Occasionally, there are papers not specific to male breast cancer that are still interesting, particularly in relation to hormone therapy. One recent example was a paper showing tamoxifen and melatonin may work together, suggesting it's better to take tamoxifen before going to bed. Of course, more important for how much benefit there is from tamoxifen may be how well it is metabolized. A meta-analysis of tamoxifen side effects showed, overall, it is well-tolerated by men, and the rate of noncompliance is low. Additional research raised concern that hormone deprivation therapy, perhaps the most effective treatment for male breast cancer, can lead to mutations in the estrogen receptor, and so circumvention of the hormone therapy. ❖

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

Risk Management in Clinical Trials: The New ICH E6 Focus

Author: Susan Leister, PhD

In *Risk Management in Clinical Trials*, Dr. Leister explains the significance of the new focus on risk management and the benefits it can reap, including directing the sponsor's limited resources to higher risk areas for better overall quality; focusing more on prevention than on the traditional monitoring approach (process improvement vs. quality control); reducing potential regulatory inspection findings; helping manage noncompliant sites/vendors/contractors; and allowing more coverage of critical areas in the same amount of time. She offers recommendations for implementing new requirements, including a quality management system that covers all stages of the trial process; identifying critical processes and key data; adopting principles of risk management (identification, evaluation, control, communication and review); meeting centralized monitoring requirements; validating electronic data processing systems; and addressing noncompliance that has the potential to significantly affect human subject protection or reliability of trial results.

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AMA CPT 2019 Professional Edition

Author: American Medical Association

This resource is designed to help healthcare professionals establish the procedural coding advantage. It covers hundreds of 2019 current procedural terminology (CPT) codes, official coding rules and clear anatomical and procedural illustrations. Updated for 2019 are CPT changes, CPT assistant and clinical examples in radiology citations, an illustrated anatomical and procedural review, coding tips throughout each section, evaluation and management reference tables, a comprehensive index, anatomical and procedural illustrations for key codes, an appendix of multianalyte assays with algorithmic analyses, an enhanced table of contents, section-specific tables of contents, a summary of additions, deletions and revisions, and multiple appendices.

www.codingbooks.com/2019-cpt-pro

Generic Drug Development: A Guide to FDA Regulation

Author: U.S. Food and Drug Administration

This guide contains all of FDA's generics-related guidances, plus internal agency policies on reviewing applications, instructions for challenging patents and lists of branded drugs with expired patents and no generic competition. Also included is information on user fees, pre-submission meetings, controlled correspondence, bio-equivalence, ANDA content and format, Paragraph IV patent certification and FDA review and approval.

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2018 Healthcare Benchmarks: Telehealth and Remote Patient Monitoring

Author: U.S. Food and Drug Administration

This 60-page report delivers the latest actionable telehealth and remote patient monitoring metrics on tools, applications, challenges, successes and return on investment (ROI) from healthcare organizations across the care spectrum. Now in its fifth edition, it documents benchmarks on current and planned telehealth and remote patient monitoring initiatives, as well as the use of emerging technologies in the healthcare space. Also included is a look at the following metrics: current and planned telehealth and remote patient monitoring programs; populations and clinical conditions targeted by telehealth initiatives; most frequently employed clinical applications, devices and technologies; the latest in funding and ROI for telehealth and telemedicine; telehealth technologies available to employees, patients and health plan members; patient monitoring devices connected to telehealth initiatives, including scales, wearables and medication compliance monitors; projected 2018 Medicare billing trends; telehealth impact on quality and utilization metrics, including healthcare access, medication adherence, patient satisfaction, hospital readmissions, hospital length of stay and more; the most successful applications of telehealth; sector-specific analysis of telehealth and remote patient monitoring trends; challenges, benefits and barriers related to the use of telehealth and monitoring; and the complete 2018 Telehealth & Remote Patient Monitoring survey tool.

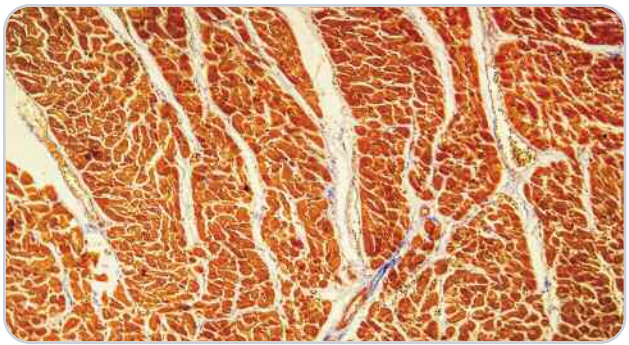
hin.3dcartstores.com/2018-Healthcare-Benchmarks-Telehealth-Remote-Patient-Monitoring_p_5287.html

IVIG Therapy Reduces In-Hospital Mortality and Ventricular Function Loss in Patients with Acute Myocarditis: Meta-Analysis

Noting the efficacy of intravenous immune globulin (IVIG) in the treatment of acute myocarditis remains controversial, Chinese investigators at the Huazhong University of Science and Technology conducted a meta-analysis of published clinical trials that evaluated IVIG therapy in adults and children with acute myocarditis. Searched databases included PubMed, Scopus, Embase, Medline, the Cochrane Library, Google Scholar and the ClinicalTrials.gov website. Pooled odds ratios (ORs) and 95 percent confidence intervals (CIs) were used to estimate the outcomes.

Thirteen studies with 1,534 cases were incorporated into this meta-analysis. Pooled results showed IVIG therapy significantly reduced in-hospital mortality (OR: 0.44, 95% CI 0.17 to 0.71, P < 0.001) and improved left ventricular ejection fraction (OR: 1.73, 95% CI 1.34 to 2.13, P < 0.001) in acute myocarditis patients. Further, patients with acute fulminant myocarditis (AFM) exhibited a significantly higher survival rate (OR: 2.80, 95% CI 1.16 to 6.77, P = 0.022) in the IVIG group.

The investigators concluded "IVIG therapy can not only result in lower in-hospital mortality and superior recovery of left



ventricular function in patients with acute myocarditis, but [can] also increase the survival rate of AFM patients. The present study provides some supportive evidence for IVIG therapy in acute myocarditis patients."

Huang X, Sun Y, Su G, et al. Intravenous immunoglobulin therapy for acute myocarditis in children and adults. Int Heart J *2019 Feb [Epub ahead of print].*

Subcutaneous Lanadelumab Treatment Reduces Attack Rate in Patients with Hereditary Angioedema

Subcutaneous administration of lanadelumab, an investigational monoclonal antibody intended for the prevention of attacks in patients with type I or II hereditary angioedema (HAE), significantly reduced the mean number of attacks compared to placebo treatment.

Patients enrolled at 41 sites in Canada, Europe, the U.S. and Jordan were randomly assigned to 26-week treatment with subcutaneous lanadelumab at dosages of 150 mg every four weeks (n=28), 300 mg every four weeks (n=29), 300 mg every two weeks (n=27) or placebo (n=41). All patients received injections every two weeks, with those in the every-four-week groups receiving placebo between active treatments.

During the treatment period, the mean number of attacks per month for the placebo group was 1.97; for the lanadelumab group, the mean numbers of attacks per month were 0.48 (every-four-week 150 mg group), 0.53 (every-four-week 300 mg group) and 0.26 (every-two-week 300 mg group). Patients receiving 300 mg of lanadelumab every two weeks experienced 83 percent fewer moderate to severe HAE attacks than placebo group patients, and 87 percent fewer attacks that required on-demand treatment. A post hoc sensitivity analysis showed 77 percent (20/26) of patients receiving 300 mg of lanadelumab every two weeks were attack-free during steady-state (day 70-182) versus 3 percent (1/37) of patients on placebo treatment.

The most commonly occurring adverse events with greater frequency in the lanadelumab treatment groups were injection site reactions (34.1 percent placebo, 52.4 percent lanadelumab) and dizziness (0 percent placebo, 6.0 percent lanadelumab). "These findings support the use of lanadelumab as a prophylactic therapy for hereditary angioedema," the authors concluded.

Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA *2018 Nov 27;320(20):2108-21.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2019, through June 30, 2019

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	$72.85	$71.68
	GAMMAGARD SD	Takeda	J1566	$119.62	$117.70
	GAMMAPLEX	BPL	J1557	$88.40	$86.98
	OCTAGAM	Octapharma	J1568	$64.94	$63.90
	PRIVIGEN	CSL Behring	J1459	$81.44	$80.13
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$84.31	$82.96
	GAMMAKED	Kedrion	J1561	$77.50	$76.25
	GAMUNEX-C	Grifols	J1561	$77.50	$76.25
SCIG	CUVITRU	Takeda	J1555	$131.69	$129.58
	HIZENTRA	CSL Behring	J1559	$101.94	$100.31
	HYQVIA	Takeda	J1575	$141.09	$138.83

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

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Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	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
	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 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	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g
	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 g

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

2018–2019 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	5 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	5 years and older	90688
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST (LAIV4)	MEDIMMUNE	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

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