

PHARMACY PRACTICE IN FOCUS: HEALTH SYSTEMS™

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Publisher's Note

Pharmacist-Led Research Highlights Key Insights and Innovations in Patient Care

With the increasing complexity of treatments and patient care seen across health systems, pharmacists continue to play a pivotal role in enhancing therapeutic outcomes and ensuring patient safety. This issue of *Pharmacy Practice in Focus: Health Systems™* delves into several significant areas of focus within pharmacy, including critical emergency interventions, management of common conditions such as xerostomia (dry mouth), the importance of medication education, and advancements in anticoagulation therapy.

In the peer-reviewed original research paper on page 11, authors Megan Haas, PharmD; Amanda Lowney, PharmD, BCPS, BCCCP, BCEMP; and Jamie Warren, PharmD, BCPS, BCCCP, CPP, present their retrospective, multicenter study evaluating the impact of early epinephrine administration on sustained return of spontaneous circulation (ROSC) and survival to hospital discharge in patients with initial nonshockable in-hospital cardiac arrest. Among 100 patients, 66% received epinephrine within 2 minutes, but there was no significant difference in sustained ROSC (40% vs 43%) or survival to discharge (11% vs 6%) compared with those who received it at 2 minutes or later.

In the peer-reviewed literature review on page 16, authors Carmen Cheung, PharmD, HBS, RPh; Ellen Guritzky, MSJ, RDH, AHFI, CHC, FADHA; and Ashley Andrew, PharmD, explore dry mouth and its etiologies, symptoms, and management strategies, emphasizing the role of pharmacists in patient education and care. The authors highlight the importance of lifestyle modifications, oral hygiene, and the use of salivary stimulants and substitutes while underscoring the need for increased pharmacist awareness and engagement in addressing this condition.

In the peer-reviewed original research paper on page 24, authors Vy P. Pham, PharmD, BCPS; Marisol Ramirez, CPhT; Amit Patel, MD; and Lan N. Bui, PharmD, MPH, BCPS, present their pharmacy-led clinical initiative in a community hospital emergency department (ED)—implemented enhanced medication education at the point of admission using a teach-back method to improve medication adherence and reduce hospital readmissions. Although the study found numerical reductions in all-cause 30-day ED revisits and hospital readmissions, the results were not statistically significant, highlighting the need for larger studies to determine the true impact of such interventions.

In the peer-reviewed literature review on page 31, authors Michelle Krey, PharmD candidate; Sophia Villa, PharmD candidate; and Jonathan Arnon, PharmD, examine the evolution of anticoagulation therapy, highlighting the emergence of factor XI inhibitors as a promising alternative to direct oral anticoagulants due to their potential to reduce bleeding risks while maintaining efficacy. The authors explore factor XI inhibitors' mechanism of action, ongoing clinical trials, and future implications for using these therapies in the prevention and treatment of thrombosis.

The research and insights presented in this issue underscore pharmacists' vital contributions to advancing patient care through innovative practices, enhanced education, and emerging therapies, as well as highlighting the need for ongoing pharmacist-led research to better realize pharmacists' impact on health outcomes.

Warm regards,
Mike Hennessy Jr
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The Prescription Drug User Fee Act: Good, Bad, or a Lot of Both?

Curtis E. Haas, PharmD, FCCP

ABOUT THE EDITOR

Curtis E. Haas, PharmD, FCCP, is chief pharmacy officer for the University of Rochester Medical Center in New York.

In this issue, Julie B. Sibbesen, PharmD; and Jeanette Rich, PharmD, provide a concise review of the new drug and biological review and approval process, focusing on the role of the Prescription Drug User Fee Act (PDUFA) and the impact it has had on shortening review times and increasing numbers of applications reviewed since the original version was enacted in 1992. However, their concise review does not focus on the mixed history of PDUFA and the controversies surrounding the program.

The original PDUFA legislation was a result of many legitimate concerns related to unfortunate delays in the approval of potentially life-altering therapies in the early days of the HIV/AIDS epidemic and the need to modernize and update the drug review and approval process. In simple terms, implementing user fees paid by the industry in exchange for predictable review and decision timelines provided a revenue stream to fund the necessary resources to expedite the review process. The original legislation required renegotiation of the agreement every 5 years, with the most recent version (PDUFA VII) being enacted in 2022. This year, negotiations are slated to begin for PDUFA VIII and must be finalized for approval by 2027.

There is no doubt that the enactment of PDUFA has had many positive effects over the past 33 years. The time from finalizing the application to approval for new drugs has been reduced by more than half, bringing potentially lifesaving or life-altering therapies to market more quickly. It has also led to a steady increase in new applications and new approvals, with a several-fold increase in the rate of new drugs coming to market compared

with pre-PDUFA approval rates. PDUFA negotiations have also created an accelerated review process for drugs considered eligible for priority review because of their breakthrough status.¹

PDUFA fees have become an increasingly important part of the FDA budget and now represent more than 65% of the Human Drugs Program budget, the largest subunit of the FDA. This has raised many concerns about conflicts of interest and comments that the FDA has essentially become a client of the pharmaceutical industry. Notably, the pharmaceutical industry also has a significant say in the negotiations concerning what is included in each version of the PDUFA legislation, raising criticisms that the industry has undue sway and influence over the agency responsible for regulating it. Some of the criticisms of PDUFA fees and how the FDA can use these fees include the following^{2,3}:

- The focus is heavily on reviewing premarketing data to facilitate drug approval, and a very small proportion of funds can be allocated to postmarketing safety surveillance. That is, the industry has negotiated limitations on the FDA's ability to monitor the safety of drugs following entry into clinical use.
- Over time, PDUFA legislation has broadened the scope of influence over FDA policy, including changes to evidentiary standards for drug approval, shortened review and approval times, industry involvement in FDA decision-making, rule changes concerning industry information dissemination to providers, and effects on market entry of generic drugs.

- PDUFA puts the FDA on the clock to meet deadlines for drug approval decisions, which has raised concerns about rushed decisions on controversial drugs with potential safety concerns.
- Recent PDUFA negotiations have increased the role of patient-centric or advocacy influence on drug approval decisions, which some scientists fear is a retreat from rigorous evidentiary standards related to safety and effectiveness and introduces more nonscientific opinions into the process.
- There are concerns that PDUFA's evolving changes with successive versions have made the FDA "too cozy" with the pharmaceutical industry.
- The 5-year cycle of renegotiation and enactment of legislation often creates a time crunch that limits adequate scrutiny and debate of what has been agreed upon by the FDA and the industry, giving the impression that the outcomes are generally favorable to the pharmaceutical industry.

The reality is that PDUFA is likely here to stay, given the high degree of dependency that the entire FDA budget has on this fee structure. Although this *pay-to-play* approach raises many ethical questions among its critics, the general consensus is that the good has outweighed the bad over the past 30-plus years and that the US has gone from lagging behind other areas of the world to being a leader in advancing cutting-edge therapeutics for rare and complex diseases.

Of course, with a new administration being responsible for negotiating PDUFA VIII and a secretary of the US Department of Health and Human Services being an outspoken critic of the FDA, it may be difficult to predict the future. If the FDA is affected by staff cuts and potential shifts in priorities based on the current administration's policy perspective, it may be

very challenging for the agency to meet its obligations under PDUFA, and the quality of the review process may suffer. Ronald Piervincenzi, PhD, CEO of US Pharmacopeia, recently summarized in a social media post the potential risks of drastic reductions in staffing or funding at the FDA, including⁴:

- delayed drug approvals,
- a decrease in overseas inspections potentially affecting the safety of the supply chain,
- lessened ability to respond during times of public health crises,
- compromised ability to regulate and ensure the quality of compounded drug products,
- decreased ability to mitigate drug shortages, and
- reduced competitiveness of the US pharmaceutical industry.

Over the past 33 years, PDUFA has played a large role in changing the drug and biologic review and approval process, with some good and some bad aspects, depending on your perspective. Keeping an eye on how PDUFA VIII negotiations affect changes in this process will be important. Perhaps more importantly, understanding global changes at the FDA—including whether PDUFA survives at all—warrants our close attention. 📌

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MDMA Rejected: The Story of a Study Participant Entrenched in Ethical Violations and a Data Breach

The health care community was left largely unaware of the controversy that occurred at one of the clinical trial sites.

Luke Halpern, Assistant Editor; and Alana Hippensteele, Lead Editor

On August 9, 2024, the FDA issued a complete response letter (CRL) for Lykos Therapeutics' midomafetamine (MDMA) capsules for the treatment of posttraumatic stress disorder (PTSD), dealing a major setback to MDMA's pathway to regulatory approval and to the general movement toward a broader acknowledgment among the health care community of the clinical benefits of psychedelic medicines.^{1,2}

In the full CRL to Lykos (which has still not been released to the public), the FDA noted that it could not approve MDMA for PTSD based on the data submitted to date, requesting that Lykos conduct another phase 3 trial to "further study the safety and efficacy" of the drug. The CRL followed the recommended rejection of MDMA on June 4, 2024, by an independent FDA advisory panel that cited questions about the reliability of the submitted clinical trial data.^{2,3}

Yet, the primary and secondary outcomes from 2 pivotal clinical trials backing MDMA's approval were successfully met. In the randomized, double-blind, placebo-controlled phase 3 MAPP1 trial (NCT03537014) and the confirmatory phase 3 MAPP2 trial (NCT04077437), treatment with MDMA led to a significant reduction in the Clinician-Administered PTSD Scale for *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) score, which measures PTSD symptom severity, in addition to a large increase in total Sheehan Disability Scale score compared with placebo.⁴ There were no serious adverse events in the MDMA arms of either trial.¹

Based on these data, many psychedelic proponents decried the rejection by the FDA, citing the significant unmet need for an effective therapy in this patient population.

"The delay in FDA approval of MDMA-assisted therapy has been heartbreaking, not just for MAPS [Multidisciplinary Association for Psychedelic Studies] but for the thousands of people still suffering from PTSD who have reached out to us, desperate for effective treatment," Betty Aldworth, director of communications and education for MAPS, an organization that has historical associations with Lykos, said in a prepared statement over email to *Pharmacy Practice in Focus: Health Systems*. "Despite support from 80 members of Congress, veterans groups, and

trauma experts, the FDA continues to delay. Many people are using psychedelics in unregulated settings because they see them as their last chance to heal."

This rejection leaves the health care community with a critical question: How could the FDA reject a drug with such strong efficacy and safety data from clinical trials and with such significant therapeutic potential? According to Michael Mithoefer, MD, former senior medical director at MAPS and clinical investigator for MDMA/PTSD studies, the phase 3 trial data show that approximately two-thirds of study participants lost the diagnosis of PTSD because of treatment with MDMA.

"If these treatments can get approved, it would be a huge leap forward," Mithoefer said in the email statement.⁵

Notably, clinical research in medicine often is not designed to investigate the social benefits of a drug, yet MDMA is particularly beneficial in supporting interpersonal and internal well-being and health. For example, clinical investigations by MAPS Israel have investigated the benefits of MDMA in healing collective trauma among 400 Israeli survivors after the terrorist attack on October 7, 2023.⁵ According to Keren Tzarfaty, cofounder and executive director of MAPS Israel, trauma can take over on a personal and social level if left unaddressed.⁵

Kevin Lanzo, PharmD, a clinical psychopharmacologist, cofounder of the Psychedelic Pharmacists Association, and psychedelic researcher familiar with the Lykos story, explained, "From a pharmacological standpoint, MDMA facilitates the development of relationships, either with others or with yourself. If you have a damaged relationship with yourself, which can be the case in mental health disorders, MDMA can help repair that, such as in the case of PTSD."

This article will dive deeper into the FDA's rejection of MDMA to understand what went wrong in this landmark effort toward an FDA approval of a psychedelic medicine, which is the first to have reached this critical juncture. At the center of the controversy that ensued following the FDA CRL, we find a clinical trial participant with significant need for treatment, as well as a complex and potentially destructive relationship between her and 2 health care

professionals at one of the clinical trial sites, leading to unauthorized access to trial data and accusations of sexual misconduct.

The Trial Participant

The podcast *Cover Story: Power Trip*, hosted by Lily Kay Ross and David Nickels, conducted a thorough investigation into the potential MDMA approval several years before the rejection occurred, with a noted interest in the experiences of participants in the trial. The podcast, a collaboration between *New York* magazine and Psymposia, an independent nonprofit media group, focused on the experiences of one participant in particular: Meaghan Buisson. In the podcast series, Buisson shared details of her negative experiences in the trial and her challenging relationship with the 2 health care professionals leading the trial site where she was a participant.^{6,7}

According to Lanzo, Psymposia as an organization may have played a role in the FDA advisory committee meeting's decision to recommend rejecting MDMA. At an open public hearing session during the meeting, 5 individuals from Psymposia—without identifying themselves as being associated with the organization—spoke out against MDMA's approval, Lanzo explained. During the open session, Psymposia made claims similar to those made in the podcast series, with one individual reading a statement on behalf of Buisson. However, Lanzo noted that it is very unlikely that any of the FDA advisory committee reviewers had, in fact, listened to the *Power Trip* podcast series that discussed Buisson's case in further detail, as well as other aspects of the MDMA clinical trials. Notably, Lanzo explained that a majority of Psymposia and *New York's* gathered reporting regarding Buisson appears to be supported by evidence.

In the podcast, Buisson said she was 19 years old when she started speed racing, which she explained can be a brutal, competitive sport. Buisson, who had a difficult childhood and experienced multiple sexual assaults during that time, pushed her body to the limit in this sport, which resulted in multiple serious injuries, including frequent traumatic brain injuries and broken bones. As her mental health deteriorated following these injuries, she began to seek out psychological treatment through various avenues, including trying several psychiatric drugs and seeking counseling from a therapist. However, this did not alleviate her symptoms.⁷

In 2014, she connected with an MDMA phase 2 clinical trial site in Vancouver, British Columbia, Canada, becoming 1 of 6 enrollees at the trial site. Her therapists were Richard Yensen, PhD, and Donna Dryer, a married couple who were medically licensed—Dryer was a psychiatrist and went to medical school and Yensen was

a psychotherapist—and part of the MAPS community. Given the nature of the psychedelics clinical trial space at this time, MAPS did not have many options available for trial investigators, according to Lanzo. However, Dryer and Yensen were qualified and, to Buisson, seemed responsible; she described Yensen as a “larger, softer, fuzzier character,” according to the podcast.⁷

Tapes Reveal Misconduct

According to podcast hosts Ross and Nickels, MDMA trial sessions typically last for 8 hours. In Buisson's case, those long sessions occurred in a cramped basement, with a twin bed in the middle of the room. Cameras used for clinical trial oversight purposes were placed in the room to document the sessions. Buisson's memory of her experience while on MDMA in that room was hazy, so she requested MAPS release her tapes to her. Once reviewed, she came to understand what had happened to her while she was under the influence in that basement.^{6,7}

While undergoing her MDMA session, Buisson recounts reliving a vivid sexual assault from her youth. While this was occurring, Yensen bear-hugged her and put his weight on her body to help her “break through,” despite Buisson's ongoing and audible protestations for him to stop. Throughout the session, both Yensen and Dryer remained closely physical with her. According to Ross and Nickels, who watched and recounted more than 75 hours of video recordings from her sessions, throughout these sessions, Yensen “is in almost constant physical contact with Meaghan,” ranging from light hand touches or brushes of the hair to lying in the bed with Buisson and Dryer. The most extreme version of this contact was when Yensen pinned Buisson's body down as she relived her past sexual assault.⁸

Ross and Nickels noted that at multiple points, Buisson cried out for Yensen to “get off me.” At one point during the recording, following a period of Yensen cuddling and nuzzling Buisson's body, Yensen can be heard kissing Buisson on the forehead after Dryer had left the room.⁸

Investigators Turned Manipulators

The videotapes that MAPS released document only part of the unfurling complex relationship between Buisson and her therapists, particularly with Yensen. The *Power Trip* hosts explain that, following the end of the phase 2 trial sessions, Buisson—who was not financially stable at the time and wanted to continue receiving MDMA treatment—decided, in collaboration with Yensen and Dryer, to move to the small remote island where they operated their clinic in order to continue the therapeutic relationship. Over a period following the trial sessions, the lines continued to blur.⁷

Lanzo explained that Buisson’s relationship with Dryer and Yensen developed to a point where she became an administrative assistant for them at their home on Cortes Island in Vancouver, helping answer emails from MAPS for her therapists and, at one point, even providing her own medical information when she was requested to do so by clinical trial investigators external to the site. Buisson was also provided access to the trial data by Yensen and Dryer as a part of her administrative assistant role, which allowed her to view clinical trial information about the other trial participants at the site.^{3,8} Notably, this breach of clinical trial site data goes against established research standards for responsibly conducted clinical trials, according to Lanzo.

Ultimately, after months of subtle manipulation, Buisson’s “dependency” on Yensen built to a point where “it became extremely normalized to curl up for hours on the sofa and cuddle together,” according to Buisson on the podcast. She explained that, over the course of a winter, Yensen progressed from touching to kissing to intercourse. Then in May 2016, when Buisson rejected further attempts, citing her discomfort with the relationship, Yensen told her over email that her experiences were not “related to reality.”⁷

In 2018, MAPS received an ethics complaint from Buisson regarding the sexual relationship that had occurred after the treatment sessions had concluded. After an investigation, both Yensen and Dryer confirmed to MAPS that Yensen was engaged in a sexual relationship with Buisson—a violation of Section 6 of the MAPS Code of Ethics for Psychedelic Psychotherapy. The investigators were barred from all MAPS-related activities and from becoming providers of MAPS-affiliated MDMA therapy in the future.⁹

In 2021, when the *Power Trip* hosts showed MAPS staff the videotapes of Buisson’s trial sessions, a compliance review of the available documentation of the trial—including all available videos—was initiated. After review, MAPS determined that Yensen and Dryer “substantially deviated from the MDMA-assisted therapy treatment manual on several occasions during the treatment period” and notified the FDA.¹⁰

An insider involved with MAPS and the clinical trial, who wished to remain anonymous for this story, provided additional context surrounding the videotapes in the trial. The insider noted that protocols for phase 2 trials considered session videos available for “process improvement” of the

psychotherapy, not proper trial data. Therefore, when Buisson filed her complaint to MAPS, the tapes weren’t looked at because MAPS did not consider them to be study data, as the allegations were not made about the sessions themselves.

“The big mistake MAPS made was, in making their public statement, they incorrectly claimed the tapes were a safety measure,” the insider said. “When Psymposia got the tapes, they were able to revive a phase 2 story, making it seem relevant to the present while flaying MAPS for ignoring the tapes.”

Journal Retraction Seals Lykos’ Fate

On August 10, 2024, a day after the FDA’s CRL being issued to Lykos, medical journal *Psychopharmacology* retracted 3 papers that studied MDMA-assisted therapy, including a meta-analysis of the pooled phase 2 trials that featured Buisson’s data. Combined with the FDA’s rejection, these journal retractions represent a major setback for Lykos, MAPS, and the overall path to MDMA’s approval.¹⁰

According to Lanzo, Buisson’s anonymous data—which she had access to once she became an administrative assistant, in addition to other participants’ data—were originally included in the submitted phase 2 paper. Notably, Lykos was not informed that Buisson was working as an administrative assistant at the trial site when they originally submitted their phase 2 paper to the journal, as Buisson was employed by Yensen and Dryer directly without any association with MAPS in her employment. However, although Lykos submitted a correction to the journal to remove her data from the original phase 2 data once they had uncovered the situation with Buisson, her data were still included in the pooled analysis, with the anonymous insider offering that Lykos was either too late or had apparently forgotten to redact those data as well.

Before the open public hearing session during the FDA advisory committee meeting, the journal allegedly asked Lykos to change the pooled analysis data. However, following the overwhelmingly negative response from the meeting, *Psychopharmacology* didn’t give Lykos the opportunity to make changes; instead, the journal quickly redacted the paper.

“The editors have retracted this article after they were informed of protocol violations amounting to unethical conduct at the MP4 study site by

researchers associated with this project,” the study authors wrote in their retraction note, referring to the conduct at Yensen and Dryer’s site on Cortes Island. “The authors have subsequently confirmed that they were aware of these violations at the time of submission of this article but did not disclose this information to the journal or remove data generated by this site from their analysis.”¹¹

The MAPS insider interviewed for this story explained how the main problem lies with MAPS’ lack of immediate response to the abuse allegations. “When they reacted, they didn’t react strong enough,” they said. “The fear is that the leadership of MAPS may not have taken the story seriously.”

This controversy has laid bare one of the many challenges of conducting clinical trials investigating psychedelic medicines: Patients in such trials are under the influence of psychoactive substances, making them vulnerable in ways that are somewhat unique to the modern clinical trial landscape. For such trials, patients require ethical and sound oversight by trial investigators, who must ensure they are safe from potential harm, not only from the patients’ own actions but also potentially from the actions of other trial investigators.

“This case [involving Buisson] emphasizes the unique challenge of researching drugs that facilitate the development of relationships,” Lanzo said. “If proper safeguards are not put in place, then cases of adverse events may be more social than physical.”

Additionally, Buisson’s case isn’t the first instance where a patient undergoing psychedelic-assisted therapy experienced sexual abuse from their therapist, either during or after treatment.¹² Clearly, the health care landscape may need to review its approach to licensure for those who provide this type of therapy to patients.

Following this landmark effort to approve MDMA, the future of Lykos, MAPS, and psychoactive medicine in clinical research remains murky. In the next article in the series, we dive further into the aftermath of the trial for MAPS and Lykos, as well as the planned future for MDMA. 🌐

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Onye Ononogbu, PharmD, MPH, BCOP, Discusses Her Journey to Advance Health Equity and Patient Care Through Research

Ononogbu discusses research, health equity, and sickle cell advancements.

Pharmacy Times interviewed Onye Ononogbu, PharmD, MPH, BCOP, on her journey into research as a pharmacist. Ononogbu is a research assistant professor in the Department of Pharmacy Practice and Translational Research and a faculty member at the Population Health Outcomes and Pharmacoepidemiology Education and Research (P-HOPER) Center at the University of Houston College of Pharmacy in Texas. She is also a hematology/oncology clinical pharmacy specialist at the UT Physicians Adult Comprehensive Sickle Cell Center. Additionally, she is a co-founder and board member of Pharmacy Initiative Leaders, Inc (PILs), an organization dedicated to coaching and equipping fourth-year pharmacy students with the tools needed to secure postdoctoral residencies, fellowships, and job opportunities, with a focus on promoting equity in the workforce.

Pharmacy Times: What brought you to research as a pharmacist, and how has research shaped your work in the field?

Onye Ononogbu, PharmD, MPH, BCOP: Since my undergraduate years, my journey into research as a pharmacist has been driven by my passion for serving the underserved and addressing health disparities within that community. My role as a hematology/oncology clinical pharmacy specialist and my focus on public health and epidemiology have allowed me to merge clinical practice with innovative research. Research has shaped my work as a seasoned clinician and an early research investigator by enabling me to address critical gaps in care, develop evidence-based tools, and advocate for equitable health care solutions through publications, presentations, and grant-funded projects.

Pharmacy Times: What is your role within the research team, and how often are you involved in pharmacist-led research?

Ononogbu: Traditionally, I play various roles. I serve as a principal investigator, co-investigator, collaborator, and research mentor to PharmD and PhD students. My responsibilities include designing studies, analyzing clinical outcomes, writing manuscripts, mentoring, and translating findings into actionable health care practices. My engagement in pharmacist-led research is deeply inspired by clinical questions arising from my practice at the UT Physicians Comprehensive Adult Sickle Cell Center and collaborative research projects.

Pharmacy Times: When getting involved with a research team, are you most frequently connected through your institution, or have associations or other groups provided opportunities for research collaboration?

Ononogbu: I primarily connect with research teams through my institutional roles at the UT Physicians Comprehensive Adult Sickle Cell Center and the University of Houston College of Pharmacy, as well as through collaborations with institutions within the Texas Medical Center. My recent NIH [National Institutes of Health]-funded grant involves a partnership with Howard University, and I have played a key role in fostering research collaborations across the nation. Additionally, my active involvement in groups focused on health equity and diversity often opens doors to broader and more impactful collaborations.

Pharmacy Times: What are some of your greatest accomplishments as a pharmacy researcher?

Ononogbu: Some of my greatest accomplishments include securing an NIH grant to investigate the connection between pain and the gut microbiome in patients with sickle cell disease; developing a project to create a tailored depression screening tool for patients with sickle cell disease; addressing inaccuracies in current methods; cofounding PILs, which has significantly improved diversity and representation within the pharmacy workforce; and being able to grow and learn from incredible mentors in this field when I wasn't sure if I knew how to do it. Seeing the fruits of my hard-earned labor has been refreshing and exciting.

Pharmacy Times: Can you share a recent publication that highlights your research area and why it stands out as a significant accomplishment?

Ononogbu: I recently published an article in *Lancet Hematology* titled "Call to Action: Equitable Comprehensive Care for Patients With Sickle Cell Disease in the USA." This work highlights the systemic barriers faced by [patients with] sickle cell, including discrimination, fragmented care as they transition from pediatric to adult services, and frequent reliance on emergency [departments] due to severe pain crises and a lack of comprehensive care. The article emphasizes the urgent need for compassionate, equitable, and multidisciplinary care models. I am extremely proud that *Lancet Hematology* recognized the importance of this issue and provided a platform to amplify this call for change. 📍

ORIGINAL RESEARCH

Impact of Time to First Epinephrine Administration on Outcomes After In-Hospital Cardiac Arrest With Initial Nonshockable Rhythm

Megan Haas, PharmD; Amanda Lowney, PharmD, BCPS, BCCCP, BCEMP; and Jamie Warren, PharmD, BCPS, BCCCP, CPP

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DISCLOSURES

None.

PRÉCIS

This study found no significant difference in the sustained return of spontaneous circulation or survival to hospital discharge based on the timing of the first epinephrine administration in these patients.

OBJECTIVE

The primary objective was to evaluate the impact of time to first epinephrine administration on sustained return of spontaneous circulation (ROSC) in initial nonshockable rhythms. The secondary objective was survival to hospital discharge.

STUDY DESIGN

This was a retrospective, multicenter, institutional review board–approved chart review evaluating adult patients with initial nonshockable rhythm after in-hospital cardiac arrest from July 1, 2020, to June 30, 2023.

METHODS

Patients 18 years and older with initial nonshockable, in-hospital cardiac arrest were included. Patients were excluded if they experienced cardiac arrest prior to hospital arrival or transitioned to hospice within 24 hours of ROSC. Patients were analyzed based on timing of the first epinephrine administration (<2 minutes and ≥2 minutes) upon identification of cardiac arrest. The χ^2 test was used to compare the primary and secondary outcomes between groups.

CONCLUSION

The results did not demonstrate a difference between timing of the first epinephrine administration on sustained ROSC in initial nonshockable rhythms.

INTRODUCTION

Cardiac arrest occurs when there is cessation of cardiac mechanical activity confirmed by signs of absence of circulation, such as no pulse and unresponsiveness. Out-of-hospital cardiac arrest is more common than in-hospital arrest; however, survival rates to discharge are higher in patients who experience in-hospital cardiac arrest.¹ The incidence of in-hospital cardiac arrest in the United States is approximately 10 per 1000 hospital admissions.¹ Survival-to-discharge rates are substantially higher in patients with an initial shockable rhythm—reported at 2 to 3 times higher than initial nonshockable rhythm.² Nonshockable rhythms are often the initial rhythms (approximately 80% of cases) noted for in-hospital cardiac arrest; however, with the introduction of rapid response teams in the hospital setting, mortality has decreased.^{1,2} Nonshockable rhythms include pulseless electrical activity (PEA) and asystole. The most common causes of in-hospital cardiac arrest are hypoxia, acute coronary syndrome, arrhythmias, and hypovolemia.^{1,3}

Epinephrine administration concurrently with high-quality cardiopulmonary resuscitation (CPR) improves survival in patients with nonshockable rhythms.³ Epinephrine, a sympathomimetic catecholamine, acts on both α - and β -adrenergic receptors. Epinephrine causes vasoconstriction through its potent effect on α -adrenergic receptors. The beneficial

STRATEGIC ALLIANCE PARTNER

NOVANT
HEALTH

effects of epinephrine are thought to be due to α -adrenergic properties, resulting in increased coronary and cerebral perfusion pressure. The American Heart Association (AHA) guidelines for CPR recommend that epinephrine be dosed at 1 mg intravenously every 3 to 5 minutes, with the first administration as soon as possible.³

Limited data are available for the optimal time to administer epinephrine in patients with nonshockable rhythms. The information that is available suggests that earlier administration of epinephrine in hospitalized patients with nonshockable cardiac arrest is associated with a higher probability of ROSC; however, no exact time frame has been established.⁴

In 2014, Donnino et al published a retrospective analysis aiming to determine whether earlier administration of epinephrine in patients with in-hospital, nonshockable cardiac arrest was associated with increased ROSC, survival, and neurologically intact survival. The findings demonstrated a significant stepwise decrease in in-hospital survival with each minute that epinephrine was delayed. When time to administration was analyzed in 3-minute intervals, they also found a significant decrease in in-hospital survival with each increasing interval.⁴

In 2021, Bakhsh et al published a retrospective analysis comparing immediate intravenous (IV) epinephrine (defined as administration within 1 minute after recognition of cardiac arrest) to early IV epinephrine (defined as administration 2 minutes or longer after recognition) in patients with in-hospital, nonshockable cardiac arrest. A total of 360 patients were included in the analysis, and sustained ROSC was achieved in 95 patients. Immediate administration of epinephrine compared with early administration was associated with statistically higher rates of sustained ROSC (15.3% vs 11.1%; $P = .04$).⁵

The results from these prior studies indicate further research is needed to correlate early administration of epinephrine in nonshockable rhythms with clinical outcomes, such as sustained ROSC and survival to hospital discharge. The current practice within the facilities included in this study is to administer epinephrine within the first 5 minutes of a nonshockable rhythm, in alignment with AHA's Get With the Guidelines–Resuscitation (GWTG-R).⁶ To date, study facilities have not routinely tracked more immediate epinephrine administration times and utilize epinephrine administration within 5 minutes as the reporting metric in nonshockable rhythms.

The purpose of this study was to compare time to first epinephrine administration with outcomes in patients

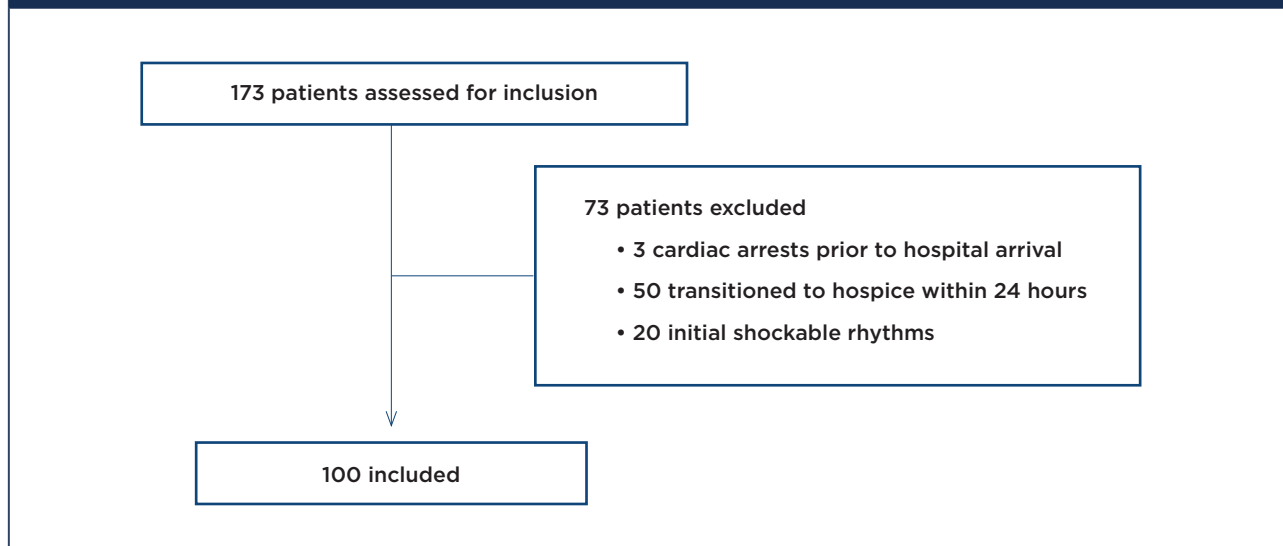
with in-hospital cardiac arrest with initial nonshockable rhythms. The primary objective was to evaluate the time to first epinephrine administration (< 2 minutes or ≥ 2 minutes) on sustained ROSC 24 hours after in-hospital cardiac arrest in initial nonshockable rhythms. The secondary objective was survival to hospital discharge.

METHODS

This was a retrospective, multicenter, institutional review board–approved chart review evaluating adult patients with in-hospital cardiac arrest from July 1, 2020, to June 30, 2023. Data were obtained from 3 facilities within a 19-hospital community health system. Patients were included if they were 18 years or older, experienced the first cardiac arrest after arriving at the hospital, had an initial nonshockable rhythm, and had the code narrator utilized for chart documentation. Patients were excluded if cardiac arrest occurred prior to arrival at the hospital or in the operating room, they were pregnant, or they were transitioned to hospice within 24 hours of ROSC. Patients in the emergency department were included if their first cardiac arrest was after arrival. *Time to epinephrine administration* was defined as the interval in minutes from recognition of loss of pulse to the first epinephrine administration. Patients were categorized into groups based on those with first epinephrine administration in less than 2 minutes and those with epinephrine administration at 2 minutes or longer from recognition of cardiac arrest. Patients were identified utilizing a data report of patients with code blue documentation in the code narrator. The code narrator is built into the electronic medical record and allows for documentation of time of each event/intervention, respiratory status, heart rate, blood pressure, cardiac rhythm, defibrillation/cardioversion (if applicable), and medication administration. Data were collected from chart documentation in the code narrator function of the electronic medical record.

Within the practice setting, personnel are trained to activate the code blue team and immediately initiate CPR upon recognition of cardiac arrest. The code blue team may include a house supervisor, physician, pharmacist, respiratory therapist, chaplain, and phlebotomist as well as rapid response nurses. Code blue team members are certified in advanced cardiac life support. Documentation of the code is performed via the code narrator. The code narrator documentation is available to be completed in real time but may also be transcribed retrospectively; both methods are instituted within the study facilities.

Descriptive statistics were used to assess the baseline characteristics. The χ^2 test was used to compare baseline

FIGURE. Screening for Study Inclusion

characteristics for nominal data, and the Mann-Whitney U test was used to compare nonparametric numerical data. The χ^2 test also was used to compare the primary outcome of sustained ROSC and the secondary outcome of survival to discharge. A *P* value less than .05 was considered significant.

We ran logistic regression models analyzing the impact of potential confounding variables with time to first epinephrine administration, initial rhythm (PEA and asystole), and CPR duration on sustained ROSC and survival to discharge. The confidence intervals were set to 95%.

RESULTS

We reviewed 173 patients for inclusion in the study (Figure) and included 100 patients with initial nonshockable rhythms. Baseline characteristics are shown in the Table. There were significant differences in baseline characteristics for rhythm type and median CPR duration. The median time to first epinephrine administration was 1 minute (IQR, 1-2 minutes), and median CPR duration was 8 minutes (IQR, 4-15 minutes). Sustained ROSC was achieved in 29 patients (29%). Survival to hospital discharge occurred in 9 patients (9%).

Epinephrine was first administered in less than 2 minutes to 66 patients (66%) and at 2 minutes or longer to 34 patients (34%). There was no difference in the ROSC achieved in patients who received epinephrine at under 2 minutes and those who received epinephrine at 2 minutes or longer (47 [71%] vs 23 [68%]; *P* = .71). There was no difference in sustained ROSC at 24 hours or longer in patients who received epinephrine in less than

2 minutes vs those who received epinephrine at 2 minutes or longer (19 [40%] vs 10 [43%], respectively; *P* = .95) or in survival to discharge (7 [11%] vs 2 [6%]; *P* = .43).

After adjusting for covariates, initial rhythm, and CPR duration, we found no association between time to first epinephrine administration and incidence of sustained ROSC at 24 hours or longer or survival to discharge. The same regression model showed no association between initial rhythm of PEA or asystole on incidence of sustained ROSC at 24 hours or longer or survival to discharge. There also was no association of duration of CPR with incidence of sustained ROSC at 24 hours or longer; however, duration of CPR had an independent effect on survival to discharge. Every 1-minute increase in duration of CPR decreased the odds of survival to discharge by 26% (OR, 0.74; 95% CI, 0.55-0.99; *P* = .04).

In a subgroup analysis of 32 patients with COVID-19, median time to epinephrine administration was 1 minute (IQR, 1-2 minutes) and 12 patients achieved sustained ROSC (38%). Epinephrine was administered in less than 2 minutes to 22 patients (69%) and at 2 minutes or longer to 10 patients (31%). Sustained ROSC was similar in patients who received epinephrine in less than 2 minutes compared with those who received epinephrine at 2 minutes or longer (36% vs 40%, respectively). No patients with COVID-19 survived to discharge.

DISCUSSION

The AHA recommends administration of epinephrine as soon as possible upon recognition of cardiac arrest and repeating it every 3 to 5 minutes.³ Our

TABLE. Baseline Characteristics				
Characteristic	Total (N=100)	<2 min (n=66)	≥2 min (n=34)	P value
Median age, years (IQR)	68 (58-74.5)	65 (58-74)	70.5 (56-78)	<i>P</i> =.56
Male, n (%)	55 (55)	34 (52)	21 (62)	<i>P</i> =.33
COVID-19, n (%)	32 (32)	22 (33)	10 (29)	<i>P</i> =.69
Race/ethnicity, n (%)				
White/Caucasian	38 (38)	21 (32)	17 (50)	<i>P</i> =.39
Black/African American	49 (49)	35 (53)	14 (41)	
Hispanic/Latino	5 (5)	3 (5)	2 (6)	
Asian	2 (2)	1 (2)	1 (3)	
Other	6 (6)	6 (9)	0 (0)	
Comorbidities, n (%)				
Heart failure	30 (30)	18 (27)	12 (35)	<i>P</i> =.39
Diabetes	47 (47)	27 (41)	20 (59)	
Coronary artery disease	28 (28)	18 (27)	10 (29)	
Arrhythmia	24 (24)	14 (21)	10 (29)	
None	18 (18)	15 (23)	3 (9)	
Rhythm type, n (%)				
Asystole	32 (32)	14 (21)	18 (53)	<i>P</i> =.002
PEA	65 (65)	51 (77)	14 (41)	
Unknown	3 (3)	1 (2)	2 (6)	
CPR duration (minutes), median (IQR)	8 (4-15)	6 (3-12)	12 (6-20)	<i>P</i> =.02
Location, n (%)				
	1 (1)	0 (0)	1 (3)	<i>P</i> =.11
	62 (62)	46 (70)	16 (47)	
	37 (37)	20 (30)	17 (50)	
Diagnosis category, n (%)*				
Cardiac	22 (22)	13 (20)	9 (26)	<i>P</i> =.47
Respiratory	38 (38)	26 (39)	12 (35)	
Central nervous system	14 (14)	12 (18)	2 (6)	
Gastrointestinal/renal	13 (13)	9 (14)	4 (12)	
Other	24 (24)	13 (20)	9 (26)	

CPR, cardiopulmonary resuscitation; IQR, interquartile range; PEA, pulseless electrical activity.

*Patients categorized in multiple diagnosis categories, if applicable

study demonstrated the attainability of immediate epinephrine administration, with a median epinephrine administration time of 1 minute (IQR, 1-2 minutes).

The results of this study showed no difference in sustained ROSC with epinephrine administration in less than 2 minutes vs at 2 minutes or longer. Conversely, in a previous retrospective study, Bakhsh et al⁵ demonstrated an association between earlier epinephrine administration and increased sustained ROSC for 24 hours.

Overall survival to discharge of 9% was lower than the GWTG-R survival to discharge of approximately 25% in nonshockable, in-hospital cardiac arrest.³ Survival to discharge was numerically higher in the group that received epinephrine in less than 2 minutes compared with the group that received it at 2 minutes or longer, although this result was not significant.

Potential confounders shown in previous studies to impact outcomes include duration of CPR, intubation during CPR, and initial rhythm (PEA vs asystole).^{2,7-9}

Baseline characteristics of this study showed a difference in median duration of CPR and initial rhythm between groups. Previous literature suggests that an initial rhythm of PEA is associated with improved prognosis compared with asystole.^{7,8} There was a greater proportion of patients with PEA than asystole in the group who received epinephrine in less than 2 minutes and a greater proportion of patients with asystole than PEA in the group who received epinephrine at 2 minutes or longer. A logistic regression showed no association between initial rhythm of PEA, initial rhythm of asystole, duration of CPR, or time to first epinephrine administration on sustained ROSC as well as no association between initial rhythm of PEA, initial rhythm of asystole, or time to first epinephrine administration on survival to discharge; however, an increase in duration of CPR independently decreased the odds of survival to discharge.

Study limitations

Limitations of this study include the retrospective nature, small sample size, unmeasured confounders (such as intubation during CPR, nature of chart documentation, inclusion of patients with unknown initial rhythms), and inability to assess delivery of high-quality CPR.

Insertion of an endotracheal tube may interfere with early administration of epinephrine; however, data on intubation during CPR was not collected or assessed. Data collection relied upon chart documentation in the code narrator. Often the code narrator is not documented in real time, which could lead to possible transcription errors. In addition, inability to assess high-quality CPR affects generalizability of results.

Moreover, patients with COVID-19 were not excluded from analysis. Thirty-two percent of patients tested positive for COVID-19 during their hospital admission. A similar proportion of patients in both comparator groups had COVID-19. Previous literature suggests an approximate 1.5% survival-to-discharge rate after in-hospital cardiac arrest in patients with COVID-19.¹⁰ In a post hoc subgroup analysis, no patients with COVID-19 survived to discharge in this study, which could have contributed to the overall lower-than-expected survival to discharge. Due to isolation

precautions for patients with COVID-19, there is a theoretical delayed time to epinephrine administration, which was not demonstrated in this study as patients with COVID-19 had a median time to epinephrine administration of 1 minute (IQR, 1-2 minutes).

CONCLUSION

Although these results demonstrate the attainability of early epinephrine administration within 1 minute of recognition of loss of pulse, they did not demonstrate an association between timing of epinephrine administration on sustained ROSC in patients with initial nonshockable rhythms. Larger studies with more robust design are needed to assess the effects of time to epinephrine administration on sustained ROSC and survival to discharge. 🌐

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LITERATURE REVIEW

Dry Mouth: Its Etiology, Symptoms, and Strategies for Management

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CONFLICTS OF INTEREST

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PRÉCIS

Pharmacists with a deeper knowledge of xerostomia are ideally positioned to help educate patients with dry mouth on making informed self-care decisions for effective symptom management and improved quality of life.

ABSTRACT

Dry mouth, or xerostomia, is a frequently occurring affliction that can negatively influence oral functioning and an individual's quality of life. It is a subjective sense of mouth dryness associated with numerous etiologies that can impair salivary gland functioning. Due to xerostomia's subjective nature, there is no single, universally effective treatment regimen, which makes finding the best approach for each patient a challenge for health care professionals (HCPs). Oral hygiene maintenance, lifestyle modifications, and use of salivary substitutes and stimulants play an important role in appropriate management of dry mouth symptoms. This article provides an overview of dry mouth and its etiology and symptoms as well as insights on management strategies that can help pharmacy professionals and other HCPs better understand the condition to inform their decision-making and the educational support they provide on symptom management.

INTRODUCTION

Dry mouth, or xerostomia, is a subjective sensation of mouth dryness that is characterized by reduced salivary flow (ie, hyposalivation; saliva production <0.1 mL/min at rest or <0.7 mL/min under stimulation) or an altered rheology of saliva.¹ Investigators in a 2018 meta-analysis reported that 27.1% of the US population has been diagnosed with dry mouth, which is more than in Europe (20.4%) and Australasia (18.6%), and suggested an increase in prevalence with age.² Based on our literature search, most studies on dry mouth have focused on older individuals, with none involving children or adolescents. Additionally, few studies have reported the occurrence of hyposalivation in children.^{3,4}

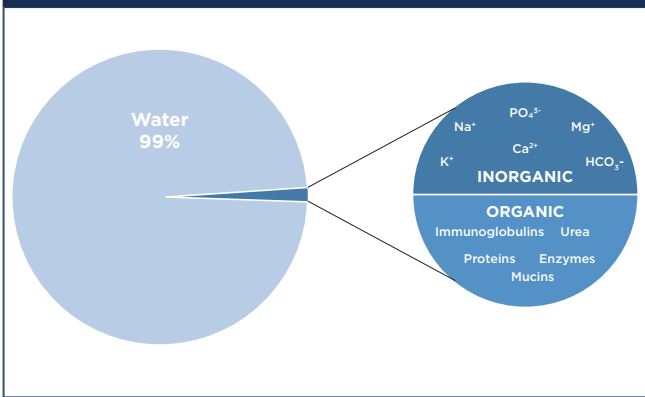
Saliva, primarily composed of 99% water and 1% organic and inorganic substances (Figure 1⁵), serves essential functions such as providing lubrication, antimicrobial action, and pH buffering as well as facilitating speech, swallowing, food digestion, and flavor diffusion.¹ Clinically, the effects of dry mouth can range from mild discomfort to impeded oral functioning, an increased risk of developing dental caries and oral infections, and a worsened quality of life (Figure 2).⁶⁻⁸ Because no cure is available for dry mouth, palliative care—including lifestyle modifications, oral hygiene maintenance, and pharmacotherapies such as salivary substitutes and stimulants—remains crucial for managing the condition.

Recent data highlight that pharmacists frequently encounter patients with oral health issues, including dry mouth.⁹ However, a significant barrier identified by pharmacists is a lack of knowledge in oral health care.¹⁰ This article aims to provide an overview of dry mouth, emphasizing its etiology, symptoms, and management strategies. By understanding these aspects, pharmacists can empower individuals with dry mouth to make informed self-care decisions and ensure effective symptom management.

PATHOPHYSIOLOGY AND OTHER FACTORS ASSOCIATED WITH DRY MOUTH

Xerostomia is not a separate clinical entity, but rather, a sign of several etiologies that can impair the functioning of the salivary glands (Table 1).^{6,7,11} Risk factors commonly associated with dry mouth include certain systemic diseases, xerogenic medications, head-and-neck radiation, developmental issues, older age, menopause, various psychological conditions, and lifestyle choices.

FIGURE 1. Salivary Constituents^{1,5,a}



Ca²⁺, calcium; HCO₃⁻, bicarbonate; K⁺, potassium; Na⁺, sodium; Mg⁺, magnesium; PO₄³⁻, phosphate.

^aSaliva is composed of mostly water and a variety of inorganic and organic components, with a select few shown here.

(AE) of prescription and OTC medications that are known xerogenic agents. Most cases are attributed to the anticholinergic effects, followed by sympathomimetic effects, vasoconstriction in salivary glands, dehydration, topical effects of inhaled medications, alterations in electrolyte and fluid balance, and changes in saliva composition. Patients who receive head-and-neck radiation therapy also commonly experience dry mouth due to radiation-induced damage to salivary glands.¹²

Developmental Issues

Rare developmental failure in salivary glands (partial or total) causes childhood xerostomia, occurring in 1 of 5000 births. Pathogenesis is unclear but linked to fetal development defects and sympathetic denervation, causing atrophy or hypertrophy in glands—and parasympathetic denervation results in glandular weight loss.¹³

Age

Age is a significant predictor of perceived mouth dryness.¹⁴ Aging induces multiple structural, functional, and metabolic alterations in salivary glands,¹⁵ and the high incidence of comorbidities and polypharmacy increases the risk of dry mouth symptoms in older adults.

Menopause

A significantly higher number of postmenopausal women experience reduced salivary flow rate and lower pH levels compared with menstruating women.¹⁶ Dry mouth can become more common in women after menopause because estrogen levels are permanently low.¹⁷

Systemic Diseases

Sjögren syndrome is the most recognized autoimmune disease associated with dry mouth and is characterized by the atrophy of the salivary glands followed by hyposalivation.¹¹ Rheumatoid arthritis, chronic juvenile arthritis, sarcoidosis, and systemic sclerosis correlate significantly with dry mouth.⁷ Other systemic diseases leading to dry mouth include diabetes, renal disease, bacterial and viral infections (eg, hepatitis C virus infection), liver disease, amyloidosis, and thyroid disease.⁷

Medication-Induced or Head-and-Neck Radiation-Induced AEs

Dry mouth is frequently observed as an adverse effect

FIGURE 2. Impact of Dry Mouth on Patients⁶⁻⁸

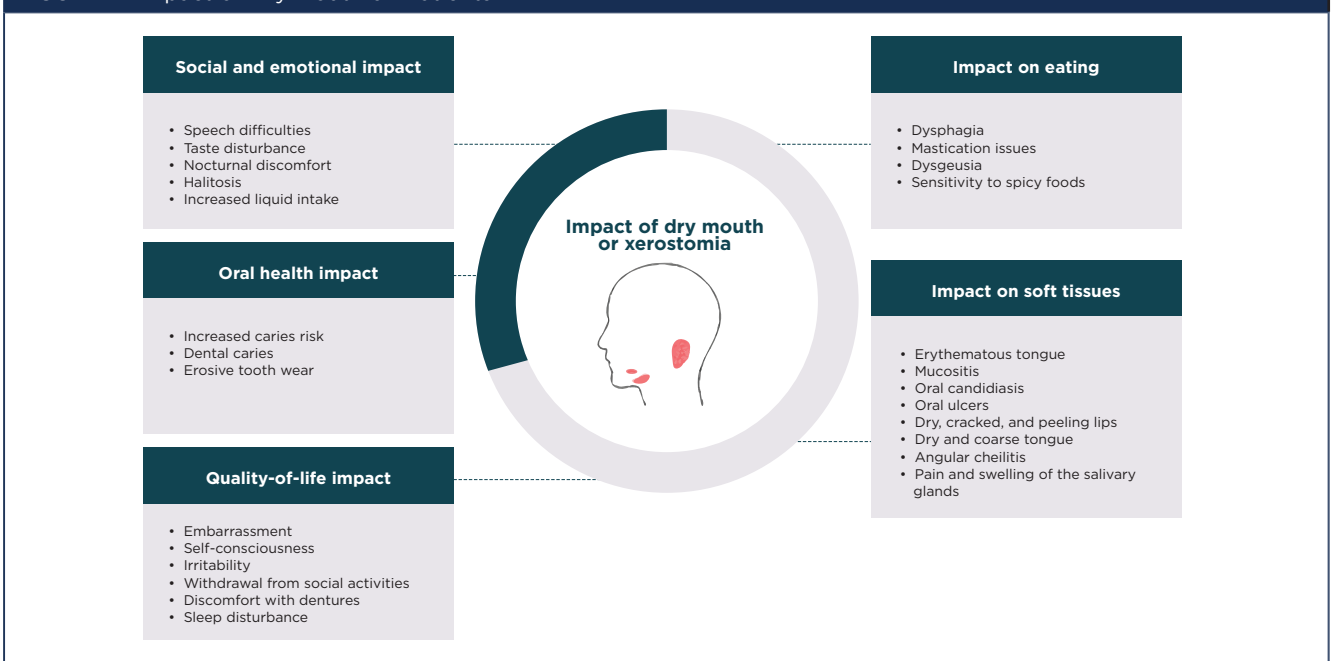


TABLE 1. Causes of Dry Mouth^{6,7,11}

Xerostomia as an adverse effect	
Xerogenic drugs-induced	Diuretics, antidepressants, antipsychotics, anticholinergics, antihistamines, neuroleptics, bronchodilators, anxiolytics, antihypertensives, opioids, immunosuppressive drugs, benzodiazepines, muscle relaxants, anticonvulsants
Radiation therapy-induced	Radiation therapy of the head and neck
Systemic factors	
Diseases	Autoimmune dysfunctions: Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Mikulicz disease/benign lymphoepithelial lesion Other: HIV/AIDS, SARS-CoV-2, hepatitis C, amyloidosis, scleroderma, diabetes mellitus, renal failure, Parkinson disease, Alzheimer disease, cystic fibrosis, chronic graft-vs-host disease, avitaminosis (vitamins B ₁ , B ₂ , B ₆ , and B ₁₂), hypercalcemia, hyperthyroidism, Addison-Biermer anemia, sarcoidosis, granulomatosis with polyangiitis, anxiety, depression, schizophrenia
Developmental issues	Salivary gland agenesis
Changes in the patient's physiology	Pregnancy, aging, menopause
Lifestyle factors	Smoking, alcohol use, caffeine use, breathing through the mouth

Psychological Conditions

Psychological conditions such as anxiety and depression show a statistically significant relationship with the rate of unstimulated salivary flow and dry mouth. Anxiety suppresses the impulses from the salivary nuclei to salivary glands, resulting in hyposalivation and dry mouth. Depression stimulates anticholinergic pathways, causing reduced salivary flow.¹⁸

Lifestyle Choices

Smoking, consuming alcohol, and drinking caffeinated beverages can alter salivary flow rate and increase the risk of dry mouth or aggravate the condition.¹⁹⁻²¹

SELF-CARE MANAGEMENT OPTIONS FOR DRY MOUTH SYMPTOMS

In the absence of a cure for dry mouth, management strategies such as lifestyle modifications, salivary stimulants, and salivary substitutes are crucial for alleviating symptoms.

Lifestyle Modifications

Good oral hygiene and adequate hydration are important for individuals with dry mouth.²² Maintaining proper oral health hygiene, including using fluoride toothpaste, flossing daily, and visiting the dentist at least twice a year, is crucial for preventing dry mouth-associated dental complications such as dental erosion, demineralization, and caries.^{23,24} Additional lifestyle modifications include using bedside humidifiers; finding ways to reduce stress; and avoiding spicy and dry food, caffeinated or carbonated drinks, alcohol, smoking, and mouthwashes containing alcohol.²²

Salivary Stimulants

Salivary stimulants, also known as sialogogues, increase salivary secretion. The salivary glands can be stimulated via pharmaceutically driven (pilocarpine or cevimeline

[Evovac; Daiichi Sankyo, Inc]), acid-driven (1% malic acid spray or 3% citric acid spray), or mechanically driven (chewing gum) approaches. Pilocarpine is typically prescribed at a dose of 5 mg 3 times a day for at least 3 months, and cevimeline is prescribed at a dose of 30 mg 3 times a day for at least 3 months.²³ Both agents are cholinergic, parasympathetic agonists, and their AEs include sweating, cutaneous vasodilation, nausea and vomiting, diarrhea, hiccups, hypotension, bradycardia, increased urinary frequency, bronchoconstriction, and vision problems.²³ If there is extensive damage to the salivary glands, individuals may not have a good response to these medications; therefore, these agents should only be considered in patients with residual salivary gland function.²³ Use is contraindicated in individuals with hypersensitivity, narrow-angle glaucoma, and uncontrolled asthma.²³ These products are only available with a prescription.

OTC sugar-free chewing gum and lozenges also are available. Sugar-free chewing gum or a lozenge can increase saliva secretion through mechanical stimulation of the major salivary glands.²⁵ A Cochrane Collaboration review reported that chewing gum increased saliva production only in individuals with residual secretory capacity.²⁵ Moreover, saliva stimulated by mechanical sucking or chewing alone has different rheological properties and does not generate the same mucoadhesive film as unstimulated saliva.²⁶

Saliva Substitutes

Saliva substitutes provide moisture, lubrication, and oral comfort by replicating some properties of natural saliva and do not alter the salivary flow in patients with dry mouth.²⁷ They come in various forms, including a mouthwash/oral rinse, a moisturizing spray, and an oral-balance moisturizing gel. Some are available over the counter, and others require a prescription (**Table 2**²⁸⁻³⁶). Alcohol-

and sodium lauryl sulfate–free products are gentle on the oral mucosa and promote enhanced patient adherence.

Clinical study data show that saliva substitutes effectively relieve dry mouth symptoms such as impaired swallowing, hoarseness, speech problems, oral pain, halitosis, and loss of taste.³⁷⁻⁴² Most patients with dry mouth and mild symptoms can sip water to achieve good short-term symptom relief; however, water is less effective in patients with moderate to severe symptoms of dry mouth because it is short acting.²⁷ Saliva substitutes provide better symptom-relieving effects on dry mouth, adhesion to oral mucosa, and persistence of taste compared with water.^{14,38-40} The duration of saliva substitutes ranges from 1.5 to 4 hours.^{37,38,41,43,44}

CONSIDERATIONS FOR PHARMACISTS

Pharmacists play a vital role in assisting patients with choosing self-care approaches and optimal OTC medicines. Although no specific guidelines are available for managing dry mouth, pharmacists should consider the following when counseling patients with the condition:

- **Medical history:** Dry mouth is often associated with underlying health conditions or medication use. Consider asking patients on multiple medications that can cause dry mouth whether they are experiencing symptoms of dry mouth after picking up their latest refill medications or starting a new medication that can cause dry mouth. During counseling, assess whether patients have any medical conditions associated with dry mouth and evaluate dry mouth symptoms by prompting patients about specific symptoms such as oral dryness. Management of dry mouth starts with a thorough evaluation, focusing on the illness and ongoing medicines. Although some medical conditions such as autoimmune or neurologic dysfunctions are not completely curable and will require ongoing palliative treatment for dry mouth, others such as nutritional imbalances or infectious conditions can be treated with a resolution that eventually relieves dry mouth. Some medications (eg, analgesics) may also be modified or replaced to address the presence of dry mouth, whereas others cannot and will require the patient to choose self-care approaches for managing dry mouth. Use of medications that cause sialorrhea, or hypersalivation, could potentially help counteract the effect of dry mouth. However, be sure to advise patients on xerogenic medications who are experiencing dry mouth to consult with their health care provider (HCP) before making any medication changes.
- **Patient education:** Improving patients' awareness through counseling and education about lifestyle modifications and proper oral hygiene is essential. Educational resources that pharmacists can use

to support these activities are available from the American Dental Association and Health Resources and Services Administration and can be found on their websites.

- **Pharmacotherapies:** Salivary stimulants and substitutes offer immediate relief for dry mouth discomfort, enhancing quality of life. Sugar-free gum may help only patients with residual salivary gland function, whereas saliva substitutes can be used as needed by all patients with dry mouth for symptomatic relief.²⁵ An ideal substitute should mimic human saliva properties, taste pleasant, and offer convenient self-administration to promote patient adherence. Understanding patient preference is essential while also considering potential AEs. A sampling of the commercially available salivary substitutes is shown in **Table 2**. In patients with radiation-induced xerostomia or Sjögren syndrome, consider the gel-based salivary substitutes, which are placed directly on the tongue and spread thoroughly inside the mouth for a long-lasting effect; their use is especially advisable before eating. Artificial saliva with oxidized glycerol triesters can be used in patients with chronic and temporary mouth dryness due to any systemic disease, stress, or aging.²⁵ Denture wearers with dry mouth can consider using a salivary substitute gel under dentures to improve comfort. In dentulous patients (ie, those with natural teeth), pH-neutral salivary substitutes containing fluorides and xylitol must be used to prevent tooth decay. Moreover, use of saliva substitutes in the form of mouth rinses containing zinc ions can help eliminate halitosis while comforting dry mouth. Calcium phosphate–containing salivary substitutes are indicated for patients with xerostomia due to radiation therapy or medicines such as atropine, antihistamines, or anticholinergic agents. Patients who are restricted to a low-sodium diet must be advised to consult their HCP before using sodium-containing products.

CONCLUSION

Dry mouth, although often overlooked,² is a common condition. Because there is no cure for dry mouth and because of its multifaceted causes, managing it presents challenges for HCPs. Pharmacists can identify patients at risk for dry mouth during patient encounters, educate patients on the condition, raise awareness by prompting patients to assess for dry mouth symptoms, and inform them of the existence of treatment options. The recommendations outlined, such as hydration strategies, healthy oral hygiene practices (eg, gentle toothbrushing at least twice daily with a fluoride toothpaste), and OTC solutions such as sugar-free chewing gums and saliva substitutes, can help relieve dry mouth symptoms. The

TABLE 2. Examples of Available Dry Mouth Products^{28-36,a}

Brand	OTC/Rx	Formulation	Ingredients	Directions for use
Biotène	OTC	Gel	Glycerin, water, sorbitol, xylitol, carbomer, hydroxyethyl cellulose, sodium hydroxide	Place gel, approximately a half-inch in length, on tongue and spread thoroughly inside mouth.
		Oral rinse	Water, glycerin, xylitol, sorbitol, propylene glycol, poloxamer 407, sodium benzoate, hydroxyethyl cellulose, methylparaben, propylparaben, flavor, sodium phosphate, disodium phosphate	Rinse with approximately 15 mL for 30 seconds and spit out. Use up to 5 times per day unless otherwise instructed by an HCP.
		Gentle oral rinse	Water, glycerin, xylitol, sorbitol, propylene glycol, poloxamer 407, potassium sorbate, hydroxyethylcellulose, flavor, sodium phosphate, cetylpyridinium chloride, disodium phosphate	Rinse with 15 mL for 30 seconds and spit out. Use up to 2 times per day; use up to 3 times per day only at the instruction of an HCP.
		Spray	Purified water, glycerin, xylitol, PEG-60, hydrogenated castor oil, VP/VA copolymer, flavor, sodium benzoate, xanthan gum, methylparaben, propylparaben, sodium saccharin, cetylpyridinium chloride	Use throughout the day as needed. Spray directly into mouth and onto tongue. Spread thoroughly inside the mouth.
TheraBreath	OTC	Lozenges	Mandarin mint: sorbitol, natural flavors, magnesium stearate, xylitol, <i>Spilanthes acmella</i> flower extract blend, zinc gluconate, rebaudioside A (derived from <i>Stevia rebaudiana</i>) Tart berry: sorbitol, maltodextrin, natural flavors, magnesium stearate (from plant sources), xylitol, malic acid, <i>Spilanthes acmella</i> flower extract blend, tartaric acid, citric acid, zinc gluconate, rebaudioside A (derived from <i>Stevia rebaudiana</i>)	Use whenever the mouth feels dry or has an unpleasant taste. Allow it to slowly dissolve in the mouth. Use 3 to 4 lozenges per day.
		Oral rinse	Water, glycerin, propylene glycol, poloxamer 407, xylitol, sodium benzoate, flavor, lysozyme, amylase, papain, amyloglucosidase, serralysin, lactoferrin, maltodextrin, <i>Spilanthes acmella</i> flower extract, sodium citrate	Rinse mouth for 1 minute with 1 capful. Use as needed.
ACT Dry Mouth	OTC	Mouthwash	Sodium fluoride 0.02%, water, glycerin, sorbitol, xylitol, poloxamer 407, betaine, propylene glycol, flavors, bisabolol, carnosine, PEG-14M, PEG-160M, <i>Zingiber officinale</i> (ginger) root extract, <i>Angelica polymorpha sinensis</i> root extract, <i>Lonicera japonica</i> (honeysuckle) flower extract, <i>Pueraria lobata</i> root extract, sodium benzoate, potassium sorbate, sodium phosphate, disodium phosphate, polysorbate 20, lactic acid, calcium disodium EDTA, cetylpyridinium chloride, sucralose, green 3, yellow 10	Use twice per day after brushing teeth with toothpaste. Vigorously swish 10 mL between teeth for 1 minute and then spit out.
		Lozenges	Isomalt, xylitol, glycerin, water, natural and artificial flavors, sucralose, β -carotene/FD&C Blue 1	Allow lozenge to slowly dissolve in mouth. Use as needed.
		Gum	Bubble fresh: xylitol, gum base, natural and artificial flavors. Less than 2% of maltitol, gum arabic, water, sorbitol, sucralose, hydrogenated soybean oil, methylcellulose, neotame, silicon dioxide, carnauba wax, lac resin, red 3, red 40, titanium dioxide (color), BHT (preservative) Soothing mint: xylitol, gum base, natural and artificial flavors. Less than 2% of maltitol, gum arabic, sorbitol, sucralose, titanium dioxide (color), silica, water, lac resin, carnauba wax, aspartame, neotame, methylcellulose, hydrogenated soybean oil, BHT (preservative)	Use as needed throughout the day. The recommended dosage is 1 piece of gum at a time. May add a second piece if desired.

BHT, butylated hydroxytoluene; FD&C, foods, drugs, and cosmetics; HCP, health care provider; PEG, polyethylene glycol; Rx, prescription, VP/VA, vinylpyrrolidone/vinyl acetate.

^aThis is not an exhaustive list of all the dry mouth products available.

continued on next page

TABLE 2. Examples of Available Dry Mouth Products^{28-36,a} (continued)

Brand	OTC/Rx	Formulation	Ingredients	Directions for use
SmartMouth	OTC	Mints	Sorbitol, xylitol, natural and artificial flavors, magnesium stearate, acesulfame potassium, zinc gluconate, artificial color	Allow mint to slowly dissolve in mouth. Use as needed.
		Oral rinse	Solution 1: purified water, sodium benzoate, sodium chlorite, carboxymethylcellulose gum, benzoic acid Solution 2: purified water, glycerin, sorbitol, poloxamer 407, poloxamer 124, zinc chloride, flavor, carboxymethylcellulose gum, benzyl alcohol, sodium benzoate, benzoic acid, sodium saccharin, sodium chloride, D&C Yellow No. 10, FD&C Blue No. 1	Rinse for 30 seconds twice per day after brushing in the morning and before bed.
OraCoat (XyliMelts, XyliGum, XyliGel)	OTC	Stick-on melts	Xylitol, acacia gum, cellulose gum, magnesium stearate, sodium bicarbonate, calcium carbonate	Place tan adhesive side of disc on gums or on the outside of a molar, upper or lower, with the white side touching cheek. Use tongue to push the disc to a comfortable spot, and do not touch it for 10 seconds to prevent disrupting the adhesion.
		Gum	Xylitol, gum base, natural flavors, sunflower lecithin, gum arabic, calcium carbonate, carnauba wax	Chew as needed throughout the day.
		Gel	Xylitol 17%, vegetable oils (zero trans fat: soybean, hydrogenated soybean, canola/palm mono- and diglycerides), water, mono- and di-potassium phosphate Ph buffer (Ph 7.4), orange oil	Spread in mouth and squish between teeth. For a long duration, place a blob in lip or cheek, lower or upper. Use during the day and while sleeping.
Allday	OTC	Dry mouth spray	Xylitol, water, glycerin, butylene glycol, flavor, methylparaben, sodium polyacrylate, propylparaben, sucralose, polyacrylic acid, sodium hydroxide, benzoic acid, EDTA	Spray directly into mouth on the tongue. Rub tongue over teeth and gums for at least 5 seconds. Use as needed.
		Gel	Xylitol, water, glycerin, cellulose gum, butylene glycol, flavor, sodium polyacrylate, methylparaben, polyacrylic acid, sodium hydroxide, propylparaben, sucralose, benzoic acid, EDTA	Place gel, approximately a half-inch in length, on tongue and spread thoroughly inside mouth. Use as needed, especially at night.
Aquoral	Rx	Spray	Oxidized glycerol triesters, silicon dioxide, aspartame, artificial flavoring	Shake gently. Spray twice (1 dose) into the mouth 3 to 4 times a day. Spread onto inflamed/dry areas of mouth with the tongue. Pump may require priming for initial use.
NeutraSal	Rx	Powder	Dibasic sodium phosphate, monobasic sodium phosphate, calcium glycerophosphate, sodium chloride, sodium bicarbonate, silicon dioxide	Dissolve 1 packet in approximately 1 ounce of water. Can be stirred. Use immediately after solution appears clear or nearly clear in the glass (about 15 seconds). Thoroughly swish half in the mouth for 1 minute and spit out. Repeat with remaining half and spit out.
SalivaMAX	Rx	Powder	Calcium, phosphate, bicarbonate	Dissolve 1 packet in 1 ounce of water. Swish half in the mouth for 1 minute and spit out. Repeat with the remaining half. Use the entire dose within 3 minutes of it dissolving in water. Repeat up to 10 times per day.

BHT, butylated hydroxytoluene; FD&C, foods, drugs, and cosmetics; HCP, health care provider; PEG, polyethylene glycol; Rx, prescription, VP/VA, vinylpyrrolidone/vinyl acetate.

^aThis is not an exhaustive list of all the dry mouth products available.

practicality of providing this type of educational support in a pharmacy underscores pharmacists' pivotal role in palliative care of xerostomia as well as their accessibility to patients. Continued collaboration between patients, pharmacists, and other HCPs promotes a holistic approach to managing this common but underrecognized condition. 🌱

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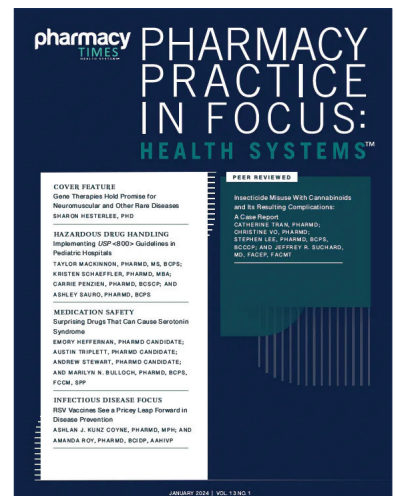
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ORIGINAL RESEARCH

Pharmacy-Led Enhanced Patient Education in the Emergency Department

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DISCLOSURES

None.

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PRÉCIS

In this retrospective study, investigators evaluated a pharmacy-led initiative in the emergency department (ED), finding a potential reduction in ED revisits and hospital readmissions, though results were not statistically significant.

OBJECTIVE

This study aimed to describe and evaluate a pharmacy-led clinical initiative during an ED visit.

STUDY DESIGN

This study is a retrospective cohort study.

METHODS

Patients 18 years or older with a history of heart failure, myocardial infarction, stroke, atrial fibrillation, or chronic obstructive pulmonary disease were included. The initiative was at a community hospital ED, where the emergency medicine pharmacist provided enhanced medication education at admission using a teach-back method. Data were collected for 3 months before (usual care) and during the intervention (enhanced care). The primary outcomes were all-cause 30-day ED revisit and hospital readmission rates. Secondary outcomes included the incidence of patients readmitted with the same illness and the cost savings. The primary outcomes were compared between the groups using χ^2 tests (statistical significance set at $P < .05$).

RESULTS

A total of 242 patients were included (121 usual vs 121 enhanced). There was a numerical decrease in all-cause 30-day ED revisits (usual 42% vs enhanced 36%, $P = .464$) and hospital readmission (usual 33% vs enhanced 25%, $P = .229$). Similarly, there was a numerical decrease in ED revisits (usual 35% vs enhanced 27%, $P = .402$) and hospital readmissions (usual 35% vs enhanced 33%, $P = .884$) due to the same illness. The pharmacy-led clinical initiative resulted in an estimated cost savings for the health system of approximately \$177,506.

CONCLUSION

Although the pharmacy-led clinical initiative indicated a potential reduction in ED revisits and hospital readmissions, these findings were not statistically significant. Larger studies are needed to determine the intervention's true impact on patient outcomes.

INTRODUCTION

Hospital readmission rates for chronic conditions are approximately 17%, with unplanned readmissions costing from \$15 billion to \$20 billion annually.¹⁻³ The Agency for Healthcare Research and Quality reports that the 5 leading all-cause 30-day adult hospital readmissions are sepsis, heart failure, diabetes with complication, chronic obstructive pulmonary disease (COPD) exacerbation, and acute/unspecified renal failure.⁴ Patients experiencing these conditions often take multiple medications, which can complicate their understanding of what each medication is for, how it works, and the importance of adhering to their prescribed regimen. This lack of understanding may result in ED visits and hospital readmissions.

Pharmacists are essential in the medication management process, as they take medication histories and perform medication reconciliations, allowing them to identify and address

medication-related concerns effectively. They provide valuable guidance on managing polypharmacy, adverse effects (AEs), and drug interactions while also educating patients about their medications to improve their understanding and adherence. These efforts have been shown to help reduce readmission rates.^{5,6}

In a systematic review and meta-analysis of randomized trials, Kelly et al investigated the associations among pharmacist counseling, medication adherence, 30-day hospital readmission, and mortality, finding evidence supporting pharmacist counseling as a means to enhance medication adherence and decrease hospital readmissions and ED visits.⁷ Also, Clark et al evaluated the impact of a pharmacist-led hospital discharge medication reconciliation process and found that it was associated with a significant reduction in medication discrepancies on the discharge medication list and the adjusted odds of 30-day hospital readmission.⁸ Although previous studies demonstrated that medication education performed during the discharge process had positive outcomes, including decreased ED revisits and hospital readmissions, limited studies are available to show the impact of patient education at admission.⁹⁻¹²

The impact of patient education at the point of admission remains underexplored, with most studies focusing on discharge procedures. Our study addressed this gap by implementing a pharmacy-led clinical initiative during the admission process in the ED. This initiative was designed to improve patients' and their caregivers' understanding of their medications at an early stage, with the goal of enhancing medication adherence and potentially reducing hospital readmissions. The primary objective of our study was to evaluate the impact of this pharmacy-led initiative by comparing all-cause 30-day ED revisits and hospital readmissions between patients who received the intervention and those who did not.

METHODS

Study Design and Setting

A pharmacy-led clinical initiative was implemented in the ED of a 260-bed community hospital from April to June 2022. The hospital has 2 full-time clinical pharmacy specialists and 2 full-time medication history pharmacy technicians who provide ED coverage and patient care. For this study, just 1 clinical pharmacy specialist and 1 medication history pharmacy technician participated, as they shared the same work schedule of four 10-hour shifts per week. The initiative focused on enhancing medication history and patient education during ED visits and was conducted exclusively during this period.

This study represents the initial implementation of a pharmacy-led clinical initiative in our institution's ED. The focus was to assess the feasibility and potential impact of this intervention on patient outcomes. This work served as an initial evaluation of the program's

effectiveness and operational integration.

A retrospective chart review was conducted to evaluate the impact of this intervention. This review compared patient outcomes from the 3 months before the intervention (January through March 2022, referred to as *usual pharmacy care*) to those during the intervention period (April to June 2022, referred to as *enhanced pharmacy care*). The usual care cohort consisted of patients who received standard pharmacy care, whereas the intervention cohort included patients who received the enhanced pharmacy-led education and medication reconciliation services. The goal was to assess changes in ED revisits and hospital readmissions between the 2 cohorts.

Participants and Cohort Selection

Patients 18 years or older who were admitted to the hospital with a history of congestive heart failure (CHF), myocardial infarction, stroke, atrial fibrillation, or COPD were included in the study. The control cohort (usual pharmacy care) consisted of patients admitted during the preintervention period, whereas the intervention cohort (enhanced pharmacy care) included those admitted during the intervention period.

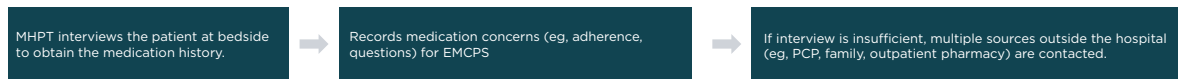
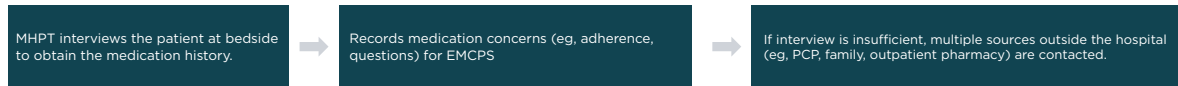
Patients were included if they were on at-home medications for any of the aforementioned conditions and had a complete medication history documented in the hospital's system. Exclusion criteria included patients who were homeless, presented with alcohol withdrawal, drug overdoses, psychosis, dementia, current altered mental status without a caregiver present, or required mechanical ventilation before or during their ED visit.

No formal matching process was used; however, baseline demographics and clinical characteristics of the 2 cohorts were compared to ensure similarity. Patients in both groups were identified through a retrospective chart review using the hospital's electronic medical record (EMR) system.

The medication history pharmacy technician performed screening for study enrollment, assessing each patient's home medications using the ED-specific dashboard. The emergency medicine (EM) clinical pharmacy specialist then confirmed eligibility through chart reviews and consultations with EM physicians. Screening and patient education were conducted during the technician's and pharmacist's regular working hours.

Intervention

The enhanced pharmacy care intervention consisted of a detailed medication history assessment followed by an educational session conducted by an EM clinical pharmacy specialist. **Figure 1** describes the intervention workflow. Initially, a trained pharmacy technician, serving as a medication history technician, collected detailed information on the patient's at-home medications. This included

FIGURE 1. Usual Care vs Enhanced Medication Education Workflow**Figure 1a. Usual Care Workflow****STEP 1: MHPT****STEP 2: EMCPS****Figure 1b. Enhanced Medication Education Workflow****STEP 1: MHPT**

Additional step: MHPT screens for study eligibility.

STEP 2: EMCPS

Additional steps: EMCPS confirms eligibility and creates a medication list.

Step 3: Patient

Additional steps: EMCPS provides additional education utilizing a teach-back approach with patients/caregivers to confirm understanding.

EMCPS, emergency medicine clinical pharmacy specialist; MHPT, medication history pharmacy technician; PCP, primary care physician.

documenting all prescribed and OTC drugs, herbal supplements, and adherence patterns. The technician also identified and documented any medication-related issues, such as discrepancies between the patient-reported medication list and the medical records, potential drug interactions, medication duplications, patient nonadherence, and any reported AEs. These issues were then communicated to the clinical pharmacy specialist for further evaluation and intervention. The technician used a standardized medication history assessment form to interview patients and/or caregivers (**Figure 2**).

After medication history was collected, patients included in the enhanced pharmacy care received educational medication intervention from the EM clinical pharmacy specialist. These in-person educational sessions focused on disease states, medication indications, administration, and monitoring instructions. To assess their understanding and to reiterate medication adherence, patients and/or caregivers are requested to perform a teach-back to the EM clinical pharmacy specialist detailing the information discussed. For individuals who could not speak or understand English or were deaf, an interpretation service provided by the institution was used. A summary of the patient's interaction and education session was documented in the pharmacy record.

All educational tools for the enhanced group were created by the EM clinical pharmacy specialist with internal department review. This study was meant to test and evaluate the feasibility and effectiveness of the tool.

Outcomes Measurement

Patients were followed up to 6 months post intervention for outcome measurement. The primary outcomes measured were all-cause 30-day ED revisit and hospital readmission rates. ED revisits were defined as any return to the hospital's ED within 30 days of the index visit. Hospital readmission was defined as any inpatient stay within 30 days after discharge from the index hospitalization.

It is important to note that these outcomes were limited to data captured within our hospital's EMR system. As a result, the analysis just included revisits and readmissions that occurred within the same health care system. This may not fully capture all patient encounters, especially if patients sought care at another facility outside our health system. This limitation meant that the results are not directly comparable to Centers for Medicare & Medicaid Services readmissions rates, which include data from multiple health care facilities and are used for value-based payments. The cost-savings calculations were derived using average cost

FIGURE 2. Medication History Assessment Checklist

Completed	Description
	<p>Obtain the following information from patients:</p> <ul style="list-style-type: none"> • Height and weight (if unable to obtain a measured weight, notify RN) • Allergies to any medications and reactions of the allergies <ul style="list-style-type: none"> ◦ Note: Please discuss with ED pharmacist prior to removing any allergies from profile • Patient pharmacy information (What pharmacy do you use? Which pharmacy would you like any new “discharge” medications sent to?)
	Enter and/or update height, weight, allergies/reactions, and patient pharmacy information in the patient's chart
	<p>For each medication (including prescription, OTC, herbal/supplement, as needed, etc), ask:</p> <ul style="list-style-type: none"> • Medication name • Formulation (immediate release vs extended-release, ointment vs cream, tablet vs capsule, etc.) • Strength • Dose • Route (by mouth, subcutaneous, etc) • Frequency (any specific times) • Indication • Last dose taken <p>Note: For patients on blood thinners (warfarin [Coumadin], rivaroxaban [Xarelto], apixaban [Eliquis], edoxaban [Savaysa], dabigatran [Pradaxa]), please inform ED pharmacist of information</p>
	<p>For any antibiotics, ask:</p> <ul style="list-style-type: none"> • Medication name • Formulation • Strength • Dose • Route (orally vs intravenously) • Frequency (any specific times) • Indication • Last dose taken • Levels/labs (mainly for patients receiving vancomycin and aminoglycosides [tobramycin, gentamicin, amikacin]) <p>Note: Communicate this info to ED pharmacist prior to communicating with providers</p>
	When contacting outpatient pharmacies (ie, CVS, Walgreens, Walmart, etc), please ask for maintenance medications filled within the last 3 months, not ALL medications
	<p>Double-check with patient with the following:</p> <ul style="list-style-type: none"> • Do you get any samples from your doctor's office? If so, what? • Prescribed medicine but not taking
	<p>Does patient have any of the following conditions:</p> <ul style="list-style-type: none"> • Congestive heart failure • Chronic obstructive pulmonary disease • Atrial fibrillation • Cerebral vascular accident • Myocardial infarction <p>If any of this is selected, notify EMP</p>

ED, emergency department; EMP, emergency medical practitioner; RN, registered nurse.

estimates from the hospital's finance department and were adjusted for diagnosis-related group, types of services rendered, volume, and the month of the visit. Readmission penalties varied depending on the payer. Our hospital received reimbursement for some readmissions, so the cost of readmission just applied if we were not reimbursed. In such cases, the hospital absorbed the financial burden and revenue loss.

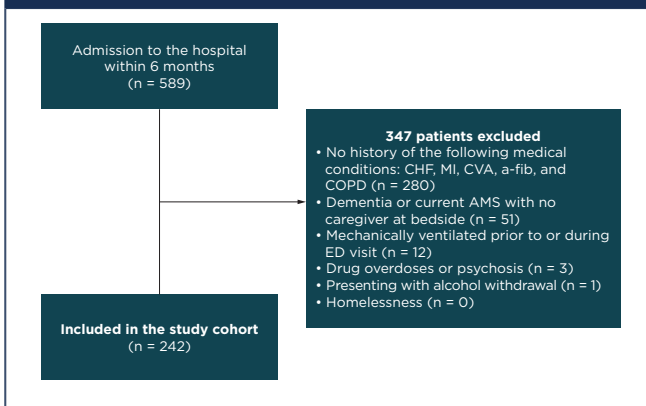
Statistical Analysis

Descriptive statistics were used to summarize patient demographics and baseline characteristics. For the primary analysis, inferential statistics were employed to compare the

outcomes between the usual care and enhanced pharmacy care cohorts. χ^2 tests were used for categorical variables, such as rates of ED revisits and hospital readmissions, whereas *t* tests or Mann-Whitney U tests were used for continuous variables, depending on data distribution. Statistical significance was defined as a *P* value of less than .05 for all analyses. Data were analyzed using the statistical software Minitab version 18.

No formal sample size was conducted before the study, as the study was limited by the availability of resources, specifically the manpower of the pharmacy team, which included just 1 full-time clinical pharmacist and 1 medication history

FIGURE 3. Consort Diagram



A-fib, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; ED, emergency department; MI, myocardial infarction.

focusing on educational interventions, it was granted an exemption from review by the Memorial Hermann institutional review board.

RESULTS

Participant Characteristics and Enrollment

Of 589 patients admitted to the hospital, 242 patients (41%) (121 usual vs 121 enhanced) were included in the study (Figure 3). Fifty-two percent of patients were female, 33% were African American, and 26% were Caucasian, with a mean age of 70 years (SD, 14) (Table 1). Of the included patients, 31% of admitted patients had more than 1 medical history, with CHF being one of the most common medical history conditions. Baseline demographics and clinical characteristics were similar between groups (Table 1).

Nonadherence was categorized into 2 types: intentional and unintentional. Intentional nonadherence occurs when a patient chooses not to follow treatment recommendations based on their beliefs and preferences. In contrast, unintentional nonadherence happens when a patient intends to follow the recommendations but encounters practical obstacles, such as poor recall or forgetting to take medication

technician. These personnel constraints, combined with the demands of clinical responsibilities, restricted the number of patients who could be included in the study.

As this study was a performance improvement project

TABLE 1. Characteristics (N = 242)

	All (n = 242)	Usual pharmacy care (n=121)	Enhanced pharmacy care (n=121)
Age, Mean 3 SD	70 3 14	70 ± 14	69 ± 14
Gender - female, n (%)	125 (52)	59 (49)	66 (55)
Race, n (%)			
Caucasian	64 (26)	33 (27)	31 (26)
African American	78 (33)	43 (35)	35 (31)
Hispanic	42 (17)	22 (18)	20 (17)
Other*	58 (24)	23 (19)	35 (31)
Past medical condition, n (%)			
CHF	42 (18)	21 (17)	21 (17)
COPD	24 (10)	9 (8)	15 (12)
Atrial fibrillation	41 (17)	21 (17)	20 (17)
MI	15 (6)	9 (7)	6 (5)
CVA	41 (17)	20 (17)	21 (18)
> 1 condition	79 (33)	41 (34)	38 (31)
Primary admission reason, n (%)			
Acute chest pain	21 (9)	11 (9)	10 (8)
CHF exacerbation	35 (14)	20 (16)	15 (12)
COPD exacerbation	16 (7)	9 (7)	7 (6)
CVA rule-out	16 (7)	8 (7)	8 (7)
Atrial fibrillation	15 (6)	8 (7)	7 (6)
Other	140 (57)	66 (54)	74 (61)
Length of stay, median (IQR)	3 (1.9-6.5)	3 (1.9-6.5)	2 (1.4-5.3)

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; IQR, interquartile range; MI, myocardial infarction.

*There was no significant difference between 2 groups across all variables.

*Other: Pacific Islander, Middle Eastern, and American Indian.

TABLE 2. Outcomes (N = 242)

	Usual pharmacy care (n = 121)	Enhanced Pharmacy Care (n = 121)	P value
Primary			
All-cause 30-day ED revisits, n (%)	51 (42)	44 (36)	.464
All-cause 30-day hospital readmission, n (%)	40 (33)	30 (25)	.229
Secondary			
ED revisit: Patients with included medical condition presenting with same illness, n (%)	18/51 (35)	12/44 (27)	.402
Hospital readmission: Patients with included medical condition presenting with same illness, n (%)	14/40 (35)	10/30 (33)	.884

ED, emergency department.

regularly. During the education session, the primary reason for at-home medication nonadherence was a lack of understanding (n = 73; 60%), followed by polypharmacy (n = 36; 30%). While there is no standard definition of *polypharmacy*, the term is commonly defined in the literature as the regular use of at least 5 medications. Consequently, we have adopted this definition for our purposes as well. The most common area of education provided to patients was medication indication (n = 54; 45%), followed by compliance (n = 42; 35%), and lastly monitoring (n = 24; 20%). The estimated median time spent on each patient was 25 minutes (range, 18-35 minutes).

Outcomes

There were numerical decreases in all-cause 30-day ED revisits (usual 42% vs enhanced 36%, $P = .464$) and all-cause 30-day hospital readmissions (usual 33% vs enhanced 25%, $P = .229$) (**Online Figure 4**). Both reductions were not statistically significant.

There were numerical decreases in ED revisits (usual 35% vs enhanced 27%, $P = .402$) and hospital readmissions (usual 35% vs enhanced 33%, $P = .884$) due to the same illness (**Table 2**).

The pharmacy-led patient education program was associated with an estimated cost savings of \$177,506 for the health care system, based on the reduction in ED revisits and hospital readmissions. The estimated cost-saving was specific to this hospital and may not be generalizable to other settings due to variations in health care costs and resource use.

DISCUSSION

Our study observed numerical reductions in all-cause 30-day ED revisits and hospital readmissions among patients who received enhanced pharmacy care during their admission (6% and 8% reductions, respectively). However, these differences were not statistically significant, indicating that we cannot be certain these reductions reflect the true effects of the intervention.

Our findings were consistent with previous research suggesting that pharmacist involvement can improve medi-

cation adherence and reduce health care use. However, this study alone does not provide sufficient evidence to claim the pivotal role of pharmacists in this setting. The clinical significance of these interventions remains to be determined through larger, adequately powered studies that can more accurately evaluate both their statistical and practical implications. Previous studies have demonstrated that education performed during the discharge process had positive outcomes, such as a decrease in ED revisits and hospital readmissions; however, limited studies are available to show the impact of outcomes on the admission side.¹³⁻¹⁵ Zemaitis et al conducted a prospective, controlled study evaluating the impact of a pharmacy-facilitated medication reconciliation and patient education model with postdischarge follow-up on 30-day readmissions. The findings resulted in a 27% reduction in readmission during the intervention period.¹⁶ In another study, Bach et al performed a meta-analysis to evaluate the effectiveness of interventions involving pharmacists to reduce hospital readmissions, finding that 55% of studies showed a statistically significant reduction in readmissions ranging from 3.3% to 30%, with most of the interventions focused mainly on patient education.¹⁷

Clinical pharmacists have a unique opportunity to improve patient care through medication education activities at the entry point of hospital admission. Our focus was primarily on the admission side for various reasons, including the fact that family members or caregivers are often present during the admission period, making it easier to gather medication history and provide education on disease states and medications. As a result, there will be overall increased understanding and adherence.

Furthermore, increased patient and caregiver knowledge, in addition to a medication list provided by the EM clinical pharmacy specialist, will facilitate a more substantial discussion with the admitting clinical team from all involved parties. The teach-back method used in our enhanced care protocol proved effective in ensuring that patients understood their medication regimens and the associated management of their conditions. This method has been endorsed in

other studies to enhance patient understanding and adherence, which are critical for preventing readmissions.¹⁸⁻²⁰ However, implementing such interventions in the high-pressure environment of the ED presented unique challenges, including time constraints and the need for pharmacists to balance multiple responsibilities. Despite these challenges, our study highlighted the potential for significant cost savings and improved patient care, supporting the argument for pharmacists' roles to be focused on care transitions. Optimally, patient education should consist of a coordinated series of efforts.

Study Limitations

This retrospective analysis did have several limitations. The effects were not necessarily generalizable to a broader population and setting because it was conducted at a 41-bed ED with a small sample size. The study's small sample size significantly affected the statistical power of the analysis.

A post hoc power analysis was conducted to assess the study's ability to detect differences in the primary outcome of all-cause 30-day ED revisits. Based on the observed effect size and assuming an 80% power and a 95% confidence level, the study would have required approximately 1037 participants per group to achieve adequate power. Given that just 121 patients were included in each group, the study was underpowered, limiting its ability to determine the true effectiveness of the pharmacy-led intervention.


Other limiting factors included a shortened intervention time and nonmatching groups; additionally, our EMR does not capture ED revisits and hospital readmissions information if patients went outside of our health system. Additional education and the review of medication use to minimize AEs, among others, may have been introduced during hospitalization and could have potentially impacted the results.

Due to the nonsignificant nature of the results, we acknowledge a potential limitation in statistical power, as no formal power calculation was conducted before the study. This limitation may have affected our ability to detect smaller but clinically meaningful differences between the groups.

As pharmacy involvement in medication history and reconciliation grows, additional research will be necessary to reproduce these findings through comparable educational interventions performed during both the admission and discharge sides. Furthermore, future studies can explore whether this educational intervention leads to improvements in in-hospital outcomes, such as reduced length of stay, appropriate medication use, fewer AEs, and enhanced adherence.

CONCLUSION

Within the 3-month study period, the pharmacy-led clinical initiative was associated with numerical reductions in ED revisits and hospital readmissions. However, these reductions were not statistically significant, and the study was underpowered to detect meaningful differences due to its small sample size. Although the results suggest a potential

benefit of pharmacist-led interventions, further research with larger sample sizes and robust study designs is needed to conclusively determine the effectiveness of these educational initiatives. 

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LITERATURE REVIEW

Factor XI Inhibitors: The Future of Anticoagulation

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DISCLOSURES

None.

PRÉCIS

Factor XI inhibitors show promise as a safer alternative to direct oral anticoagulants for preventing and treating thrombosis, offering similar efficacy with reduced bleeding risk.

ABSTRACT

Anticoagulation therapy has been evolving since the early 1900s with substantial advancements that have helped shape the treatment of indications such as atrial fibrillation and venous thromboembolism. Direct oral anticoagulants (DOACs) have been deemed the gold standard of treatment for these indications. However, the increased risk of bleeding that comes with DOAC use has proven to be a significant limitation. Currently, factor XI inhibitors are undergoing clinical trials for use in the prevention and treatment of thrombosis. These agents have promising clinical profiles, offering similar efficacy as the current gold standard while presenting with fewer bleeding incidents. Findings from phase 2 clinical trials comparing factor XI inhibitors with DOACs, dual antiplatelet therapy, or placebo showed that the inhibitors had no significant increase in bleeding and exhibited similar efficacy to currently accepted therapy. Phase 3 clinical trials are comparing therapies such as factor XI inhibitors abelacimab (MAA868; Anthos Therapeutics), asundexian (BAY-2433334; Bayer), and milvexian (BMS-986177/JNJ-70033093; Bristol Myers Squibb and Johnson & Johnson) with low-molecular-weight heparins, DOACs, antiplatelet therapies, or placebo; many of these trials have upcoming completion dates. As ongoing clinical trials provide insight into these agents, we will learn about their efficacy and safety profiles. Although there are essential barriers to cross before their clinical use, they have the potential to advance the progress of anticoagulation. This review discusses current anticoagulation therapy, the mechanism of action of factor XI inhibitors, and individual factor XI inhibitors that are active in clinical trials.

INTRODUCTION

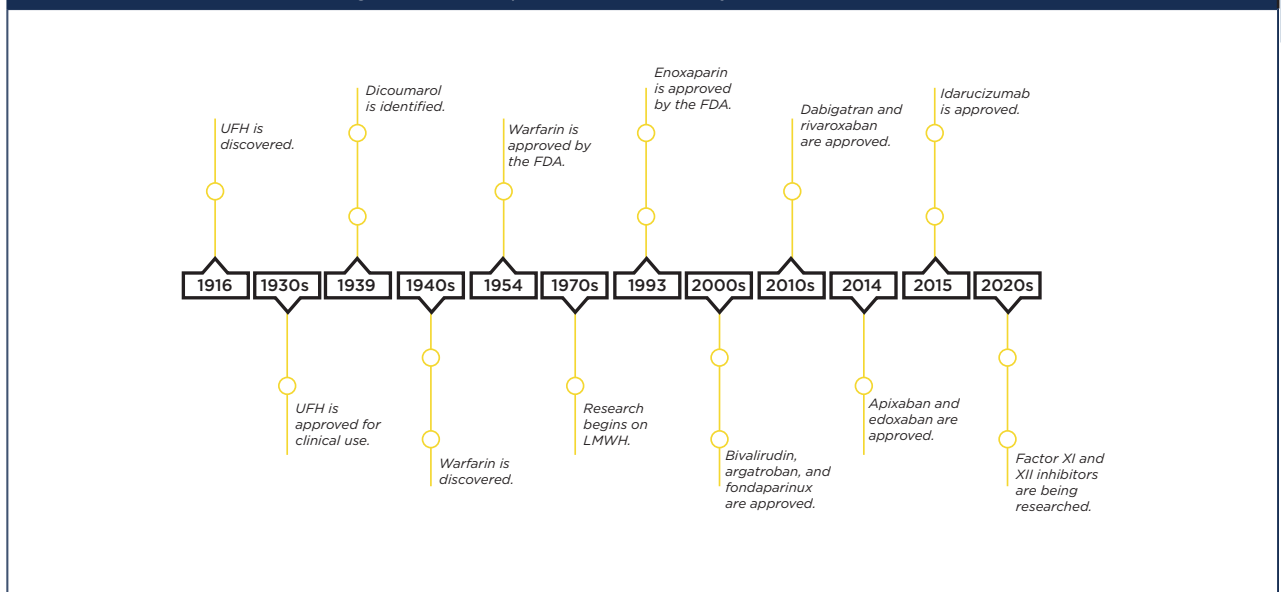
Direct oral anticoagulants (DOACs) are the current mainstay of treatment and prevention of thrombosis. DOACs and vitamin K antagonists (VKAs), such as warfarin, are utilized for many indications, including atrial fibrillation, venous thromboembolism (VTE), and mechanical heart valves. DOACs eliminated the need for routine international normalized ratio (INR) monitoring and decreased dietary restrictions that accompany VKAs; however, there are limitations with these current treatment options.

New anticoagulants targeting factors in the intrinsic or contact coagulation pathway are under development. Factor XI (FXI) inhibitors are particularly promising new agents being investigated in clinical trials for atrial fibrillation, ischemic stroke, VTE, and more. By inhibiting factors in the intrinsic pathway, these agents can potentially prevent and treat thromboembolic complications while lowering the bleeding risk in patients who utilize them. This article addresses the unmet needs in anticoagulation therapy, how FXI inhibitors could overcome the challenges faced, and FXI clinical trials to date.

HISTORY OF ANTICOAGULATION

In 1916, unfractionated heparin (UFH) was the first anticoagulant drug discovered, and it was approved for clinical use in the 1930s (**Figure 1**¹⁻⁴). UFH inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, and XIa. This inhibits coagulation by preventing fibrin formation.

In 1939, dicoumarol was extracted from moldy clover following investigation of a mysterious disease in which cattle and sheep were dying from internal bleeding.¹ In the 1940s to 1950s, warfarin was further derived from dicoumarol because it had more favorable pharmacokinetics; it was approved by the FDA in 1954. Warfarin also provided

FIGURE 1. Timeline of Anticoagulation Therapies From Discovery of UFH to DOACs¹⁻⁴

DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

the advantage of an orally administered anticoagulation option. This was in contrast to its predecessor, which required intravenous or subcutaneous administration.

Following the development of dicoumarol and warfarin, understanding of thromboembolic diseases grew, leading to the discovery of key players in the coagulation cascade and the derivation of low-molecular-weight heparins (LMWHs) from UFH in the 1970s. Although LMWHs are also injectable, they provide the benefit of being administered as a fixed dose, which reduces the need for regular concentration monitoring and provides the option for outpatient treatment.² LMWHs include enoxaparin (Lovenox; Sanofi-Aventis), dalteparin (Fragmin; Pfizer), and tinzaparin (Innohep; LEO Pharma). These agents inhibit thrombin and FXa; however, FXa is predominant. Enoxaparin was approved by the FDA in 1993, dalteparin in 1994, and tinzaparin in 2000.³

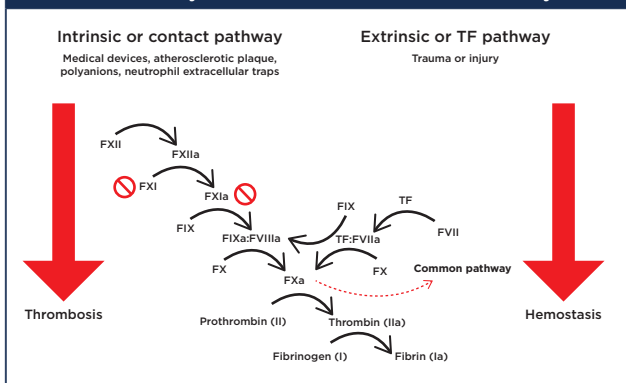
UFH and LMWHs can reduce VTE complications in hip or knee arthroplasty and during prolonged immobilization from surgical procedures.⁴ They are also used in acute coronary syndromes to treat and prevent thrombosis complications. Fondaparinux (Arixtra; GSK), which inhibits only FXa, was approved by the FDA in 2001.³ Fondaparinux is a synthetic form of injectable direct thrombin inhibitors, including bivalirudin (Angiomax; Meitheal Pharmaceuticals) and argatroban (Novastan; Mitsubishi Tanabe Pharma Corporation), which were approved in the 2000s.² Fondaparinux was also approved for the prevention and treatment of VTE and is conveniently dosed once daily due to its longer half-life.⁴

Injectable direct thrombin inhibitors bivalirudin and argatroban also were approved by the FDA in the early 2000s.³ Bivalirudin is used as an alternative to UFH in patients undergoing percutaneous coronary interventions, and argatroban is used as an alternative to heparin for patients with heparin-induced thrombocytopenia.⁴

Newer DOACs include the oral direct thrombin inhibitor dabigatran (Pradaxa; Boehringer Ingelheim), as well as oral direct FXa inhibitors rivaroxaban (Xarelto; Johnson & Johnson and Bayer), apixaban (Eliquis; Bristol Myers Squibb), and edoxaban (Savaysa; Daiichi Sankyo Company). Dabigatran and rivaroxaban were approved by the FDA in the early 2010s.³ They were followed by apixaban, which was approved by the FDA in 2012, and edoxaban, which was approved in 2015. In 2018, the FDA approved the monoclonal antibody idarucizumab (Praxbind; Boehringer Ingelheim), which is used as a reversal agent for dabigatran.³

DOACs quickly grew in popularity and replaced other anticoagulation therapies because of their ease of oral administration and ability to bypass the heparin bridging period for most indications. DOACs' quick onset of action means that heparin bridging is not routinely needed. Originally, patients would have to be treated with heparin for 5 to 7 days upon admission, then slowly transition to a VKA. This increased bleeding risk because the 2 anticoagulants were administered simultaneously. DOACs also do not require frequent monitoring and do not have any dietary restrictions.²

Fortunately, newer anticoagulants, such as DOACs

FIGURE 2. Coagulation Cascade of the Intrinsic or Contact Pathway and the Extrinsic or TF Pathway^{20,21}

F, factor; TF, tissue factor.

Factor XI resides in the intrinsic or contact pathway.

and direct thrombin inhibitors, also have minimal food and drug interactions. Although these medications still have some drug interactions, they are considerably fewer than those associated with warfarin.⁵ Dark leafy greens and oils are the primary sources of vitamin K, and many processed food items also contain substantial amounts. Warfarin interferes with cyclic interconversion of vitamin K and its 2,3-epoxide (vitamin K₁ epoxide), so when vitamin K is added to the diet, the anticoagulant effect of warfarin may fluctuate.⁶ Generally, if patients have a constant amount of vitamin K in their diet, their health care provider will be able to keep their INR stable. With most of the newer anticoagulants eliminating the need for this consistency, patients can eat a wider variety of foods. This has led to overall better health for patients and more dietary freedom. Notably, although rivaroxaban must be taken with food, there are no dietary restrictions. Since the discovery of DOACs in 2010, a new class of anticoagulants has yet to hit the market.

LIMITATIONS WITH CURRENT ANTICOAGULATION THERAPY

Anticoagulation therapy aims to control thrombosis while maintaining hemostasis. Current available therapies have shown efficacy in the prevention and treatment of thrombosis; however, the increased risk of bleeding has called attention to the need for safer options. In clinical trials, DOACs were shown to be at least as effective as heparin and warfarin for the prevention of stroke in patients with atrial fibrillation and the prevention and treatment of VTE. DOACs were also associated with lower rates of intracranial bleeding.⁷⁻¹¹

Between 2017 and 2019, anticoagulants were the most common cause of drug-related emergency department (ED) visits in the US.¹² Out of the current available

anticoagulant therapies, DOACs have a more favorable risk-benefit profile. The rates of anticoagulation-related ED visits were lower with DOACs when compared with VKAs such as warfarin.¹³ Despite DOACs' more favorable overall risk-benefit profile, they were found to cause more gastrointestinal bleeding than warfarin.¹⁴

DOACs have also led to unfavorable results in certain indications that require patients to take warfarin, such as mechanical heart valves and triple-positive antiphospholipid syndrome.^{15,16} In addition, DOACs have not been adequately tested in patients with severely impaired renal function, impaired liver function, or extremes of body weight.^{17,18}

Anticoagulation is an important developing field of medical research. With the limitations of current anticoagulant therapies, there remains a need for new therapies to provide additional options for patients.

MECHANISM OF ACTION OF FACTOR XI INHIBITORS

The proposal of FXI as a target for anticoagulation stems from hemophilia C, a rare genetic FXI deficiency disorder. The prevalence is 1 in every 1 million people worldwide but is reported more frequently in people of Ashkenazi, Arabic, and Iraqi Jewish descent.¹⁹ Hemophilia C is associated with reduced risk of thrombosis and increased bleeding tendencies. To understand how FXI can be used as a clinical target of interest, we must first assess its role in the coagulation cascade.

The coagulation cascade can be segmented into 2 initial pathways, extrinsic and intrinsic, which later converge into the common pathway (Figure 2^{20,21}). The extrinsic pathway is activated by trauma or injury to the vessel, which exposes tissue factor (TF) to the blood. The newly exposed TF becomes bound to calcium and factor VIIa to form the TF:VIIa complex. This complex is able to activate FX, turning it into FXa, and enters the common pathway to form a stable clot. The TF:VIIa complex also converts FIX to FIXa, which has a cofactor of FVIIIa.²¹ This extrinsic or TF pathway serves to bring the body back to hemostasis after experiencing trauma by forming a clot at the site of bleeding.^{20,21}

The intrinsic pathway is activated by triggers within the body, such as atherosclerotic plaques, various polyanions, neutrophil extracellular traps, and implanted medical devices.^{20,21} In the presence of these triggers, FXII self-activates and starts a signaling cascade that activates FXI, then FIX, and subsequently FX, which brings us back to the common pathway and production of thrombin and clot formation. FXI/XIa serves as a positive feedback mechanism to thrombin, therefore exponentially increasing the production of thrombin and causing a rapid expansion of the thrombus.²⁰ This pathway is the cause of pathological thrombus formation and

is the mechanism behind thromboembolic diseases.

Current anticoagulation therapies primarily target FX, the first step in the common pathway. This leads to FX inhibitors exerting their anticoagulation effects in both settings of hemostasis and thrombus formation, leading to an increased bleeding risk following injury or trauma.

The promise of FXI/XII inhibitors is the potential to uncouple the intrinsic and extrinsic pathways and stop pathological thrombus formation while avoiding hemostasis.²¹ The inhibition of the intrinsic or contact pathway would allow the prevention of thrombus formation within the body while still allowing the blood to clot when a person is injured.

FACTOR XI VS FACTOR XII

As anticoagulation research continues, FXI and FXII have been identified as promising drug targets. These intrinsic pathway factors have been shown in animal studies to be important in thrombosis and nonessential in hemostasis.²² Although FXII deficiency is not associated with abnormal bleeding, extrinsic pathway FVII and FVIII deficiency results in severe bleeding and the need for prophylactic therapies.²² Patients with FXI deficiency have reported bleeding episodes, and one study's results showed that FXI-deficient patients have a greater risk for clinically relevant bleeding.²³ Although this risk is mild, it is still of concern.

FXII as a target would seem more favorable as a potential agent with no risk of bleeding, but there are other characteristics to consider. Concerns of FXII as a drug target include the contribution of FXII to thrombosis initiated by TF, potential for feedback activation of FXII by thrombin to bypass FXIIa inhibition, and weak epidemiology data linking FXII to thrombosis.²⁴

Although epidemiologic studies have shown links between FXI levels and thrombosis, links were not found between FXII and thrombosis.²⁵ In these studies, those with congenital FXI deficiency were observed to have lower incidences of ischemic strokes, VTE, and myocardial infarction (MI).²⁵ However, FXII did not show similar findings. Other studies have found that patients with higher FXI levels are more prone to ischemic stroke and VTE.²⁶ These studies present the link of coagulation factor levels with the risk of thrombosis to be stronger for FXI than for FXII.²⁷ Characteristics of FXI and FXII as targets for anticoagulation are summarized in **Table 1**.²²⁻²⁷

FXI's central role in coagulation and inflammation gives FXI inhibitors the potential to be efficacious against antiphospholipid syndrome or thrombosis secondary to blood contact with medical devices.²⁴ This unique position allows inhibition of FXI to be effica-

TABLE 1. Comparison of FXI and FXII as Targets for Anticoagulation²²⁻²⁷

	FXI	FXII
Factor deficiency	Low bleeding risk	No bleeding risk
Epidemiologic studies	Stronger	Weaker
Inhibition bypass	None	Thrombin could bypass FXIIa inhibition.
Clinical trials	Phase 2 and phase 3	Preclinical trials

F, factor.

cious in indications not well treated with FXa inhibitors and instead requiring treatment with warfarin.

THE FACTOR XI INHIBITORS

Mechanisms to inhibit FXI include antisense oligonucleotides (ASOs), monoclonal antibodies (mAbs), and small-molecule drugs. Each approach varies in pharmacokinetic and pharmacodynamic properties (**Table 2**²⁸).

Most FXI inhibitors exhibit minimal renal elimination and are hepatically metabolized. These pharmacokinetics suggest potential drug-drug interactions and the accumulation of the drug in patients with kidney and liver impairments.²⁴

SMALL MOLECULES

The small molecule FXI inhibitors include asundexian (BAY-2433334; Bayer) and milvexian (BMS-986177/JNJ-70033093; Bristol Myers Squibb and Johnson & Johnson). These agents reversibly bind to FXIa and block its activity, inhibiting progression through the intrinsic or contact pathway in the coagulation cascade.

Asundexian has a limited degree of renal elimination, whereas milvexian is primarily metabolized through the hepatic cytochrome P450 system, with a limited amount undergoing renal elimination.²⁹ Although most milvexian is eliminated through the liver, trial results revealed no significant difference in pharmacokinetics between patients with mild or moderate hepatic impairment and healthy individuals.³⁰ Phase 3 clinical trials are ongoing for both of these agents.

Asundexian and Milvexian Clinical Trials

Phase 2 clinical trials have studied FXI inhibitors in efficacy and safety compared with DOACs and placebo. PACIFIC-AF (NCT04218266) was a randomized, double-blind study that compared asundexian at 20 or 50 mg once daily with apixaban 5 mg twice daily (2.5 mg twice daily if the criteria for dose reduction

TABLE 2. Current FXI Inhibitors in Clinical Trials and Their Properties²⁸

	Small molecules		Monoclonal antibodies			Antisense oligonucleotides
Drug	Asundexian	Milvexian	Abelacimab	Osocimab	Xisomab	Fesomersen
Phase of development	Phase 3	Phase 3	Phase 3	Phase 2	Phase 2	Phase 2
Mechanism of action	Reversibly binds FXIa and blocks activity		Binds to FXI or FXIa and blocks activity			Reduces the hepatic synthesis of FXI
Onset of action	Rapid		Rapid			Slow
Offset of action	Rapid		Slow			Slow
Administration route	IV or oral		IV or SC			SC
Frequency of administration	Daily		Monthly			Weekly to monthly

F, factor; IV, intravenous; SC, subcutaneous.

were met) for stroke prevention in patients with atrial fibrillation³¹; 753 patients were included in the study. Efficacy outcomes included ischemic stroke, systemic embolism, MI, or cardiovascular (CV) death. Safety outcomes included major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). Results indicated that patients taking asundexian 20 or 50 mg once daily had lower bleeding rates when compared with those taking apixaban with similar efficacy rates.³¹

PACIFIC-STROKE (NCT04304508) was a randomized, double-blind, placebo-controlled study investigating asundexian at 10, 20, or 50 mg once daily compared with placebo in patients with acute noncardioembolic ischemic stroke in addition to antiplatelet therapy.³² The primary efficacy outcome was the dose-response effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischemic stroke at or before 26 weeks. The primary safety outcome was major or clinically relevant nonmajor bleeding, as defined by the ISTH. This trial did not show a reduction in the composite of covert brain infarction or ischemic stroke and did not show an increase in the composite of bleeding when compared with placebo.³²

PACIFIC-AMI (NCT04304534) was a randomized, double-blind, placebo-controlled study investigating asundexian at 10, 20, or 50 mg once daily compared with placebo in patients within 5 days of their MI.³³ Study participants also received dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor. The primary efficacy outcome was a composite of CV death, MI, stroke, or stent thrombosis. The investigators found that asundexian, in addition to dual antiplatelet therapy, resulted in dose-dependent, near-complete inhibition of FXIa activity without a significant increase in bleeding.³³

AXIOMATIC-SSP (NCT03766581) was a randomized, double-blind, placebo-controlled, dose-finding trial that compared milvexian at 25 mg once daily or

25, 50, 100, or 200 mg twice daily vs placebo.³⁴ The dose response of milvexian was studied for recurrent ischemic cerebral events and major bleeding events in patients with recent ischemic stroke or transient ischemic attack. This therapy was added to dual antiplatelet therapy. Study findings did not indicate a reduction of symptomatic ischemic stroke or covert brain infarction or a significant increase in bleeding risk.³⁴

OCEANIC-AF (NCT05643573) was a phase 3 clinical study designed to evaluate the efficacy and safety of asundexian compared with apixaban in patients with atrial fibrillation at risk for stroke. This randomized, multicenter, double-blind, double-dummy trial is assessing the potential of asundexian as an alternative anticoagulation therapy. Participants received asundexian once daily and apixaban matching placebo twice daily, with an active comparator of participants who received apixaban 2.5 or 5 mg twice daily with asundexian matching placebo once daily. Primary end points included the time to first occurrence of composite of stroke or systemic embolism, time to first occurrence of major bleeding, time to first occurrence of composite of stroke, systemic embolism, and major bleeding. This study aimed to provide insights into the potential role of asundexian in the management of stroke risk in patients with atrial fibrillation. This trial was terminated early due to the inferior efficacy of asundexian compared with apixaban. This decision was made by an independent monitoring committee.³⁵

OCEANIC-STROKE (NCT05686070) is a phase 3, randomized, placebo-controlled study designed to evaluate the efficacy and safety of asundexian compared with placebo in patients who have recently experienced an ischemic stroke or transient ischemic attack. Given the high recurrence risk in this population, identifying a safe and efficacious therapy is of paramount importance. This multicenter trial is comparing the rates of stroke recurrence and major bleeding events between the

asundexian and placebo arms. Participants will receive either once-daily asundexian or a matching placebo for a duration ranging from 3 to 31 months. The study protocol includes regular follow-up assessments conducted every 3 months, either in person or via telephone, to monitor patient outcomes and safety. Participants in OCEANIC-STROKE trial must be 18 years or older with a recent history of noncardioembolic stroke. This comprehensive investigation aims to provide crucial insights into the potential role of asundexian in secondary stroke prevention, addressing a significant unmet need in cerebrovascular disease management. The study is projected to conclude by October 2025.³⁶

LIBREXIA-AF (NCT05757869) is a phase 3, double-blind, double-dummy, parallel-group study designed to assess the efficacy and safety of milvexian vs apixaban in patients with atrial fibrillation to prevent cardioembolic stroke or VTE. Participants receive milvexian at 100 mg twice daily and placebo that matches apixaban; participants receiving the active comparator receive apixaban at 2.5 or 5 mg twice daily. The primary end point is the time to first occurrence of stroke and non-central nervous system systemic embolism. This study's estimated completion date is May 2027.³⁷

LIBREXIA-STROKE (NCT05702034) is a phase 3, randomized, double-blind, placebo-controlled study designed to assess the efficacy of milvexian compared with placebo to reduce the risk of recurrent ischemic stroke. Patients receive milvexian at 25 mg twice daily or placebo. Antiplatelet therapy, following international and local guidelines, is required for all participants. This study includes patients who have experienced an ischemic stroke, characterized by a neurological deficit due to acute brain infarction, with a National Institutes of Health Stroke Scale score of 7 or less. The use of an anticoagulant in secondary stroke prevention would be a novel indication. Antiplatelet agents are the mainstay of treatment following an initial stroke; however, this study will provide insight on whether milvexian has the potential to be an effective option as well. This study is projected to be completed by December 2026.³⁸

The LIBREXIA-ACS trial (NCT05754957) will assess whether milvexian, in addition to antiplatelet therapy standard care, is superior to placebo in reducing the risk of major adverse CV events, including CV death, MI, and ischemic stroke. This phase 3, randomized, double-blind, placebo-controlled, event-driven trial is investigating the safety and efficacy of milvexian following a recent acute coronary syndrome. Patients are randomly assigned to receive milvexian at 25 mg twice daily or placebo. The primary outcome will be time to the first occurrence of a major adverse CV event,

defined as ischemic stroke, MI, or CV death. This trial is estimated to be completed by October 2026.³⁹

MABS

Abelacimab (MAA868; Anthos Therapeutics), osocimab (BAY 1213790; Bayer and Aronora), and xisomab 3G3 (AB023; Aronora) are mAbs that bind to FXI or FXIa. These agents are not metabolized by cytochrome P450, eliminating the potential for drug-drug interactions through this mechanism. These mAbs are predominantly eliminated by phagocytic cells and the reticuloendothelial system.²⁹

Osocimab and Xisomab Clinical Trials

A small double-blind phase 2 trial (NCT03612856) evaluated 2 doses of xisomab compared with placebo in patients with end-stage renal disease undergoing hemodialysis. The study demonstrated xisomab's safety, as it reduced the frequency of occlusive events necessitating hemodialysis circuit exchange without compromising hemostasis.⁴⁰ There are currently no dose reductions needed for renal or hepatic impairments.

Phase 3 clinical trials for osocimab and xisomab have not started, and confirmation from larger trials is needed before these agents are to be considered for approval and clinical use. Phase 3 clinical trials are ongoing for abelacimab.

Abelacimab Clinical Trials

LILAC-TIMI 76 (NCT05712200) is an ongoing phase 3 clinical study evaluating the efficacy and safety of abelacimab at 150 mg monthly compared with placebo in patients diagnosed with atrial fibrillation or atrial flutter. The study focuses on individuals who are traditionally considered at high risk for anticoagulation therapy because of elevated bleeding risk factors. Participants are required to have at least 1 significant bleeding risk factor, such as daily use of antiplatelet medication, history of bleeding in a critical anatomical area, renal disease, frailty, or a history of recurrent falls. The primary objective is to assess whether abelacimab can provide a safe alternative for anticoagulation in patients who are typically deemed too high risk for standard anticoagulation therapy. This study aims to address an important clinical need for patients who require thromboprophylaxis but have contraindications to current anticoagulation options. The study's estimated completion date is March 2025.⁴¹

Patients with malignancies are at an increased risk of thrombotic events and often need antithrombotic therapy for VTE prophylaxis. The phase 3 clinical ASTER trial (NCT05171049) is designed to evaluate the efficacy

and safety of abelacimab compared with apixaban in the treatment of cancer-associated VTE. This randomized, open-label, blinded end point evaluation compares monthly administrations of abelacimab 150 mg with apixaban 10 mg followed by 5 mg twice daily over a 6-month treatment period. The study is assessing the relative merits of these 2 anticoagulation strategies in patients with cancer-associated VTE. Primary end points include the incidence of bleeding events, rates of treatment discontinuation, and VTE recurrence. Investigators seek to provide valuable insights into optimal anticoagulation management for oncology patients at risk of thrombotic complications. This study is estimated to be completed in September 2025.⁴²

MAGNOLIA (NCT05171075) is a phase 3 multicenter, blinded end point study designed to evaluate the efficacy and safety of abelacimab 150 mg monthly compared with dalteparin in patients with VTE and concomitant gastrointestinal or genitourinary malignancies. Dalteparin will be administered daily at 200 IU/kg/d for the first month and then 150 IU/kg/d thereafter. During the 6-month treatment period, monthly administration of abelacimab is compared with daily injections of dalteparin. Primary end points encompass VTE recurrence rates, incidence of bleeding events, and treatment discontinuation rates. This investigation aims to provide valuable insights into the management of cancer-associated thrombosis, potentially offering an alternative to the current standard of care with a more convenient dosing regimen. This trial is projected to be completed in September 2025.⁴³

ASOs

Fesomersen (Ionis) is currently the only ASO in clinical development for thrombosis indications. This agent reduces the hepatic synthesis of FXI and has a limited degree of renal elimination.²⁸ In a phase 2 study (NCT02553889), fesomersen was investigated in patients with end-stage renal disease undergoing hemodialysis. The results indicated that fesomersen was well-tolerated and did not increase the incidence of major bleeding events compared with placebo.⁴⁴ Furthermore, the pharmacokinetics of fesomersen remained similar regardless of whether it was administered before or after hemodialysis.⁴⁴ Phase 3 studies are needed to confirm whether this agent can safely and effectively progress in clinical development.

LIMITATIONS AND FUTURE DIRECTIONS

The FXI inhibitors undergoing clinical trials have potential roles in anticoagulation therapy. Although clinical trials continue, there are various potential

indications for which FXI inhibitors could be indicated. Clinical indications in which DOACs are the mainstay of treatment and prevention, such as atrial fibrillation and VTE, are routes to explore with FXI inhibitors. Contraindications and patient populations in which DOACs are not currently used are also potential areas to dive into with these new agents. Testing in clinical contexts, such as acute coronary syndrome or ischemic stroke, where there is no foreseeable use of anticoagulants at this time, could be other indications to study. Data from early clinical trials of FXII inhibitors will provide insight regarding the potential path forward.

The use of these agents in real practice will require confirmation from larger clinical trials. The results of ongoing phase 3 clinical trials will either further confirm or exclude places in therapy for FXI inhibitors. If approved for clinical use, postmarketing trials will hold a lot of value regarding the safety profile of these agents as they enter practice for long-term use. 🌐

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Expanded Use of Long-Acting Injectables for HIV and HIV Prevention

As HIV treatment and prevention evolve, the use of long-acting injectables and their role in combating the HIV epidemic grows.

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DISCLOSURES

None.

Long-acting injectables (LAIs) are a relatively newer option for HIV treatment and prevention. Although injectable regimens may not be preferable to all patients due to fear of needles or limited transportation to the clinic, some people living with HIV (PLWH) may prefer infrequent injections rather than daily oral medications. Reasons for preferring LAIs can include challenges with adherence to oral medications or with stigma related to having these medications in their home. For patients facing these challenges, LAIs may significantly improve quality of life. Further, data continue to be published in different patient populations, showing that these injectable therapies remain safe and efficacious in a variety of patients.

LA Cabotegravir/Rilpivirine

LA cabotegravir/rilpivirine (LA CAB/RPV; Cabenuva; ViiV Healthcare) has been FDA approved since January 2021 as a complete regimen for the treatment of HIV in patients who are virologically suppressed. It can be administered either every 4 or every 8 weeks intramuscularly by a health care professional (HCP) and does not require an oral lead-in period. Outside of patients who are virologically suppressed, more recent data have emerged supporting its use in patients unable to achieve or maintain viral suppression on oral antiretroviral therapy (ART).

In a demonstration project done by the Ward 86 HIV clinic in San Francisco, California, 57 patients with viremia were started on LA CAB/RPV.¹ Among this cohort, 54 patients (95%) achieved virologic suppression by a median of 33 days. Of note, 1 patient did not achieve

viral suppression until after their fifth injection, and 1 patient required the addition of lenacapavir (LEN; Sunlenca; Gilead Sciences, Inc) to achieve viral suppression.

In a smaller study from the University of Mississippi Medical Center in Jackson, 12 patients with persistent viremia were started on LA CAB/RPV.² All patients achieved viral suppression within 3 months of starting therapy.

Additionally, a model-based analysis using a simulated cohort of patients similar to that of the Ward 86 clinic showed that LA CAB/RPV had substantial improvements in viral suppression, engagement in care, and survival over 3 years and beyond, with greatest benefit in patients with lower CD4 counts at therapy initiation.³ A commonality in these studies was that LA CAB/RPV was coupled with significant case management/social services, multidisciplinary support, and close follow-up.

Based on this growing body of data, the US Department of Health and Human Services HIV/AIDS guidelines and the International Antiviral Society (IAS)–USA HIV treatment guidelines were recently updated to recommend use of LA CAB/RPV on a case-by-case basis in select patients with persistent virologic failure who are unable to take oral ART despite intensive adherence counseling, who do not have evidence of resistance to CAB or RPV, and who have high risk for disease progression (CD4 count < 200/ μ L or history of AIDS-defining complications). Additionally, the IAS–USA HIV treatment guidelines recommend that patients be included in shared decision-making with their HCP, with intensive follow-up and case management services available.^{4,5} If virologic response is inadequate, the guidelines recommend drug resistance testing.

STRATEGIC ALLIANCE PARTNER



CAB for PrEP

LA CAB (Apretude; ViiV Healthcare) was approved as HIV preexposure prophylaxis (PrEP) in December 2021. It is administered intramuscularly by an HCP every 8 weeks and does not require an oral lead-in period. Its approval was based on the phase 2b/3 HPTN 083 study (NCT02720094), showing that LA CAB was superior to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada; Gilead Sciences, Inc) for PrEP in cisgender men and transgender women.⁶ A subsequent study, HPTN 084 (NCT03164564), showed that LA CAB was also superior to TDF/FTC in women.⁷ Additional substudies have been done from both HPTN 083 and 084 that further support the use of LA CAB.

In a follow-up analysis of HPTN 083, investigators looked at the efficacy rate of LA CAB after the first year of unblinded therapy and found that LA CAB maintained its superior efficacy compared with TDF/FTC, with a 65% reduction in incidence of HIV infection.⁸ In a subanalysis of HPTN 084 in pregnant women, which was presented at the 25th International AIDS Conference (AIDS 2024), LA CAB was shown to be safe and well tolerated, supporting the use and/or continuation of LA CAB in this population.⁹ There were also no apparent negative effects of LA CAB on infant outcomes.

Lenacapavir

LEN is the newest antiretroviral and is a first-in-class capsid inhibitor, which was FDA approved in December 2022.¹⁰ Not only does LEN represent a novel mechanism of action to treat HIV, but it is also the longest-acting injectable ART currently on the market.

After a short oral lead-in period, LEN is administered subcutaneously by an HCP every 6 months, which may provide a significant advantage to PLWH who struggle with daily medication adherence or have difficulty with more frequent transportation to the clinic. Its current labeled indication shows it is to be used in combination with other antiretroviral agents in heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 infection after failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations; this indication is based on the results of the CAPELLA trial (NCT04150068).¹¹

There are now several ongoing studies that may expand the use of LEN beyond treatment for patients with MDR HIV. For example, CALIBRATE (NCT04143594) was a phase 2 trial that showed the potential use of LEN in treatment-naïve patients, indicating that a phase 3 study in this population may be conducted in the future.¹²

At the 2024 Conference on Retroviruses and Opportunistic Infections, there was a case series presented of PLWH (n=34) who were placed on an injectable-only treatment regimen (CAB +/- RPV plus LEN). The patients in this series demonstrated resistance to RPV but faced significant social challenges and adherence issues with oral ART. Although this regimen is not FDA approved, 94% of the patients in this series achieved virologic suppression on this regimen.¹³ This series supports more research into injectable-only CAB/LEN regimens for PLWH with resistance who are unable to take standard oral medications.

LEN for PrEP


A topic of interest for LEN in 2024 seemed to be related to its use as PrEP. There are 5 phase 3 trials (the PURPOSE trials) ongoing for LEN in PrEP for different patient populations. The PURPOSE 1 trial (NCT04994509) results brought a standing ovation at AIDS 2024, as the findings demonstrated 100% efficacy and 0 cases of HIV when LEN was used for PrEP in high-risk cisgender African women (n = 2134) vs 16 cases on oral TDF/FTC and 39 cases on tenofovir alafenamide fumarate/FTC.¹⁴ The results of PURPOSE 1 were simultaneously published in the *New England Journal of Medicine*.

The results of the PURPOSE 2 trial (NCT04925752) were published at the end of November 2024.¹⁵ PURPOSE 2 explores PrEP in cisgender men, transgender women, transgender men, and gender nonbinary individuals and includes patients from the US, Argentina, Brazil, Mexico, Peru, Puerto Rico, South Africa, and Thailand. LEN had 99.9% efficacy in preventing HIV in this population, with only 2 incident cases in the LEN group (n = 2179).¹⁶

PURPOSE 3 will evaluate PrEP for cisgender women in the US, and PURPOSE 4 will evaluate PrEP among persons who inject drugs in the US. PURPOSE 5 is now enrolling patients interested in PrEP in the UK and France.

Of note, LEN currently comes with a high cost in the US, at an estimated \$15,600 per dose and approximately \$42,000 for the first year, including the oral lead-in. This significant financial burden makes it essential for pharmacists to assist with evaluating a patient's insurance and connecting them with Gilead patient assistance programs (PAPs).¹⁷ In some good news, however, Gilead recently signed royalty-free voluntary licensing agreements to generic manufacturers in 120 low- and lower-middle income countries to support low-cost access in high-incidence, low-resource countries.

Conclusion

Pharmacists who care for PLWH and patients interested in PrEP should remain informed about the emerging uses for CAB/RPV, CAB, and LEN to support optimizing ART regimens with these injectable options for a patient's lifestyle and financial feasibility. Utilizing these regimens is typically most successful with a multidisciplinary approach, specifically with pharmacists assessing for drug interactions, as well as providing support for navigating PAPs and candid patient counseling that emphasizes the importance of coming to injection appointments to avoid increasing drug resistance. 

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Heart Failure With Improved Ejection Fraction Is a Rising Focus in Cardiovascular Care

This subset of heart failure requires unique therapeutic considerations.

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DISCLOSURES

None.

Heat failure (HF) is a complex medical condition that affects millions of patients globally. The disease state is characterized by the heart's inability to adequately fill with or eject blood.¹ Suboptimal ventricular function can be due to compromises in the function or structure of the heart, and common causes include chronic comorbid conditions such as hypertension or ischemic heart disease.²

In the United States alone, it is estimated that more than 6.7 million Americans older than 20 years have HF. By 2030, that number is expected to rise to 8.5 million.² Additionally, HF readmission rates are a common metric for which hospitals can be financially penalized; therefore, optimizing care for patients with HF is a top priority among health care professionals for numerous reasons.

Hospital pharmacists are uniquely positioned to care for patients while they are acutely ill and identify medication-related issues that could have contributed to their hospitalization. In the outpatient setting, pharmacists can work to prevent future hospitalizations for patients with HF through various services, such as medication counseling and identifying barriers to care.

Classification and Treatment

The 2022 American Heart Association/American College of Cardiology HF guidelines formally introduced a new category of HF called HF with improved ejection fraction (HFimpEF).¹ Patients with HFimpEF previously had a left ventricular ejection fraction (LVEF) at 40% or less but then saw an improvement in their LVEF to greater than 40%. In the past, different terms such as *HF-recovered EF* and *heart failure with preserved*

ejection fraction (HFpEF)-improved were used to describe this subset of patients, but they did not accurately represent the true physiologic disease status.^{1,3}

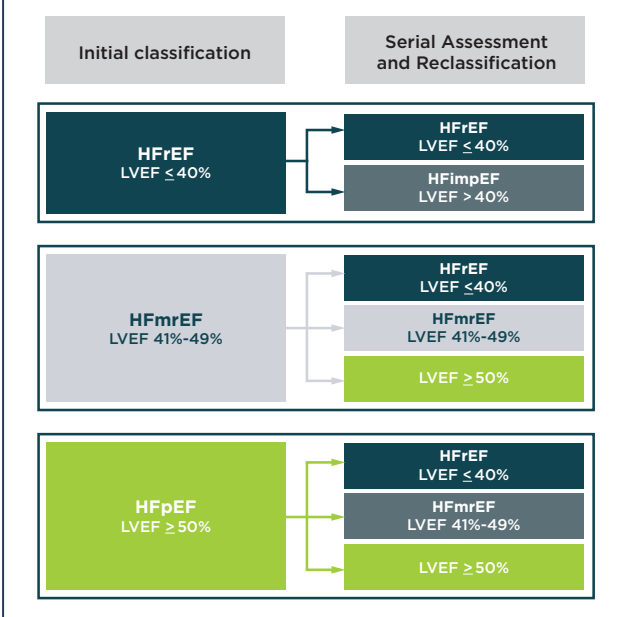
It is important to note that patients with HFimpEF have not fully recovered from HF, and they are not cured of the disease. Rather, these patients can be more accurately described as in remission from HF.¹ HF is a lifelong disease that requires long-term medical management, and patients can clinically improve or worsen throughout their treatment duration.

At one point, patients with HFimpEF were diagnosed with HF with reduced ejection fraction (HFrEF) and were ideally receiving a combination of guideline-directed medical therapy (GDMT) agents with an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, an angiotensin receptor–neprilysin inhibitor, a β -blocker, a sodium-glucose cotransporter 2 inhibitor, or a mineralocorticoid receptor antagonist. Currently, the guidelines recommend that patients with HFimpEF should be continued on GDMT to prevent HF and left ventricular dysfunction relapse.¹ Even patients who may become asymptomatic should continue treatment with GDMT because of the risk of HF relapse with GDMT withdrawal.

Evaluating a patient's LVEF is essential in diagnosing and managing HF. Ejection fraction, along with other laboratory values and symptoms, is used to classify patients into 1 of the 4 different subsets of HF and influences which treatments will be utilized.

Avoiding Misclassification of HFimpEF

Trending a patient's LVEF is important in tracking the trajectory of their HF and determining their clinical status (**Figure 1**). Analyzing a patient's LVEF from at least

FIGURE. Classification and Trajectories of HF Based on LVEF¹

HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

2 different occasions is especially important in patients with HFimpEF because they could be mistakenly treated as if they fell under a different category of HF. For example, if a patient with HF receives an echocardiogram in the hospital and their LVEF is 50%, they would be considered to have HFpEF. In this case, the guidelines would not support initiating a β -blocker unless there was a compelling indication. However, if the same patient had a previous echocardiogram showing their LVEF was 35%, they would now fall under the HFimpEF category. This would indicate that the patient's previous therapies helped improve their LVEF and that they should continue their medication regimen to prevent clinical worsening.

The TRED-HF Trial and Continued GDMT Use


The TRED-HF trial (NCT02859311) was conducted to examine the effects of a phased withdrawal of HF GDMT in patients with previous dilated cardiomyopathy. Between April 2016 and August 2017, 51 patients were enrolled in the study and randomly assigned to either continue their current GDMT regimen (n=26) or undergo a phased withdrawal of their GDMT agents (n=25). Patients were included in the study if they were asymptomatic and had their LVEF improved from 40% or less to 50% or greater. Patients also needed to have a normalized left ventricular end-diastolic volume indexed to body surface area and a plasma N-terminal fragment of the prohormone brain natriuretic

peptide (NT-proBNP) concentration of less than 250 ng/L.

The primary end point was HF relapse within 6 months and was defined by the presence of a reduction in LVEF by more than 10% and to less than 50%, an increase in left ventricular end-diastolic volume by more than 10% and to higher than the normal range, a 2-fold rise in baseline NT-proBNP concentration and to more than 400 ng/L, or clinical evidence of HF. Baseline characteristics were similar between the 2 groups, but idiopathic dilated cardiomyopathy, previous atrial fibrillation, and previous unplanned HF admissions were more common among patients in the treatment withdrawal group.

Within the first 6 months, 11 (44%) patients in the treatment withdrawal group met the primary end point of HF relapse compared with 0 patients assigned to continue treatment (event rate, 45.7%; 95% CI, 28.5-67.2; $P = .0001$). Additionally, secondary analyses showed worsening Kansas City Cardiomyopathy Questionnaire scores, reduced LVEF, and nonsignificant increases in NT-proBNP and LV volumes following the withdrawal of HF GDMT. Although a relatively small sample size limits the trial, the results suggest that continued GDMT usage in patients with HFimpEF is crucial in maintaining HF remission.⁴

Conclusion

Most of the published literature surrounding HF treatment is largely dominated by the topics of HFrEF and HFpEF. However, HFimpEF is a significant subset of HF that deserves attention. As medication experts, pharmacists provide valuable input in managing patients with HF and optimizing HF GDMT. 

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Cost-Effective Pharmacotherapy for Patients With Diabetes

Pharmacists can help patients with diabetes save money.

Matthew Butler, PharmD, BCACP

ABOUT THE AUTHOR

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DISCLOSURES

None.

In 2025, the Inflation Reduction Act is set to help people with Medicare Part D prescription drug coverage benefit from a new \$2000 out-of-pocket cap on prescription drug costs.¹ However, for some patients significantly below the poverty line, this cap may not be sufficient to support ongoing access to their diabetes medication. Additionally, patients who are not eligible for Medicare may continue to need financial assistance. With the increased cost of medicines, many patients are at risk for nonadherence, which can lead to worse glycemic management and increased microvascular and macrovascular complications from diabetes.² However, cost-effective strategies can help patients save money while optimizing their diabetes care.

Enroll Patients in Patient Assistance Programs

Many drug companies offer patient assistance programs (PAPs) for expensive, brand-name diabetes medications. PAPs are programs provided by manufacturers through which eligible patients can receive medications at no cost. Eligibility criteria differ based on the manufacturer but generally require patients to be at or below a certain household income threshold and have Medicare or no insurance coverage. Some programs require patients to apply for and be denied low-income subsidies through Medicare before approving PAP applications. Some common diabetes medications with associated PAPs are shown in the **Table**.

Manufacturer Savings Cards and Prescription Coupons

Many expensive brand-name medications, including glucagon-like peptide-1 (GLP-1) and GLP-1/glucose-dependent insulinotropic polypeptide receptor

agonists (for example, injectable semaglutide [Ozempic; Novo Nordisk] and tirzepatide [Mounjaro; Eli Lilly and Company]) have manufacturer savings cards to help bring down out-of-pocket costs. Patients present these cards to the pharmacist, who then bills them as secondary insurance. Of note, most savings cards require patients to have commercial or private insurance, and they exclude patients who have state or federal prescription drug coverage, such as Medicaid or Medicare. Some savings card payments may count toward deductibles, depending on individual insurance plans. Alternatively, patients can use prescription coupons such as GoodRx to help bring drug costs down. It is essential to inform patients that prescription coupons are not insurance and that drug savings may vary depending on the pharmacy used.³

Prescription coupon cards are not limited to medications, however. Many of my patients struggle to afford their continuous glucose monitors (CGMs), which monitor their blood glucose levels at home. Some CGMs, such as the Dexcom CGM, offer these coupons on their website.³ For patients who do not qualify for CGMs based on insurance requirements, Dexcom also offers an OTC product called the Stelo, intended for people not taking insulin who are at least 18 years old.⁴ Patients can buy the Stelo as a one-time purchase or through a subscription plan on Dexcom's website.⁴ For those who would like to use this long-term, investing in a subscription plan can save up to 15%. These devices are also eligible for flexible spending accounts and health savings accounts, pretax savings accounts that allow patients to set aside money for out-of-pocket health care expenses.⁵

TABLE. PAPs for Expensive Brand-Name Diabetes Medications		
Manufacturer	Medications	Eligibility criteria ^a
Novo Nordisk Inc	<ul style="list-style-type: none"> -Semaglutide injection (Ozempic) -Oral semaglutide (Rybelsus) -Liraglutide (Victoza) -Insulin degludec and liraglutide (Xultophy) -Insulin aspart (Fiasp) -Human insulin (Novolin N) -Insulin aspart (NovoLog) -Insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) -Insulin degludec (Tresiba) 	<ul style="list-style-type: none"> -Be a US citizen or legal resident -Have a total household income that is at or below 400% of federal poverty level -Have Medicare or no insurance -Not be enrolled in or qualify for any other federal, state, or government program, such as Medicaid, low-income subsidy, or VA benefits
AstraZeneca Pharmaceuticals LP	<ul style="list-style-type: none"> -Dapagliflozin (Farxiga) -Dapagliflozin and metformin hydrochloride extended release (Xigduo XR) 	<ul style="list-style-type: none"> -Be a US resident; citizenship is not required -Have a total household income at or below 300% of federal poverty level -Have Medicare or no insurance -Not be enrolled in or qualify for any other federal, state, or government program such as Medicaid, low-income subsidy, or VA benefits
Eli Lilly and Company	<ul style="list-style-type: none"> -Dulaglutide^b (Trulicity) -Insulin glargine (Basaglar) -Insulin lispro (Humalog) -Insulin isophane human (Humulin N) -Insulin lispro-aabc (Lyumjev) 	<ul style="list-style-type: none"> -Be a US resident -Have a total household income at or below 400% of federal poverty level^c -Have Medicare or no insurance -Not be enrolled in or qualify for any other federal, state, or government program such as Medicaid, low-income subsidy, or VA benefits
Boehringer Ingelheim Pharmaceuticals	<ul style="list-style-type: none"> -Linagliptin (Tradjenta) -Empagliflozin/linagliptin (Glyxambi) -Linagliptin/metformin HCl (Jentadueto) -Linagliptin/metformin HCl extended release (Jentadueto XR) -Empagliflozin/metformin HCl (Synjardy) -Empagliflozin/metformin HCl extended release (Synjardy XR) -Empagliflozin/linagliptin/ metformin HCl extended release (Trijardy XR) -Empagliflozin (Jardiance) 	<ul style="list-style-type: none"> -Be a US resident -Have a total household income at or below 250% of federal poverty level -Have no health insurance or insurance does not cover medication -Have Medicare but cannot afford medication and do not qualify for Medicare Extra Help Program (low-income subsidy)

HCl, hydrochloride; PAPs, patient assistance programs; VA, Veterans Affairs.

^aEligibility as of January 2025.

^bNew applications for brand-name dulaglutide (Trulicity) are currently not accepted, except for limited medical circumstances.

^cAt or below 400% of the federal poverty level for brand-name dulaglutide (Trulicity).

Avoid Unnecessary Duplicate Therapy

Although this trend has declined over time, some prescribers still prescribe GLP-1 receptor agonists alongside DPP-4 inhibitor therapy. Because these medications work in a similar mechanism (with

little to no additional synergistic benefit), patients are better off being on 1 of these medications only. In most cases, we opt for the GLP-1 agonist over DPP-4 inhibitors due to superior hemoglobin A_{1c} lowering and cardiovascular benefits with most of the

commonly used options (subcutaneous semaglutide, dulaglutide, and liraglutide). In contrast, DPP-4 inhibitors do not share this additional benefit.⁶

Use Combination Medications When Clinically Appropriate


One medication we use frequently in practice is empagliflozin/metformin HCl extended-release tablets (Synjardy XR; Boehringer Ingelheim) after a patient can tolerate and is stable on metformin and empagliflozin separately. One benefit is that this medication reduces pill burden and can be preferable for patients who are hesitant to add another drug to their regimen. Because empagliflozin/metformin HCl extended-release tablets contain extended-release metformin, patients may tolerate it better than the immediate-release formulation.⁶ Some medications contain 3 drugs, such as empagliflozin/linagliptin/metformin (Trijardy; Boehringer Ingelheim and Eli Lilly), 2 of which are brand-name medications (empagliflozin [Jardiance; Boehringer Ingelheim and Eli Lilly] and linagliptin [Tradjenta; Boehringer Ingelheim]). Switching to a medication like empagliflozin/linagliptin/metformin when clinically appropriate can save a patient from paying for 2 separate, expensive brand-name medications each month, potentially improving adherence and outcomes.

The use of combination drugs can also apply to common comorbidities associated with diabetes, such as hypertension. If patients can tolerate them, it may be beneficial to use combination blood pressure regimens (for example, ACE inhibitor/thiazide combinations) to aid with adherence, which can lead to better blood pressure control.

Spread Medicare Costs Out Over the Year

Starting in 2025, patients can spread

their out-of-pocket drug spend into monthly payments. Members who enroll will be billed by the plan and pay \$0 at the pharmacy point of sale. Patients may be a good fit for this option if they filled a prescription costing over \$600 or spent more than \$2000 on the Part D prescription plan in the prior plan year.⁷

To make the most of this program, counsel patients to enroll as early as possible in the year, as costs will be spread out over more months, lowering their monthly bill. Advise patients to visit their health or drug plan website or call their plan for more information.⁷ 

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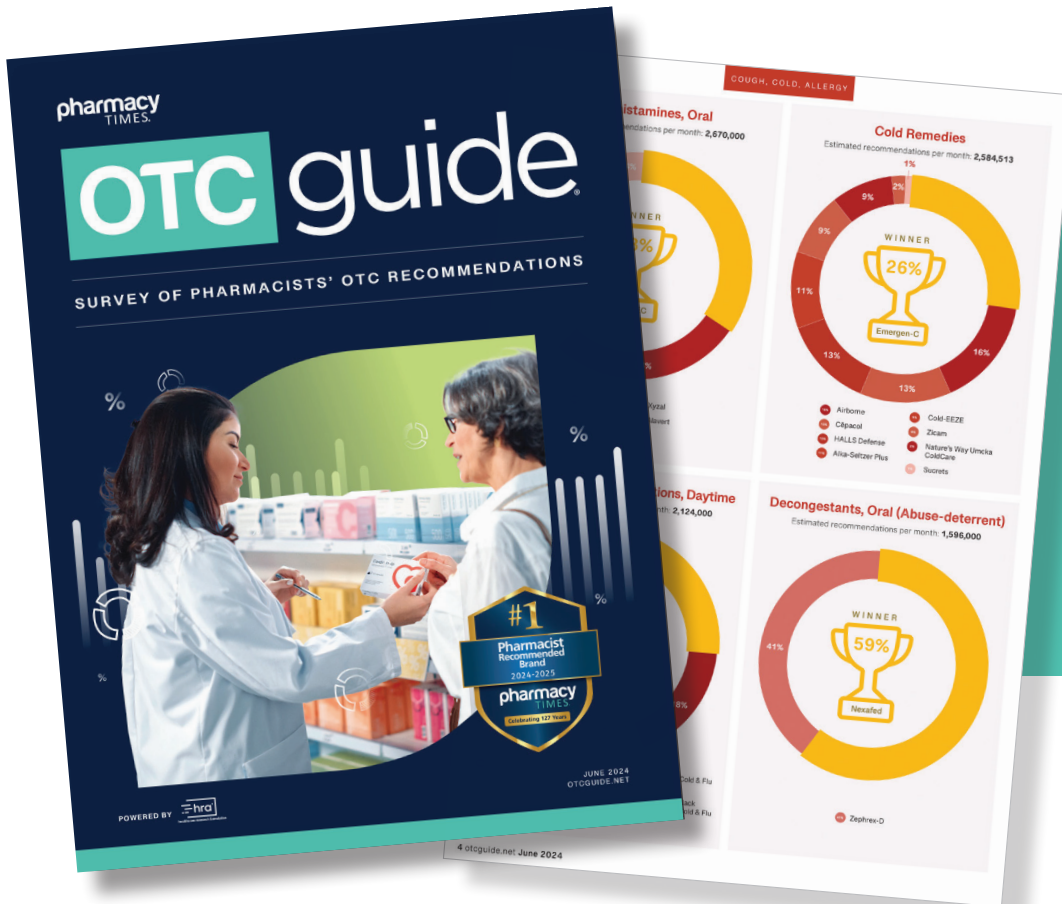
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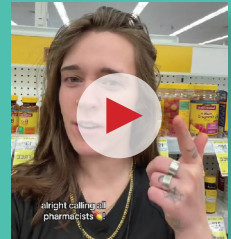
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Understanding the FDA Approval Process and PDUFA Dates

The FDA reviews NDAs and BLAs to approve medications for sale and marketing in the US with decisions required by the PDUFA date.

Julie B. Sibbesen, PharmD; and Jeanette Rich, PharmD

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Since 2015, the FDA has approved an average of 47 new medications each year. In 2024, there were 50 new drugs, with 48% approved as first in class; additionally, 52% received orphan drug designation targeting rare diseases, and 66% used one or more expedited programs, including fast track designation, breakthrough therapy designation, priority review designation, and accelerated approval.¹

Federal Food, Drug, and Cosmetic Act and Public Health Service Act

The Federal Food, Drug, and Cosmetic (FD&C) Act was passed by the US Congress in 1938. The act granted authority to the FDA to regulate the safety of food, drugs, medical devices, and cosmetics. This legislation replaced the Pure Food and Drug Act of 1906 and was introduced following the death of more than 100 patients who ingested elixir sulfanilamide.²

In 1944, the Public Health Service (PHS) Act was enacted, providing a legislative framework for the provision of public health services. This act encompasses biological products and defines them as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, and analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings.” Biologics also meet the definition of drugs under the FD&C Act.³

Approval Process

To ensure that medications marketed in the US are safe and effective, the FDA’s Center for Drug Evaluation and Research (CDER) reviews new drug applications (NDAs). CDER oversees both prescription

and nonprescription or OTC drugs, with OTC drugs being brought to the market following the NDA process or through an OTC monograph. It is the responsibility of the company seeking approval to analyze the medication and subsequently submit supporting evidence for review.⁴ This evidence is derived from data collected from human clinical trials, including information on safety, efficacy, dosages, indications, and drug metabolism of a medication. Based on this research, the FDA decides whether to approve the application to market the medication.⁵

Types of Drug Applications

Types of applications submitted to CDER include investigational new drug, NDA, abbreviated NDA, OTC drug, and biologic license application (BLA).⁶ This article specifically focuses on NDAs and BLAs.

NDAs are the formal requests that drug sponsors submit to the FDA for approval of new pharmaceutical agents for sale and marketing in the US.⁷ Biological products, a subset of drugs, are regulated by both CDER and the Center for Biologics Evaluation and Research. These products fall under the FD&C Act but are licensed under the PHS Act, and a BLA is required for biologic products that need licensure under the PHS Act.³ The primary goal of both NDAs and BLAs is to provide sufficient evidence for the FDA to make critical decisions regarding the medication.

Key decisions by the FDA for NDA/BLA submissions include the following⁷:

- Safety and effectiveness
- Appropriate package insert
- Adequate manufacturing practices

Changes to NDAs or BLAs, such as updates in packaging, labeling, inactive

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TABLE 1. Applications to Market an NDA, ANDA, or Biologic⁹

Index
Labeling: Draft or final printed labeling
Summary
Chemistry section
Nonclinical pharmacology and toxicology section
Human pharmacokinetics and bioavailability section
Clinical microbiology section
Clinical data section
Safety update report
Statistical section
Case report tabulations
Case report forms
Patent information on any patent that claims the drug/biologic
A patent certification with respect to any patent that claims the drug/biologic
Establishment description
Debarment certification
Field copy certification
User fee cover sheet
Financial disclosure information
Other (specify)

ANDA, abbreviated new drug application; NDA, new drug application.

ingredients, or indications, are handled through supplemental applications, referred to as sNDAs and sBLAs. A medication would require an NDA or BLA if it was changed to have a different active ingredient, different route of administration, or different dosage forms that would necessitate an additional clinical trial to establish efficacy and safety. These are still approved through CDER, with changes incorporated into labeling and prescribing information, and the drug can then be marketed and prescribed according to the updated and approved changes.⁸

Prescription Drug User Fee Act

The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and collects user fees on human drug applications for review, including applications for approval of a new drug submitted under the FD&C Act or licensure of certain biological products of the PHS Act (Table 1).^{9,10} PDUFA was introduced to address concerns over the FDA’s ability to review and approve drugs in a timely manner. Congress reauthorizes PDUFA every 5 years (currently

PDUFA VII), providing an opportunity to enhance the program.

Prior to the PDUFA, average approval decision times were between 21 and 29 months. The time is now half that, with 10 months being the average. For drugs designated with priority review, the timeline is reduced to 6 months from when the application is accepted.¹¹ Priority review designations are granted to medications that provide treatment of disease states that previously did not have any available options or may offer major advances in treatment.⁵

PDUFA dates refer to the latest date by which the FDA must respond to NDAs or BLAs.¹² Once the FDA accepts a filing for the approval of a drug, the agency must complete its review process within 6 or 10 months, depending on whether the application was designated as a priority or standard review.⁵ Overall, the PDUFA date serves as the anticipated FDA approval date, if approved (Table 2).¹²⁻¹⁴

Examples

The FDA approved benzgalantamine (Zunveyl; Alpha Cognition Inc), a novel oral therapy, for the treatment of Alzheimer disease, on July 26, 2024. The manufacturer submitted the NDA on September 27, 2023, with an original PDUFA date of July 27, 2024—10 months from submission. Studies demonstrated that benzgalantamine, a prodrug previously known as ALPHA-1062, achieves the same therapeutic effects as galantamine with improved gastrointestinal tolerability and without the incidence of insomnia impacting adherence and patient quality of life.¹

The FDA’s decision regarding injectable nivolumab and hyaluronidase (Opdivo Qvantig; Bristol Myers Squibb) was made on December 27, 2024. This decision was made 2 days in advance of the PDUFA date of December 29, 2024, which had moved up from its original date of February 28, 2025. Nivolumab, a PD-1 immune checkpoint inhibitor used to treat several types of cancer, is currently administered as a 30-minute intravenous infusion every 2 to 4 weeks. However, the BLA sought approval to administer the medication subcutaneously. This approval makes nivolumab the first PD-1 inhibitor approved for subcutaneous administration, which would be more convenient for patients.¹³

Complete Response Letters

After reviewing NDAs or BLAs, the FDA may either approve the application or issue a complete response letter (CRL). A CRL is a regulatory action indicating

TABLE 2. PDUFA Dates in 2025¹⁴

Generic (brand or pipeline name as applicable; manufacturer)	Route	Indication	Application	PDUFA
Reproxalap (ADX-102; AbbVie/Aldeyra Therapeutics)	Ophthalmic	Dry eye	NDA	April 2, 2025
Elamipretide (MTP-131; Stealth BioTherapeutics)	Subcutaneous	Barth syndrome	NDA	April 29, 2025
Sodium Dichloroacetate (SL-1009; Saol Therapeutics)	Oral	PDCD	NDA	May 27, 2025
Hydrocortisone (ET-400; Eton Pharmaceuticals)	Oral	Adrenocortical insufficiency	NDA	May 28, 2025
Acoltremon (AR-15512; Alcon/Aerie Pharma)	Ophthalmic	Dry eye	NDA	May 30, 2025
Clesrovimab (MK-1654; Merck & Co)	Intramuscular	RSV infections	BLA	June 10, 2025
Sebetralstat (KVD900; KalVista Pharmaceuticals)	Oral	Hereditary angioedema	NDA	June 17, 2025
Lenacapavir (GS-6207; Gilead)	Oral; Subcutaneous	Prophylaxis to reduce risk of sexually acquired HIV-1	NDA	June 19, 2025
Copper Histidinate (CUTX-101; Zydus/Sentynl Therapeutics/Fortress Biotech/Cyprium Therapeutics)	Subcutaneous	Menkes disease	NDA	June 30, 2025
Sepiapterin (PTC923; PTC Therapeutics/Censa Pharmaceuticals)	Oral	Phenylketonuria	NDA	July 29, 2025
Aceclidine (LNZ100; LENZ Therapeutics)	Ophthalmic	Presbyopia	NDA	August 8, 2025
Brensocatic (INS1007; AstraZeneca/Insmed)	Oral	Bronchiectasis	NDA	August 12, 2025
Vatiquinone (PTC743; Dainippon Pharmaceutical/ Edison Pharma/PTC Therapeutics)	Oral	Friedreich's ataxia	NDA	August 19, 2025
Donidalorsen Sodium (IONIS-PKK-LRx; Ionis Pharmaceuticals)	Subcutaneous	Hereditary angioedema	NDA	August 21, 2025
Zopapogene Imadenovec (PRGN-2012; Precigen)	Subcutaneous	RRP	BLA	August 27, 2025
Rilzabrutinib (PRN1008; Sanofi/Principia Biopharma)	Oral	Immune thrombocytopenia	NDA	August 29, 2025
Lecanemab (Leqembi; Eisai/Biogen)	Subcutaneous	Alzheimer's disease	BLA	August 31, 2025
Paltusotine (Paltusotine; Crinetics Pharmaceuticals)	Oral	Acromegaly	NDA	September 25, 2025
Aficamten (CK-274; Cytokinetics)	Oral	Hypertrophic cardiomyopathy	NDA	September 26, 2025
Riboflavin 5'-Phosphate (Epioxa; Glaukos)	Ophthalmic	Keratoconus	NDA	October 20, 2025
Plozasiran (ARO-APOC3; Arrowhead Pharmaceuticals)	Subcutaneous	FCS	NDA	November 18, 2025
Lerodalcibep (LIB003; LIB Therapeutics)	Subcutaneous	Hypercholesterolemia	BLA	December 12, 2025

BLA, biologics license application; FCS, familial chylomicronemia syndrome; NDA, new drug application; PDUFA, prescription Drug User Fee Act; PDCD, pyruvate dehydrogenase complex deficiency; RRP, recurrent respiratory papillomatosis; RSV, respiratory syncytial virus.

that the application cannot be approved in its current form. This decision may arise from concerns related to key factors such as safety and effectiveness, labeling, or Good Manufacturing Practices. In response, drug companies have several options: they can withdraw the application, request a hearing, or resubmit the application after making the necessary updates.¹⁵

Examples

A total of 16 medications in 2024 received a CRL due to various reasons. Most recently, Lykos Therapeutics received a CRL for its midomafetamine-assisted psychotherapy for posttraumatic stress disorder, with a request to provide additional phase 3 trial data examining safety and efficacy.^{14,16,17} Regeneron

Pharmaceuticals, Inc, was also issued a CRL for linvoseltamab in relapsed/refractory MM due to a preapproval inspection at a third-party manufacturer, with a plan for reinspection by the FDA.¹⁷ Both parties will need to submit additional information required for the FDA to reconsider approval of these medications.

Conclusion

The FDA's drug approval process involves several key components and essential information for evaluation. To initiate the review of new medications, drug sponsors submit NDAs or BLAs. This allows the FDA to assess the drug's safety and effectiveness, packaging labeling, and manufacturing processes. The FDA is required to decide by the established PDUFA date, which can be either 6 or 10 months after submission. If the application is approved, this date becomes the official approval date. However, if a CRL is issued, sponsors can either withdraw their application or resubmit it for review. 🌐

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Enhancing Patient Care in Heart Failure–Related Anemia Through Improved Communication, Monitoring, and Education

Pharmacists can optimize management of this condition with intravenous iron therapy guidance.

Aislinn Antrim, Managing Editor

Although ensuring medication adherence and implementing intravenous (IV) iron therapy remain significant challenges, pharmacists can enhance care for patients with heart failure–related anemia by providing improved intrateam communication, closely monitoring patients, and providing patient education. According to guidelines from the European Society of Cardiology (ESC), American College of Cardiology (ACC), and American Heart Association (AHA), iron deficiency is defined as a serum ferritin level of less than 100 µg/L or between 100 and 300 µg/L with a transferrin saturation (TSAT) of less than 20%.¹

During a *Pharmacy Times*[®] Clinical Forum in Chicago, Illinois, moderator Francesco Ferrante, PharmD, a clinical cardiology pharmacist at Northwestern Medicine, noted some differences in definitions. For instance, the ESC also considers serum ferritin below 100 ng/mL or levels between 100 and 299 with a TSAT less than 20%.²

“We’re starting to see some observational studies that show that serum iron concentration and TSAT may actually be more closely linked to prognosis rather than purely serum ferritin alone,” Ferrante said during the event. “This may be a better indicator of patients who are truly iron deficient who may benefit from therapies.”

Iron deficiency can be classified as absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin 100–300 ng/mL with TSAT < 20%). Absolute iron deficiency is characterized by depletion of iron stores due to low intake, poor absorption, increased demand, or chronic hemorrhage, whereas functional iron deficiency is caused by impaired mobilization of stored iron due to inflammation and elevated hepcidin levels.³

Among patients with heart failure, the prevalence of iron deficiency is approximately 50%, although it increases to 80% in acute heart failure exacerbations, and higher rates are observed in New York Heart Association (NYHA) class 3 and 4.¹ Iron deficiency anemia occurs in approximately 30% of stable heart failure patients and escalates to 50% among those who are hospitalized, contrasting sharply with less than 10% prevalence in the general population.¹

The panelists agreed that their protocols can vary when deciding which patients are eligible for IV iron therapy, although most said their upper limit for comfort would be patients with ferritin levels at or above approximately 500 µg/L. Panelist Christine Cunningham, PharmD, BCCP, a cardiology clinical pharmacist at Northwestern Memorial Hospital, explained that in some cases, ferritin levels can be falsely elevated, such as in patients with low TSAT and iron stores. In such cases, she said she leans toward continuing with IV iron treatment.

Ferrante said he has noticed a decrease in patients using oral iron, particularly among those on warfarin therapy who are at high risk for gastrointestinal bleeding. Although he noted that the IRONOUT-HF trial (NCT04080908) did not demonstrate clinical benefit, other studies have shown that oral iron may still be useful, especially when higher doses are not suitable. Therefore, Ferrante said he is still willing to use oral iron in his practice, emphasizing that, “something may be better than nothing.”

The treatment landscape for anemia has changed significantly in recent years, with multiple trials supporting the use of ferric carboxymaltose (FCM) injection (Injectafer; Daiichi Sankyo). For instance, the CONFIRM-HF trial (NCT02026635) administered IV FCM in doses ranging from 500 to 2000 mg at various intervals. Data showed significant improvement in the 6-minute walk test and reduced hospitalizations for worsening heart failure, with no severe adverse reactions reported.⁴ Furthermore, the FERRIC-HF trial (NCT00125996) compared 200 mg IV FCM weekly vs placebo in 304 patients and found a statistically significant improvement in NYHA functional status. Specifically, 47% of patients who received FCM showed improvement vs 30% in the placebo group, and self-reported scores were also significantly better in the FCM arm.⁵

In the AFFIRM trial (NCT00000556), investigators focused on cardiovascular death and hospital admissions, differentiating patient outcomes based on hemoglobin levels. Investigators found a similar adverse effect rate with FCM compared to placebo.⁶ Further, the IRONMAN

trial (NCT02642562) showed a statistically significant decrease in composite outcomes of cardiovascular death and hospital admissions compared with usual care.⁷

Taken together, these data and current guidelines suggest IV iron supplementation for symptomatic individuals with iron deficiency in heart failure, according to the panelists. Ferrante noted that ESC guidelines specify particular formulations such as FCM or ferric derisomaltose, whereas AHA/ACC/Heart Failure Society of America guidelines recommend screening without specific suggestions regarding IV formulations. Oral iron supplementation is generally not recommended for patients with heart failure because of poor absorption.^{1,2}

However, IV formulations have their own challenges, according to the panelists. For instance, clinicians have debated the benefits of high-dose IV iron vs multidose regimens. Although high-dose IV iron is generally favored, potential disadvantages include infusion site reactions and the risk of hypophosphatemia, which can arise from increased FGF23 receptor activity leading to excessive phosphate excretion in the kidneys. Formulary challenges are also common for clinicians looking to use high-dose IV iron.

“We just institutionally have had a lot of reticence to add the high-dose formulations to formulary, particularly ones that are 2-dose strategies that are very expensive on the inpatient side and that potentially could be cost generating on the outpatient side,” said panelist Sajni Patel, PharmD, BCCP, clinical pharmacy coordinator of cardiology services at UChicago Medicine. “I can only really speak to the iron sucrose [200 mg every 48 hours for] 5 doses and hope that they stay there for 10 days. A lot of times, we just don’t get all the doses in, so then it’s a lot of coordination on the outpatient side, hoping that you can get the patient their drug and that it’s paid for, and that they can get an infusion chair and that all of it works out when they’re passed off to somebody else.”

Panelist Andrew Johnson, PharmD, clinical pharmacist specialist in cardiology at UChicago Medicine, noted that the pharmacist on the inpatient team typically coordinates those handoffs and dose changes.

“It’s usually the pharmacist on the inpatient team on the day of discharge, which unfortunately can be a large burden because you’re trying to coordinate [everything] within a specific time window before [the patient] leaves the hospital while you’re taking care of everybody else,” Johnson said. “Unfortunately, our providers aren’t putting in the referrals, don’t know how to dose it, so...you have to hold their hand through it.”

Patient monitoring is crucial and is a key area where pharmacists are needed. For instance, for patients who

may be at risk of iron overload, pharmacists are particularly qualified to consider their entire care plan when making dosing decisions. Panelist Alissa Shega, PharmD, BCCP, an inpatient cardiology pharmacist at UChicago Medicine, said she considers blood products that the patient may also be receiving. For each unit of red blood cells a patient receives, she subtracts 1 dose of iron.

“I do something similar in that gray area where you have an anemic patient who’s got some signs of active [infection] or you’re depleting blood products because their hemoglobin drops below a threshold for [coronary artery disease] with heart failure, for example,” Patel said. “In those folks, I tend to be a little more reticent to give them a full dose if their iron studies are borderline.”

Similarly, panelist Nicole Saccone, PharmD, a clinical pharmacy specialist at Advocate Aurora Health, said she closely monitors postoperative cardiac surgery patients and does not routinely administer IV iron to patients soon after surgery.

“I feel like we wait for them to get out of that acute phase, and then a lot of them come out with transfusion needs. Because of that, I stay away from [IV iron],” Saccone said. “So, most of the patients I’m [administering IV iron] in, it’s like a readmission after a cardiac surgery...and not like a routine [postoperative procedure].”

Although guidelines provide a framework for managing anemia in heart failure, the optimal approach requires individualized patient assessment. Factors such as ferritin and TSAT levels, the presence of inflammation, and the risk of gastrointestinal bleeding must be carefully considered when determining the most appropriate treatment, whether oral or IV iron. Recognizing the potential for falsely elevated ferritin levels and the limitations of oral iron in certain populations underscores the need for careful clinical judgment and a collaborative approach to patient care. Further research is needed to optimize treatment protocols and ensure that all patients with heart failure–related anemia receive the most effective and appropriate therapy.

Pharmacists play a crucial role in navigating all of these considerations and treatment decisions. By staying abreast of evolving guidelines and diagnostic criteria, such as the increasing importance of TSAT alongside ferritin levels, pharmacists can effectively identify and advocate for appropriate treatment strategies. Through improved intrateam communication, diligent patient monitoring, and comprehensive education, pharmacists can optimize medication adherence, facilitate timely IV iron therapy when indicated, and ultimately improve outcomes for this patient population. 🌐