

# PHARMACY PRACTICE IN FOCUS: HEALTH SYSTEMS™

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Pharmacists' Role in Antibiotic Stewardship: Understanding Spectrums to Combat Resistance

KARDARIUS BYES FELTON, PHARMD CANDIDATE; RON WELCH, PHARMD, BCPS, BCIDP; AND VICTORIA BYERLY, PHARMD

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Paradoxical Hypotension After Inadvertent Intravenous Administration of Epinephrine

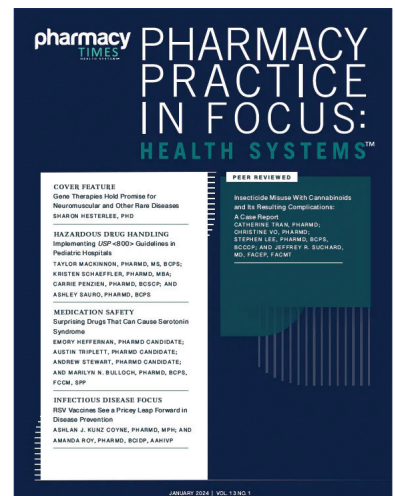
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Submissions are welcome for peer review and original research that are focused on the work and practice of pharmacy professionals.

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## Publisher's Note

# Advancing Patient Safety and Health Care Efficiency: The Critical Role of Pharmacists

**P**armacists play a pivotal role in advancing patient safety, optimizing health care efficiency, and managing complex therapies. By addressing medication errors, implementing cost-saving strategies, and navigating the challenges of novel treatments, pharmacy professionals contribute to improved treatment outcomes and enhanced care delivery.

In a peer-reviewed case report on page 16, authors Kwang Yoon, PharmD, BCPS, BCEMP; Stephanie Mojumdar, PharmD; Rodney Fullmer, DO, MBS, FACEP, FACOEP; and Kimberly McCarthy, MS, BSN, RN, discuss the case of a 50-year-old man with mild allergic symptoms who was mistakenly given a high dose of intravenous epinephrine (1 mg) instead of the intended 0.3-mg intramuscular injection. This led to the patient experiencing chest pain, abnormal electrocardiogram findings, elevated cardiac enzymes, and prolonged hypotension. The patient's condition improved with fluid resuscitation, avoiding the need for vasopressors or invasive interventions, and he was discharged after stabilization. This case highlights the rare paradoxical hypotensive effects of epinephrine overdose and underscores the importance of implementing safeguards, such as prefilled epinephrine auto-injectors, to prevent dosing errors and enhance patient safety.

In the peer-reviewed case description on page 21, authors Miranda Beau-doin Rampone, PharmD, MSCS, CSP; Bryce A. Edwards, PharmD, RPh; Allison Spaulding, PharmD; and Leslie Ochs, PharmD, PhD, BCPS, discuss the significant impact of an infusion and specialty clinical pharmacist (ISCP) position at a Veterans Affairs (VA) health care system in improving cost efficiency and satisfaction among veterans and specialty providers. Over \$1.3 million in annual projected cost avoidance was achieved through medication conversions and dose optimizations, while 89% of veterans and 94% of providers expressed high satisfaction with the ISCP's services. These findings emphasize the value of ISCPs in optimizing specialty medication use, enhancing patient care, and supporting health care teams in both VA and private sector clinics.

In a peer-reviewed case report on page 12, authors Jordan Krumanocker, PharmD, CPP, BCACP; and Geena Eglin, PharmD, BCACP, CSP, CPP, describe a case of a 61-year-old woman experiencing a probable infusion reaction during her first evinacumab-dgnb (Evkeeza; Regeneron Pharmaceuticals, Inc) home infusion, marked by a drop in heart rate and blood pressure, dizziness, and shortness of breath, requiring discontinuation of the infusion and the administration of emergency treatment. Evinacumab-dgnb, an angiopoietin-like 3 inhibitor, is a novel cholesterol-lowering agent approved for treating homozygous familial hypercholesterolemia. The report highlights safety concerns with evinacumab, limited clinical practice data on its use, and the need for more research on infusion reactions and potential strategies to mitigate them.

These cases underscore the diverse and essential contributions of pharmacists in improving patient care, reducing costs, and addressing safety concerns. From preventing medication errors to managing complex therapies and enhancing health care efficiency, these peer-reviewed papers highlight the critical role of pharmacy professionals in navigating the evolving health care landscape.

Warm regards,  
**Mike Hennessy Jr**  
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# Site of Care Restrictions: There Are Risks and Rewards, but for Whom?

Curtis E. Haas, PharmD, FCCP, Editor in Chief

## 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, a case report by authors Jordan Krumanocker, PharmD, CPP, BCACP; and Geena Eglin, PharmD, BCACP, CSP, CPP, describes an infusion reaction during treatment with evinacumab-dgnb (Evkeeza; Regeneron Pharmaceuticals, Inc), a monoclonal antibody approved for the treatment of homozygous familial hypercholesterolemia.<sup>1</sup> This is a relatively new drug that is rarely used and has little published experience related to the safety of this treatment and what clinicians should expect when initiating therapy. While this article is noteworthy for expanding awareness of the potential risks of evinacumab infusions, I find it even more valuable for the concerns it highlights relating to alternative sites of care, especially for the first infusion of an infrequently used drug.

In this case report, the female patient was forced by payer policy to receive this drug at home for the first time, likely being administered by a home care nurse who had no experience whatsoever with this drug. The drug was also provided by a specialty pharmacy that otherwise had no relationship with this patient, for the sake of presumably saving the payer some money. After experiencing an acute infusion-related reaction, the patient was rushed to an emergency department to receive treatment for the adverse effect. Fortunately, the patient made a full recovery. However, the question remains: Is at-home administration really a safe strategy for the first infusion of a drug with which the health care professionals involved have little to no experience? Also, more importantly, this drug is no longer considered to be a treatment option for this patient, who is likely destined to suffer from premature vascular disease

due to undertreated familial hyperlipidemia. Further, there is a reasonable chance that if she had therapy initiated in a proper setting involving a multidisciplinary team that was familiar with managing infusion reactions, she could have been supported through the infusion and allowed to receive future doses of the drug with proper precautions in place. Saving a few dollars by using an alternative site of care may have destined this patient to ineffective treatment options and premature onset of cardiovascular disease.

This case report raises the question: How did we get to a point where payers will rationalize forcing patients into alternative sites of care to receive often complex therapies from people who otherwise have no therapeutic relationship with the patient? It is certainly not welcomed by the specialty team ultimately responsible for the treatment decisions and the patient outcomes resulting from those decisions, and it is not a safe thing for the patient. It is recognized that for patient convenience and perhaps lower out-of-pocket costs, the use of home infusion or alternative treatment centers may be an option, but that determination should be based on shared decision-making between the patient and their care team. That shared decision-making should include an assessment of the risk inherent to the treatment involved, previous tolerance of the therapy, and any patient-specific factors. For the case reported in this issue, it is highly unlikely anyone would have considered giving the first infusion of a new drug with little safety data in the patient's home to be a clinically sound plan. If the reaction had been more severe and the patient had been seriously harmed or died because of delays in emergency treatment, it

would have been a tragedy with much of the liability likely coming back to those who ordered the treatment and not those who wrote the restrictive payer policy.

Plain and simple, the alternative site of care challenge comes down to money. I have sat through several meetings in which a policy is explained on the basis that health centers, especially academic health centers, are paid too much to provide this care and that it can be provided at a much lower cost in a strip mall infusion center or the patient's home. The health centers defend their costs based on overhead and availability of comprehensive services for managing all levels of complexity of infusion therapy; however, one thing that is not fully discussed during these meetings is that health centers are paid higher rates for infusion because the payers have agreed contractually to those rates. The payer representatives present it as though they are forced to pay a higher cost billed by the provider, when they are only required to pay what they contractually agreed. Why would a payer agree to terms that on the surface are disadvantageous to the payer and their employer clients? It is certainly not because their contract negotiators are naive or dim. Provider agreements with large medical centers are very complex, and there is a lot of "horse trading" that is involved. The payer wants commodity rates for common admissions, procedures, and tests to establish community rates for those high-volume charges. Further, to ensure complex services are available in the community, there are often concessions for specialized care or lower volume tests and procedures. From the health systems' perspective, this allows the losses on commodity cases to be made up on specialty cases and overall have

a sustainable financial position.

Once the ink on the contract is dry, all too often payer policy changes start to occur that cherry-pick options from the medical center, such as infusion and high-cost diagnostic procedures, that are profitable. The stand-alone infusion centers or diagnostic centers are not in the same position of being able to negotiate losers and winners across a broad spectrum of services and therefore must negotiate more competitive rates for the narrow spectrum of services they provide. This cherry-picking on the part of payers is disingenuous and violates the spirit, if not necessarily the letter, of a payer-provider contract.

Many health centers have decided to respond by getting into the community-based infusion center business to compete with stand-alone infusion centers. However, this approach runs the risk of unnecessarily duplicating resources in order to not lose business, which, in the big picture, further increases the cost of health care. Others have negotiated lower rates for lower complexity infusion services to remove the financial incentive to shift patients to stand-alone treatment centers, but many payer policies have been written in a way to exclude any health system–owned infusion sites from consideration.

Currently, it is not entirely clear what the best answer is, but payers and providers need to come to the table to make sure there are safe approaches that balance good care with reasonable costs. Furthermore, if infusion care is not one of the concessions the payers are willing to make in complex payer agreements, that should be defined at the negotiation table and not picked out of the agreement after the deal is finalized. 🌐



# Pharmacists' Role in Antibiotic Stewardship: Understanding Spectrums to Combat Resistance

Pharmacists ensure responsible antibiotic use, combating resistance through tailored therapies.

Kardarius Byes Felton, PharmD candidate; Ron Welch, PharmD, BCPS, BCIDP; and Victoria Byerly, PharmD

## ABOUT THE AUTHORS

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**Victoria Byerly, PharmD**, is a clinical pharmacist at Methodist Dallas Medical Center in Texas.

Pharmacists play a critical role in the management of antibiotics, particularly as antibiotic resistance continues to rise. Understanding the spectrum of antibiotics, narrow- or broad-spectrum, is essential for pharmacists to make informed decisions in both empirical and definitive therapy. This knowledge enables pharmacists to select the most appropriate treatment for infections, monitor patient outcomes, and adjust therapy as needed. Failure to appropriately target the causative pathogen can lead to increased resistance, treatment failures, and adverse outcomes.

Antibiotics transformed human health by reducing mortality from severe infections, marking their discovery as one of the most impactful scientific medical advancements.<sup>1,2</sup> Clinically, the antibiotic spectrum of activity, which defines bacterial pathogen targets and elimination capabilities, is the key to their efficacy.

Antibiotics are classified as broad-spectrum or narrow-spectrum based on their ability to treat different bacterial groups.<sup>3</sup> Narrow-spectrum antibiotics treat only very specific bacterial strains, whereas broad-spectrum antibiotics can target a larger range of pathogens.<sup>3,4</sup> Understanding the antibiotic's spectrum is crucial to determine its use as empirical or definitive therapy in clinical practice, but to do so, we need to understand how bacteria are further classified.

## Gram-Positive Bacteria

Gram-positive bacteria, including species such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecium*, are clinically significant pathogens that can cause a variety of infections. Gram-positive bacteria have far thicker cell walls than

those of gram-negative bacteria, providing structural integrity and protection. This thick peptidoglycan layer is vital for the survival of these organisms, making them a primary target for antibiotics such as  $\beta$ -lactams, which inhibit cell wall synthesis.<sup>5-7</sup> In 1995, gram-positive organisms accounted for 62% of all bloodstream infections (BSIs), increasing to 76% by 2000, whereas gram-negative organisms were responsible for 22% and 14% of BSIs in these years, respectively.<sup>8-10</sup>

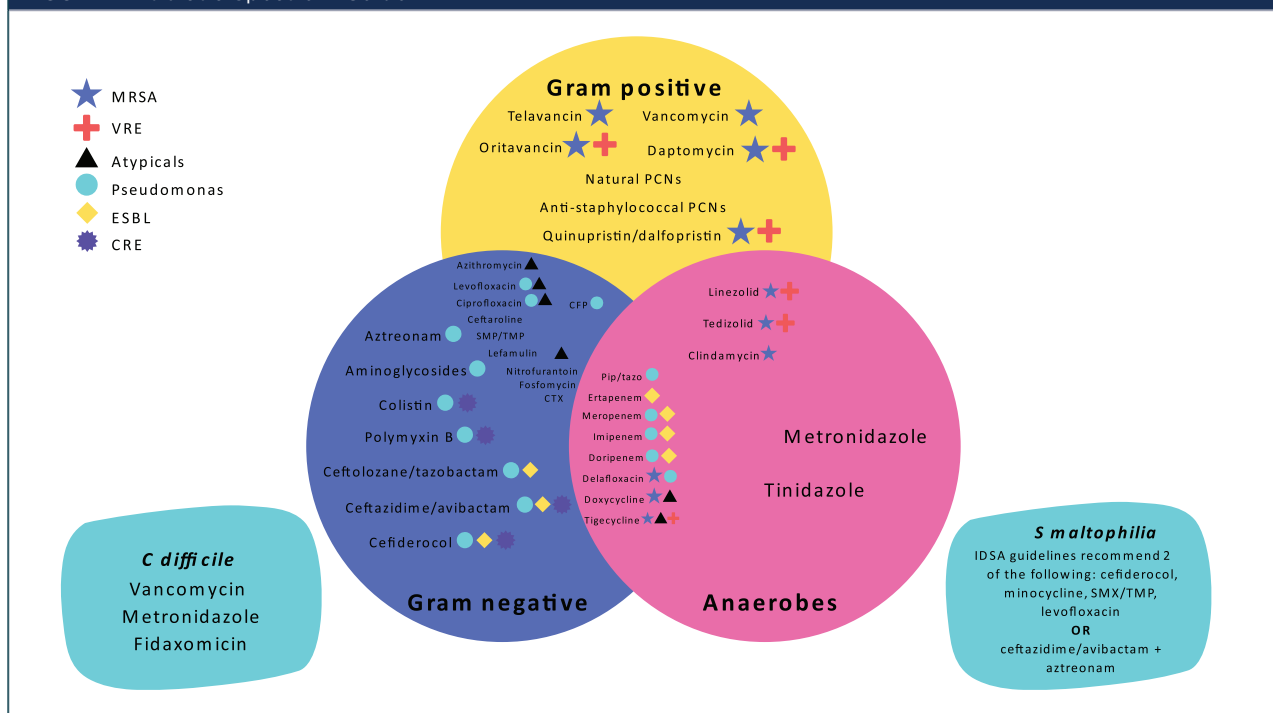
The development of antibiotic resistance in gram-positive bacteria is the explanation for this phenomenon. Resistance mechanisms arise primarily through 2 strategies: enzymatic degradation via the production of  $\beta$ -lactamases or by reducing the affinity and susceptibility of their target sites.<sup>11-13</sup> According to the *2019 Antibiotic Resistance Threat Report*, methicillin-resistant *S aureus* caused 323,700 infections in hospitalized patients, resulting in 10,000 deaths and a financial burden of \$1.7 billion in health care costs. Further, vancomycin-resistant enterococci emerged in the 1990s due to widespread vancomycin use, with over 70% of *E faecium* now resistant to vancomycin, a foundational antibiotic for these infections.<sup>8</sup> Despite ongoing efforts, many gram-positive strains remain resistant, as illustrated in the **Figure**, which highlights the various antibiotics used against these organisms. It is notable to mention here that cephalosporins lack activity against *Enterococcus* species due to expression of low-affinity penicillin-binding proteins.<sup>14</sup>

## Gram-Negative Bacteria

Gram-negative bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*,



FIGURE. Antibiotic Spectrum Guide



*C difficile*, *Clostridioides difficile*; CFP, cefoperazone; CRE, carbapenem-resistant *Enterobacteriales*; CTX, cerebrotendinous xanthomatosis; ESBL, extended-spectrum  $\beta$ -lactamases; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *Staphylococcus aureus*; PCN, penicillin; pip/tazo, piperacillin and tazobactam; *S maltophilia*, *Stenotrophomonas maltophilia*; SMX/TMP, sulfamethoxazole and trimethoprim; VRE, vancomycin-resistant enterococci.

Antibiotics are not listed in any particular order. This chart is for educational reference. It is not all-inclusive. It is intended as an educational tool to guide practitioners in understanding antibiotic spectrum. Clinical judgment and reference to specific guidelines are essential for optimal therapy selection.

have a more complex cell envelope, including an outer membrane that acts as a barrier to many antibiotics.<sup>15,16</sup> This membrane contributes to the intrinsic resistance of gram-negative bacteria.<sup>15,16</sup> Gram-negative bacteria are responsible for a wide array of infections, including urinary tract infections, pneumonia, and bacteremia.<sup>7,17</sup>

The rising prevalence of antimicrobial resistance among gram-negative bacteria is a critical challenge in clinical practice, which leads to the continual development of novel antibiotics and therapeutic approaches. New resistant strains, specifically those resistant to carbapenems, have emerged and are creating treatment challenges.<sup>1,8</sup> Carbapenem-resistant *Enterobacteriales* (CRE) species are often resistant to multiple drug classes, such as  $\beta$ -lactams, fluoroquinolones, and aminoglycosides, owing to the production of carbapenemases—enzymes that degrade carbapenems—combined with porin alterations and efflux pumps.<sup>19,20</sup> As a result, treatment options for these resistant strains are limited. However, agents such as ceftazidime-avibactam (Avycaz; AbbVie) and ceftolozane-tazobactam (Zerbaxa; Merck) have proven effective against certain carbapenemase-producing strains.<sup>19,21</sup> Developing antibiotics that target CRE has become a major focus in the drug development industry.

Gram-negative resistant organisms have become increasingly difficult to treat over the years. Due to this, the Infectious Diseases Society of America releases guidance on the treatment of antimicrobial-resistant gram-negative infections annually.<sup>23,24</sup> The **Figure** illustrates various antibiotics used to combat infections caused by other gram-negative bacteria.

## Anaerobes

Anaerobes, such as *Bacteroides fragilis* and *Clostridium* species, are significant causes in infections in hypoxic environments, such as deep tissue infections or abscesses. Anaerobes play a critical role in various environments, including the human gut, where they contribute to digestion and overall gut health.<sup>9</sup> However, they can also become pathogenic, particularly in hypoxic environments such as chronic wounds, where they contribute to persistent infections that are challenging to treat.<sup>9</sup> Understanding the metabolic pathways and oxygen tolerance mechanisms of anaerobes is essential for developing effective treatments for infections caused by these organisms.<sup>10</sup> Gradually, more resistant strains of anaerobic bacteria are being reported.<sup>8</sup> *Clostridium perfringens* has shown significant resistance to

penicillin and clindamycin (Cleocin; Pfizer).<sup>11</sup> Over a 13-year study, susceptibility of *C perfringens* to clindamycin decreased from 91% to 60% whereas penicillin susceptibility dropped from 82.1% to 65.9%.<sup>11</sup> Common antibiotics used to treat anaerobic infections include metronidazole (Flagyl; Pfizer), clindamycin,  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations, and carbapenems. The Figure illustrates the current medications used to treat infections caused by *Clostridium* and other anaerobic bacteria.

## Atypicals

Atypical bacteria lack conventional cell walls, making  $\beta$ -lactam antibiotics ineffective. Atypical bacteria are not readily classified by traditional Gram staining methods and exhibit unique characteristics that distinguish them from typical bacteria.<sup>22,23</sup> Some atypical bacteria, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, can function as obligate or facultative intracellular pathogens.<sup>22,23</sup> Therefore, their ability to reside within host cells makes them more challenging to detect and treat.<sup>22,23</sup>

Atypical bacteria are difficult to culture using standard laboratory techniques.<sup>22,23</sup> Because atypical bacteria are often resistant to  $\beta$ -lactam antibiotics, drugs of choice for these bacteria are macrolides, tetracyclines, and fluoroquinolones.<sup>22,23</sup>

## The Role of the Pharmacist

Antibiotics are lifesaving medications but their effectiveness is threatened by increasing antibiotic resistance. This emphasizes how crucial it is to use antibiotics cautiously to reduce the risk of resistance development. Pharmacists play a pivotal role in the management of bacterial infections through antibiotic stewardship, ensuring that antibiotics are used responsibly and effectively. As medication experts, pharmacists are tasked with overseeing the proper selection, dosing, and duration of antibiotic therapy, tailoring these decisions to the individual patient's needs. It is important for pharmacists to know the spectrum of activity of antibiotics to ensure appropriate empiric therapy is selected based on classic pathogens and recognize gaps in antibiotic coverage, should the patient's status continue to decline.

From an interprofessional perspective, pharmacists play a crucial role in educating both health care providers and patients about the proper use of antibiotics. Pharmacists ensure that antibiotics are

not overused, misused, or abused, which is critical in preventing resistance. This education encompasses understanding when antibiotics are necessary and how they should be taken, and the consequences of inappropriate use.

Moreover, pharmacists are actively involved in monitoring antibiotic therapy. This includes tracking adverse effects, interactions, and resistance patterns to ensure that treatment is still safe and effective. They analyze patient-specific factors, such as age, comorbidities, and renal function, to adjust therapy as needed. Additionally, pharmacists stay informed about emerging resistance data, enabling them to suggest prompt modifications to treatment regimens based on the latest evidence. Their interventions not only improve individual patient outcomes but also contribute to the broader goal of reducing antibiotic resistance on a population level.

## Conclusion

The spectrum of antibiotics is an important topic due to more agents coming to market, ongoing overuse of broad-spectrum antibiotics, and the array of empiric treatment options with patient-specific factors and sensitivity results when available. Sensitivity results may not be available for days, so pharmacists knowing if the identified pathogen is even covered the current antibiotic is vital.

Antibiotic resistance is progressively compromising the efficacy of antibiotics, even though they were pivotal in transforming modern medicine. Complex bacterial mechanisms, like those found in gram-positive, gram-negative, and atypical bacteria, are the source of this resistance and call for cautious, customized treatment approaches. In order to ensure appropriate usage, prevent misuse, and modify therapy in light of patient-specific characteristics and developing resistance data, antibiotic stewardship is essential. Personalized and evidence-based treatment is necessary to support the effectiveness of antibiotics, and pharmacists are at the forefront of therapeutic management and education. Knowing the antibiotic spectrum of coverage is crucial for pharmacists to ensure the selection of the most appropriate therapy, optimize treatment efficacy, and minimize the risk of antibiotic resistance. 🌐

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## CASE REPORT

# Potential Safety Concerns With Evinacumab

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## DISCLOSURES

None.

## PRÉCIS

This case report depicts a probable infusion reaction in a 61-year-old woman prescribed evinacumab for the treatment of familial hypercholesterolemia.

## ABSTRACT

Familial hypercholesterolemia (FH) is a genetic disorder that affects the metabolism of low-density lipoprotein particles and leads to abnormally high levels of cholesterol earlier in a patient's life. Evinacumab-dgnb (Evkeeza; Regeneron Pharmaceuticals, Inc) is an angiopoietin-like 3 inhibitor approved in 2021 for the treatment of patients with homozygous familial hypercholesterolemia. This case report depicts a probable infusion reaction in a 61-year-old woman prescribed evinacumab for treatment of FH. During the first infusion, the patient experienced a drop in both heart rate and blood pressure, accompanied by dizziness and shortness of breath. This report reveals potential safety concerns with the administration of this novel cholesterol-lowering agent. Given that the medication has limited use because of its specific indication and that there is little literature available regarding that use, this case report emphasizes the need for more clinical practice examples regarding infusion reactions with evinacumab and highlights potential safety considerations with its administration.

## TAKEAWAY POINTS

- This case study provides additional information on the safety of evinacumab (Evkeeza; Regeneron Pharmaceuticals, Inc) administration while considering the limited literature data on evinacumab infusion reactions.
- Evinacumab is a novel therapy for homozygous familial hypercholesterolemia (FH) approved for use in the US.
- FH is a genetic disorder that affects the metabolism of low-density lipoproteins and leads to abnormally high levels of cholesterol earlier in a patient's life.
- Emerging data show that FH may be more common than historically thought.

## CASE REPORT

Hyperlipidemia is an asymptomatic condition of high levels of fat particles in the blood.<sup>1</sup> If hyperlipidemia is left untreated, over time the fat particles deposit in blood vessel walls and increase the risk of heart attack and stroke.

Familial hypercholesterolemia (FH) is a genetic disorder that affects the metabolism of low-density lipoprotein (LDL) particles, leading to abnormally high levels of cholesterol earlier in life, increasing the likelihood of heart attacks and stroke at a younger age.<sup>2</sup>

Historically, FH has been thought to occur in 1 in every 500 individuals. However, more recent data estimate that FH occurs in 1 in every 200 to 300 individuals.<sup>2</sup> There are 2 types of FH: heterozygous FH (HeFH) and homozygous FH (HoFH). HeFH refers to FH when only 1 defective copy of the gene is inherited; in HoFH, both inherited copies are mutated. FH can be monogenic (only 1 lipid-lowering gene is defective) or polygenic (multiple lipid-lowering genes are defective). HoFH is much rarer than HeFH. Individuals with HoFH tend to present with higher LDL levels (>400 mg/dL vs >190 mg/dL) at a younger age (childhood) and have poorer or no response to standard lipid-lowering medications.

With no gold standard for diagnosis, the presence of a positive mutation on genetic testing is the most widely acknowledged means of diagnosis. There are 3 genetic variants associated with FH: the LDL receptor (*LDLR*), *APOB*, and *PCSK9* genes. All 3 encode

proteins that play key roles in the regulation of cholesterol.<sup>3</sup> Even with these identified genes, it is estimated that approximately 30% to 40% of patients with a diagnosis of FH have negative genetic testing. This is likely attributed to the wide range of unknown genetic mutations that cause FH that are still undiscovered; a patient with a yet-to-be-discovered FH genetic mutation would appear to have a negative genetic test result.<sup>2,3</sup> For this reason, a clinical diagnosis of FH is frequently given in practice.

A clinical diagnosis of FH is based on a combination of several factors, including response to certain cholesterol-lowering medications, such as a diminished or no response to PCSK9 inhibitors; untreated LDL greater than 200 mg/dL; and a positive family history of premature heart disease. When genetic testing is unavailable or inconclusive, clinicians often rely on clinical diagnosis for FH. Tools such as the Simon-Broome Diagnostic Criteria or Dutch Lipid Clinic Network Score also aid clinicians when making a clinical diagnosis.

Evinacumab-dgnb (Evkeeza; Regeneron Pharmaceuticals, Inc) is an angiopoietin-like 3 (ANGPTL3) inhibitor approved in 2021 for the treatment of patients with HoFH. It is indicated as adjunct therapy to other maximally tolerated LDL-lowering therapies for the treatment of patients 5 years or older with HoFH. Evinacumab is a weight-based intravenous (IV) infusion dosed at 15 mg/kg that is mixed in a maximum volume of 250 mL of 0.9% normal saline or 5% dextrose. The final concentration of the diluted solution ranges between 0.5 mg/mL and 20 mg/mL, depending on patient weight, and is administered over 60 minutes every 4 weeks. The LDL-lowering effects can be seen as early as 2 weeks after initiation.

The most common adverse effect (AE) of evinacumab is nasopharyngitis; its frequency is greater than 10%.<sup>5</sup> Safety data are based on pooled results from 2 clinical trials that included 81 patients treated with evinacumab 15 mg/kg every 4 weeks.<sup>5-7</sup> Anaphylaxis was reported in 1 patient (1.2%) in the treatment group and 0 (0%) patients in the placebo group.<sup>5,7</sup> Furthermore, infusion reactions occurred in 6 patients treated with evinacumab (7%) compared with 2 patients (4%) in the control group.<sup>5-7</sup> Manufacturer labeling recommends slowing or discontinuing the infusion if hypersensitivity reactions occur.

Based on the low number of patients receiving

this therapy, evinacumab's specific indication, the lack of literature on its use outside of manufacturer labeling, and the lack of clinical data, this case aids in the awareness of potential safety considerations with the administration of evinacumab.

#### PATIENT CASE

The patient was a 61-year-old White woman referred by her cardiologist to a pharmacist-run lipid clinic. She had elevated LDL despite having received PCSK9 inhibitor therapy; she also was to be assessed for HoFH.

- *Lipid panel at time of referral:* direct LDL, 294 mg/dL; calculated LDL, 241 mg/dL; total cholesterol, 340 mg/dL; triglycerides, 135 mg/dL; high-density lipoprotein, 71 mg/dL
- *Pertinent imaging:* CT calcium score, 417.8, 99th percentile
- *Physical examination:* negative for arcus or tendon xanthoma
- *Family history:* premature coronary artery disease
- *Mother:* maternal baseline LDL, 388 mg/dL; positive history of heart disease,
- *Father (deceased):* positive for hypertension, heart failure, diabetes
- *Medication regimen at time of referral:* evolocumab (Repatha; Amgen) 140 mg/mL subcutaneously once every 14 days (05/2019-10/2019 and restarted 12/2022)
- *Previous medication trials:* atorvastatin (Lipitor; Pfizer) (patient unable to recall dose/duration/frequency, unable to obtain from medical record) and rosuvastatin (Crestor; AstraZeneca) (patient unable to recall dose/duration/frequency, unable to obtain from medical record). Patient stopped both due to myalgias, severe muscle pain, and/or joint pain. She stopped ezetimibe (Zetia; Merck) 10 mg daily (04/2017-07/2017) because of myalgias, severe muscle pain, and/or joint pain.
- *Past medical history:* anxiety, attention deficit hyperactivity disorder, breast cancer, carcinoid tumor of rectum, chronic fatigue syndrome, chronic lower back pain with sciatica, colitis, coronary artery disease, depression, familial hypercholesterolemia, fibromyalgia, hypertension, insomnia, post-COVID-19 condition (PCC), osteopenia, vitamin D deficiency



At her initial lipid clinic visit, genetic testing for FH was requested because of the patient's partial response to PCSK9 inhibitor therapy (22% reduction in LDL rather than the expected approximately 60% reduction based on package insert) and untreated LDL greater than 400 mg/dL (LDL 430; 01/2019). Genetic testing could not be obtained because it was denied by the insurance company (estimated out-of-pocket expense for the patient was \$1200). Therefore, clinical diagnosis of HoFH was designated in the setting of untreated LDL greater than 400 mg/dL and the patient's partial response to evolocumab. The patient was deemed a candidate for evinacumab therapy by meeting the criteria for a clinical diagnosis of HoFH.

Approved for infusion at an independent location outside of the health system or home infusion, the patient elected for home infusion. At the time of first infusion, the patient weighed 58 kg, resulting in an evinacumab dose of approximately 866 mg. The medication was supplied by Orsini Specialty Pharmacy. Premedications were not selected for administration because the patient did not have a history of infusion reactions and premedications are not recommended by package labeling.

Forty-five minutes into the first infusion of evinacumab, the patient experienced decreases in her heart rate (from 84 to 64 bpm) and blood pressure, which were noted by the home infusion nurse. The patient reported feeling dizzy and short of breath. Infusion subsequently was stopped due to the concern for hypersensitivity and infusion reaction. Normal saline and 1 injection of intramuscular epinephrine were administered.

Patient was brought to the emergency department (ED) via ambulance. Emergency medical services (EMS) gave the patient 25 mg of diphenhydramine.

- *EMS report:* skin warm and clammy, chest clear with equal lung sounds, abdomen soft and nontender
- *ED review of systems:* respiratory normal breath sounds, no respiratory distress, no wheezing/rales/bronchi, no chest tenderness; cardiovascular normal heart rate, regular rhythm; skin warm, dry, no erythema, no rash

The patient received IV famotidine 20 mg once and methylprednisolone 125 mg once while in the ED. After observation and being deemed stable, she was discharged home.

The patient elected to discontinue treatment with evinacumab but continued taking evolocumab every 14 days.

## LITERATURE REVIEW

According to current evinacumab clinical trial data, anaphylaxis was reported in 1 patient in the intravenous treatment group (n=73). According to the trial investigators, during the second infusion of 15 mg/kg, the patient experienced "dizziness, chest pressure, tingling in the arms and legs, shortness of breath, pruritus, decreased blood pressure, and increased heart rate." The infusion was discontinued and treated with oral diphenhydramine. No patients with adverse events in the intravenous treatment group died.<sup>7</sup> Based on the pooled safety data (n=81), infusion reactions occurred in 6 (7%) of the treatment group vs 2 (4%) in the placebo group. Infusion reactions included infusion site pruritus, pyrexia, muscular weakness, nausea, and nasal congestion.<sup>5-7</sup> Manufacturer labeling recommends slowing infusion, at a rate designated by prescriber, if infusion reactions occur.<sup>5</sup> Use of premedications to mitigate potential infusion reactions is up to the provider. Gaudet et al sought to assess the long-term safety and efficacy of evinacumab in adults and adolescents with HoFH.<sup>8</sup> This was an open-label, single-arm, phase 3 trial that included 116 patients 12 years or older who were evinacumab naive or had received evinacumab in prior clinical trials. Trial investigators reported that most treatment-emergent adverse events (TEAEs) were mild or moderate in severity and the safety profile was consistent with the phase 3 ELIPSE trial (NCT03399786). The most common TEAEs were nasopharyngitis (n=23), influenza-like illness (n=16), and headache (n=19).<sup>8</sup>

Utilization of the Naranjo Scale leads to the conclusion that a drug-related AE was possible in this case report. With this conjecture, there are multiple limitations to consider. Because the patient received the infusion and rescue medications through a home infusion company, the authors were unable to gain access to the administering nurse's encounter notes and recorded blood pressures, but they did have access to the patient's heart rate data. The supplying drug company was also unable to provide any written infusion reaction protocols regarding the use of this medication.

The use of evinacumab in clinical practice is limited. Due to its low utilization, the existing data to reference regarding infusion reactions and/or the use of premedications are limited beyond the manufacturer labeling data and initial clinical trials. Other limiting factors include that this case was heavily based on patient-reported synopsis of events and subjective symptoms depicted in limited

medical record documentation from various providers. Although this reaction may have been drug induced, we cannot eliminate the possibility that the patient's symptoms could have been a vasovagal response to the infusion or IV access itself. Additional factors to note include that the patient had a past medical history of being positive for PCC and anxiety, both of which may have contributed to the patient's constellation of symptoms during infusion.

Although the patient had been approved for infusion at an independent location outside of the health system or home infusion, the patient could not receive infusion at an independent infusion center because of institutional policies that prevent medications from an outside pharmacy to be received or administered, thus forcing the patient to receive this medication via home infusion. Evinacumab can be dispensed only through the Orsini Specialty Pharmacy for home infusions. In addition to patient preference, patient coverage plans and benefits help determine the treatment setting (home vs clinical setting) and acquisition channel (specialty distributor vs contracted specialty pharmacy). The authors would like to point out that home infusions can come with additional risks, especially when administering first doses of IV medications. The risk to patients is thought to revolve around the home environment having less intensive monitoring, less access to a collaborative health care team, and a lack of immediate access to urgent medical treatment in the event of an acute reaction, which may result in delayed care or increased need for escalation of care. Baker et al also found that infusion reactions administered at home were more likely to occur after the first infusion and result in increased escalation of care due to AEs and increased ED visits or hospital admissions.<sup>9</sup>

#### CONCLUSION

This case depicts a likely infusion reaction to evinacumab. Based on the available literature, a retriial could be considered with the use of premedications and a slowed infusion time to mitigate the potential of another infusion reaction

occurring. Minor infusion reactions that are nonfatal, such as infusion site pruritus and vasovagal responses, can be avoided by using premedications or administering the infusions in health care settings. Based on our speculation of infusion reaction and the patient's preference, a retriial was not pursued. This report reveals potential safety concerns with the administration of a novel cholesterol-lowering agent. It also emphasizes the need for more clinical practice examples, given the limited information regarding infusion reactions and use of premedications with this agent, as well as bringing awareness to potential safety considerations with the administration of evinacumab. 🌐

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## CASE REPORT

# Paradoxical Hypotension After Inadvertent Intravenous Administration of Epinephrine

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## DATA AVAILABILITY

No data were used to support this study.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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## PRÉCIS

We present a case of rarely reported paradoxical hypotension after accidental epinephrine overdose for suspected anaphylaxis to raise awareness of the potentially fatal cardiovascular complications of epinephrine toxicity.

## ABSTRACT

Epinephrine, the standard treatment for anaphylaxis, is a lifesaving medication that can cause detrimental complications due to wrong-dose or wrong-route errors. Although the known toxicities of epinephrine such as tachycardia, hypertension, and cardiomyopathy are well documented, epinephrine's paradoxical and prolonged hypotensive effects following overdose are rarely reported. In this case, a 50-year-old man presented to the emergency department with concerns about and symptoms of an allergic reaction. Parenteral epinephrine, antihistamine, and corticosteroid were ordered to manage the suspected anaphylaxis. The patient was inadvertently administered an intravenous push of concentrated epinephrine 1 mg (1 mg/mL) instead of the intended 0.3-mg intramuscular injection, which resulted in clinical manifestations including abnormal electrocardiogram results, elevated cardiac enzymes, and prolonged hypotension that required multiple fluid boluses and continuous infusion to stabilize his blood pressure. Fortunately, the patient responded well to fluid therapy and did not require vasopressors or invasive interventions. Our intention with this case is to add to the limited existing literature on hypotensive effects of epinephrine overdose and increase awareness of the potentially fatal cardiovascular complications. Moreover, we recommend implementing institutional precautionary measures such as stocking epinephrine allergy kits or prefilled epinephrine auto-injectors to help prevent administration errors and ensure patient safety during allergy treatment.

## INTRODUCTION

Epinephrine is the first-line therapy for anaphylaxis. It works by causing vasoconstriction, increased cardiac output, and bronchodilation via activation of the adrenergic receptors ( $\alpha_1$ ,  $\beta_1$ , and  $\beta_2$ ) to counteract anaphylactic reactions such as hypotensive shock, throat swelling, or difficulty breathing.<sup>1</sup> The recommended adult dose for the indication is 0.3 to 0.5 mg via intramuscular (IM) injection, which may be repeated every 5 to 10 minutes if necessary.<sup>2</sup> Because limited data are available on epinephrine overdose associated with anaphylaxis management and resultant cardiovascular adverse events, Campbell et al compared rates of epinephrine overdose and cardiovascular complications between routes of epinephrine administration

among patients with anaphylaxis in the emergency department (ED) and found numerous instances of iatrogenic overdose of epinephrine—all occurring with intravenous (IV) bolus administration—that resulted in cardiovascular toxicities, including tachycardia, hypertension, and myocardial ischemia.<sup>3</sup>

To add to the literature on the rarely reported hypotensive effects of epinephrine overdose, we present a case in which a patient with suspected anaphylaxis was accidentally given 1 mg of concentrated epinephrine (1 mg/mL) via IV push instead of the intended 0.3-mg IM injection, resulting in unexpected hypotension, elevated troponins, and abnormal electrocardiogram (ECG) results.

**CASE REPORT**

A 50-year-old man presented to the ED with concerns about an allergic reaction—reporting an itchy rash and swelling of the arms and legs—that began 10 hours prior and progressively worsened. He also reported episodes of dull, nonradiating chest pain that had resolved before arriving at the hospital and said he was not having difficulty breathing. He reported no recent exposure to new products, such as soaps or detergents, and no changes in dietary intake. The patient had no significant medical history and no known allergies and had not taken any medications before arrival. His initial vital signs at triage were unremarkable: blood pressure (BP), 130/78 mm Hg; heart rate, 78 beats per minute (bpm); respiratory rate, 20 breaths per minute; and oxygen saturation as measured by pulse oximetry (Sp<sub>o</sub><sub>2</sub>), 96%. A comprehensive metabolic panel, serial serum cardiac troponin I tests, and an ECG were ordered in triage and came back normal during the patient's 7-hour stay in the waiting area. This prolonged wait time was due to a high volume of patients in the ED and several hours of electronic health record (EHR) downtime.

The EHR was back online by the time the patient was roomed. The emergency medicine (EM) nurse then reassessed his vital signs, which were BP, 108/51 mm Hg; heart rate, 73 bpm; respiratory rate, 18 breaths/min; Sp<sub>o</sub><sub>2</sub>, 97%; and temperature, 98.1 °F. Next, the EM physician—who suspected acute allergic reactions triggered by an unidentified cause—evaluated the patient; entered orders into the EHR for commonly used treatments for anaphylaxis, including IM epinephrine (0.3 mg), IV dexamethasone (10 mg), and IV diphenhydramine (50 mg); and verbally communicated the orders to the nurse. Because at that time a technical interface issue was causing medication orders to not cross over from the EHR to the automated dispensing cabinet (ADC), all medications were removed from the ADC using the override function, including the epinephrine 1 mg (1 mg/mL) ampule. Medication barcode scanning was done for dexamethasone in the medication administration record (MAR) but not for diphenhydramine or epinephrine. The nurse proceeded to administer all medications based on verbal orders, with no other personnel present in the room.

Shortly after, the patient reported experiencing sudden, sharp, intensifying chest pain that was distinct from the symptoms he had prior to hospital arrival. The nurse immediately recognized the error: All medications had been administered via IV push, including epinephrine 1 mg when 0.3-mg IM was intended. The patient's BP dropped to 69/41 mm Hg with a mean arterial pressure of 50 mm Hg; his heart rate, respiratory rate, temperature, and Sp<sub>o</sub><sub>2</sub> remained within the normal range. The error was reported to the EM physician and administrators. It was later discovered that epinephrine and diphenhydramine had been mistakenly entered as outpatient-clinic orders instead of

inpatient orders, which explained why those medications were not displayed in the MAR for the nurse to confirm the ordered dose and route and to scan the medications.

The patient said he was not having difficulty breathing, throat swelling, dizziness, or any other symptoms besides chest pain. He received boluses of normal saline in response to the acutely developed hypotension (see **Table** for vital signs, troponin trend, and normal saline fluid treatments during the patient's hospital stay). Due to suspected cardiovascular toxicity following an epinephrine overdose, the EM physician initiated a comprehensive diagnostic workup, including D-dimer assessment, chest x-ray, computed tomography angiogram (CTA) of the chest, repeat troponin I testing, ECG, and echocardiogram. The chest x-ray showed no abnormalities. A blood test taken 45 minutes after the anaphylaxis treatments revealed an elevated D-dimer level of 2.870 µg/mL, with no baseline for comparison (reference range, < 0.50 µg/mL).<sup>4</sup>

A subsequent CTA of the chest performed 3 hours later ruled out pulmonary embolism and coronary calcifications. A repeat ECG 4 hours after the medication error showed mild diffuse ST-segment elevation and elevated levels of troponin I (Table). However, a bedside echocardiogram conducted by the cardiologist 5 hours post medication error demonstrated normal ejection fraction and preserved wall motion. An emergent angiocardiology was ordered after the abnormal ECG but canceled after the normal echocardiogram results. The patient's chest pain resolved after a few hours, and the hives, rashes, and swelling resolved after anaphylaxis treatments. However, the patient was admitted to the cardiac intensive care unit due to the epinephrine overdose and the resultant, persistent hypotension and demand ischemia (ie, when myocardial oxygen demand is greater than myocardial oxygen supply<sup>5</sup>). Repeat testing of troponin I showed levels peaking at 247.89 ng/L (Table). Because the patient was administered normal saline boluses and given continuous infusion (approximately 5-6 liters over 24 hours), his systolic BP gradually improved to readings in the 80s to 90s mm Hg (Table).

The patient was deemed stable and discharged the next day after normalization of ECG findings, a decline in troponin I levels, and a negative nuclear stress test. He remained asymptomatic at the outpatient cardiology follow-up appointment 3 weeks later.

**DISCUSSION**

Therapeutic dose and route of epinephrine vary depending on the indication. For example, IM administration of 0.3 to 0.5 mg for adults (0.01 mg/kg to 0.5 mg for pediatric patients) is considered safe and effective for treating anaphylaxis, and a 1-mg (1 mg/10 mL) IV push is recommended during cardiac arrest.<sup>6</sup> In refractory anaphylaxis, a slow IV push (over 5 minutes) of 0.05 to 0.1 mg (using the 1 mg/10 mL solution

**TABLE.** Vital Signs, Troponin Trend, and NS Fluid Treatments During the Patient's Hospital Stay

Day	Military time	Troponin I level <sup>a</sup> (ng/L)	Heart rate (beats/min)	Blood pressure (mm Hg)	MAP (mm Hg)	NS IV fluid treatment	
1	01:48		78	130/78	95		
	02:13	2.98					
	03:47	<2.50					
	06:38	<2.50					
	09:05		73	108/51	70		
	<b>09:50</b>	<b>Medication error: administration of epinephrine 1-mg IV push</b>					
	10:10		87	69/41	<b>50<sup>b</sup></b>		
	10:16		82	71/43	<b>52<sup>b</sup></b>	1 L NS bolus	
	10:28		67	72/41	<b>51<sup>b</sup></b>		
	10:52		68	71/38	<b>49<sup>b</sup></b>		
	11:04		72	74/40	<b>51<sup>b</sup></b>		
	11:10	55.24					
	11:16		71	76/45	<b>55<sup>b</sup></b>		
	11:29		65	84/52	63		
	11:42		64	76/50	<b>59<sup>b</sup></b>		
	12:00		61	82/47	<b>59<sup>b</sup></b>	1 L NS bolus	
	12:43	205.28					
	12:46		67	77/47	<b>57<sup>b</sup></b>		
	13:01		66	87/49	62		
	13:31		71	90/55	67		
	14:00		67	88/54	65		
	14:40		74	93/51	65		
	15:29		83	92/51	65	1 L NS bolus	
16:26		70	84/50	61			
17:03		62	90/52	65			
17:36		81	89/52	64			
18:57		69	93/50	64	NS 125 mL/h		
20:00		69	79/45	<b>56<sup>b</sup></b>	NS 125 mL/h		
21:00		78	88/55	66	NS 125 mL/h		
21:58	247.89				1 L NS bolus		
23:08		90	88/52	64	NS 125 mL/h		
2	00:30		62	84/49	61	NS 125 mL/h	
	02:30					NS 125 mL/h	
	04:05		67	92/54	67	NS 125 mL/h	
	07:59		70	103/57	72	NS 125 mL/h	
	08:59	94.92				NS 125 mL/h	
	11:46		70	101/55	70	NS 125 mL/h	
	13:20					NS stopped	
15:44		74	113/60	78			

IV, intravenous; MAP, mean arterial pressure; NS, normal saline.

<sup>a</sup>Institutional (Endeavor Health Swedish Hospital) reference range for high-sensitivity troponin I, men: 0.00-53.60 ng/L.

<sup>b</sup>Bold readings denote MAP less than 60 mm Hg.

further diluted in 10-mL normal saline) may be employed with stringent monitoring until an epinephrine IV infusion (0.01-0.2 mcg/kg/min) is available.<sup>6</sup>

Epinephrine exerts its effects by stimulating adrenergic receptors, leading to increases in BP and heart rate.<sup>1</sup> Thus, the most expected responses from epinephrine overdose are

the exaggerated pharmacological effects of epinephrine, such as hypertension and tachycardia. In this case, the patient received 1 mg of epinephrine (1 mg/mL) via IV bolus push, exceeding the dose for refractory anaphylaxis by 10 to 20 times.<sup>6</sup> Subsequently, the patient developed chest pain and hypotension, which we suspect were caused by the epinephrine overdose.

Epinephrine at low doses has a greater affinity for  $\beta$  receptors, whereas epinephrine at higher doses activates  $\alpha$  receptors.<sup>7</sup> Activated  $\beta$  receptors cause increased heart rate, myocardial contractility, and dilation of coronary arteries.<sup>7</sup> Stimulated  $\alpha$  receptors lead to increased vasoconstriction of cardiac and vascular smooth muscles.<sup>7</sup> Yasue et al suggested that severe coronary artery spasms followed by Prinzmetal angina were mediated by activation of  $\alpha$  receptors.<sup>8</sup> In a case report where a patient developed acute chest pain and an ECG showed widespread ischemia after they accidentally received 2 mg of IV epinephrine instead of naloxone, the author hypothesized that the  $\alpha$  effect induced by epinephrine overdose resulted in vasoconstriction of coronary arteries, causing vasospasm and decreased coronary artery perfusion.<sup>9</sup> The acute chest pain and ECG change consistent with myocardial ischemia as seen in our patient after epinephrine overdose could be explained by these theories.

Cusumano et al discussed cases of epinephrine-induced hypotension and addressed the risks associated with large-dose, push-dose pressors.<sup>10</sup> There is a theory that epinephrine overdose causes a biphasic pattern of BP, where BP significantly declines soon after the expected hypertensive response; it is postulated that  $\alpha$  receptors are initially stimulated, causing an increase in BP, and then the more sensitive  $\beta$  receptors continue to respond, resulting in peripheral vasodilation and hypotension.<sup>10,11</sup> Krishnamoorthy et al found that in healthy, anesthetized rats, a single IV bolus dose of epinephrine 100 mcg/kg—comparable to 17 mcg/kg in humans (a typical dose used for cardiac arrest)—resulted in a significant systolic BP drop 10 minutes after administration.<sup>11</sup> However, it is unclear whether our patient experienced brief hypertension or tachycardia before the development of hypotension because the first recorded vital signs were approximately 20 minutes after the IV bolus push of epinephrine. Although the underlying mechanism is not fully understood, we speculate that our patient's prolonged hypotension could be the result of myocardial ischemia followed by coronary spasm and peripheral vasodilation from continuously stimulated  $\beta$  receptors after epinephrine overdose. The sequence of activation of various subtypes of adrenergic receptors and the subsequent physiological events in epinephrine overdose merit further study.

In this patient's case, it is difficult to determine whether the therapeutic dose of IV diphenhydramine that was

coadministered with epinephrine further potentiated the hypotension. Although a few case reports document antihistamine-induced hypotension, they do not describe ECG changes or cardiac ischemia like those observed in our patient.<sup>2,12</sup>

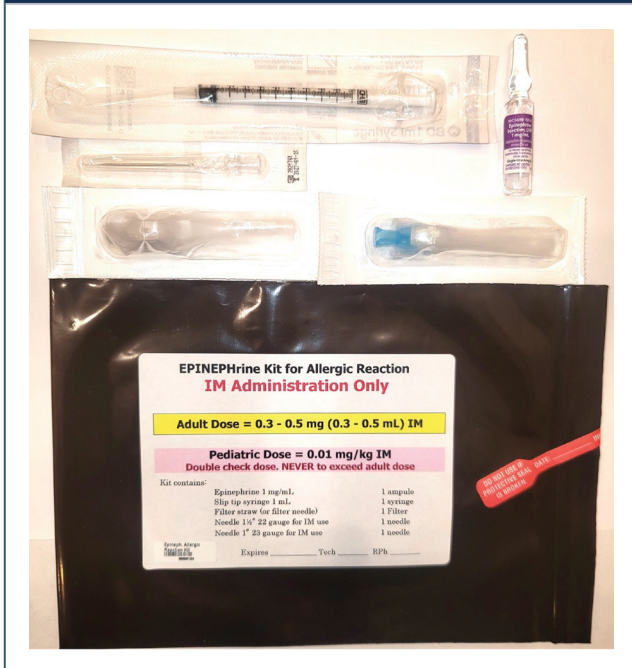
Based on the temporal relationship between the administration of anaphylaxis treatments and the onset of hypotension in this patient, it is probable that the epinephrine overdose caused hypotension and cardiotoxicity.<sup>13</sup> It is unlikely that the patient's acutely developed hypotension was the progression of mild to moderate allergic reaction to severe anaphylactic shock because the patient was hemodynamically stable before treatments.

Rapidly administering the first-line therapy of IM epinephrine is vital for effective anaphylaxis management. It is not recommended to delay epinephrine until breathing difficulty worsens or shock occurs.<sup>2</sup> Clinicians should be aware that antihistamines and corticosteroids are not first-line therapies because they do not adequately address severe symptoms associated with anaphylaxis.<sup>2</sup> These medications are used for mild allergic reactions or as adjuncts to epinephrine for supportive symptom relief, so these therapies should be considered after reassessing the effects of IM epinephrine and should not be ordered emergently or simultaneously with epinephrine.<sup>2</sup> This approach also reduces nurses' cognitive burden (ie, managing multiple parenteral routes) and decreases the risk of potential administration errors.<sup>14</sup>

In our patient's case, however, epinephrine should have been deemed unnecessary because the patient did not exhibit anaphylactic symptoms during his long wait times in the ED. The patient's cutaneous allergic symptoms could have been effectively managed by corticosteroids and antihistamines. Clinicians must be mindful that epinephrine—a lifesaving yet high-risk medication—can cause severe, unintended harm when used incorrectly.<sup>3</sup> Moreover, toxic doses and clinical toxic effects of epinephrine can vary significantly from case to case, and there are no standardized guidelines for treating epinephrine overdose. For instance, a 51-year-old man died after receiving a 3-mg dose of epinephrine (presumed via IM route) for an allergic reaction.<sup>15</sup> Conversely, another case involved the accidental IV administration of an extremely high (5-mg) dose of epinephrine, intended for nebulization, which did not result in cardiac arrest or death but did require intensive monitoring and treatment.<sup>16</sup>

Many institutions have comprehensive safety medication systems, such as computerized provider order entry, ADC, and barcode medication administration. However, human errors or technology issues are ineliminable. Continued systemic institutional efforts should be made to prevent errors in epinephrine administration. These efforts include promoting error reporting to facilitate learning from



**FIGURE.** Epinephrine Allergy Kit Used at Our Institution

mistakes, providing regular education on the various indications and dosages of epinephrine, and addressing potential risks associated with its incorrect use. Additionally, the use of institutionally prepacked epinephrine allergy kits, commercially prepacked epinephrine convenience kits, or prefilled epinephrine auto-injectors can reduce the risk of inadvertent epinephrine overdose and prevent costs associated with medication error.<sup>17,18</sup> After this patient, Endeavor Health Swedish Hospital implemented a modification in which concentrated epinephrine ampules were replaced with pharmacy-prepared epinephrine allergy kits in ADCs in both ED and inpatient units. Each kit contains an epinephrine ampule, a filter needle, IM needles, and a slip-tip 1-mL syringe with clear dosing and route instructions (Figure). Since this change was implemented approximately 2 years ago, no errors related to IV push of concentrated epinephrine or incorrect dosing in allergy treatments have been reported.

## CONCLUSION

Epinephrine overdose can trigger various and potentially fatal cardiovascular reactions, yet there is no standardized approach to managing epinephrine toxicity. We aim for this case to raise awareness of the paradoxical hypotensive effects of inadvertent IV epinephrine administration and add to the limited existing literature. Although in this patient the hypotension was resolved with only fluid resuscitation and effective management of transient cardiotoxicity, clinicians need to be aware of the

potentially life-threatening consequences of epinephrine when erroneously administered. Implementing institutional precautionary measures is an essential step in mitigating errors involving this high-alert medication and improving patient safety. 🌐

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## CASE DESCRIPTION

# Cost Avoidance and Satisfaction Associated With Clinical Pharmacy Services in a Veterans Affairs Specialty Clinic

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## DISCLOSURES

The authors have declared no potential conflicts of interest.

## PRÉCIS

An infusion and specialty clinical pharmacist is a valuable integrated member of the health care team as demonstrated by cost avoidance and high satisfaction reported by both veterans and specialty providers.

## PURPOSE

Demonstrate the impact of an infusion and specialty clinical pharmacist (ISCP) utilizing cost avoidance and satisfaction of services.

## METHODS

Cost avoidance was measured by totaling local and national conversion initiatives as well as intravenous immunoglobulin (IVIG) and tafamidis (Vyndamax; Pfizer) dose optimizations for fiscal year (FY) 2023 (October 2022-September 2023) and the first half of FY 2024 (October 2023-March 2024). Satisfaction with the ISCP services was assessed via veteran and specialty provider questionnaires, which consisted of Likert scale items, yes/no responses, and open-response questions. Veterans and providers were invited to participate in the questionnaire via email, SMS text messaging, or phone.

## RESULTS

Cost avoidance was calculated from 10 conversion initiatives and 2 medication dose optimizations. A total of 148 conversions were completed in addition to 5 IVIG and 2 tafamidis dose optimizations. The total annual projected cost avoidance was over \$1.3 million. Veteran response rate to the questionnaire was 58.5% (79/135); 89% of those who responded were satisfied with the clinical attributes of the ISCP. Provider response rate was 89.5% (17/19); 88% of those who responded reported being "very satisfied" with clinical attributes of the ISCP. Regarding clinical experience, 94% of providers reported being "very satisfied" or "somewhat satisfied" with the ISCP's clinical experience.

## CONCLUSION

The ISCP is a key member of the specialty team, a determination based on projected cost avoidance and high satisfaction expressed by both veterans and specialty providers. The results support the value of ISCP positions in VA and private sector specialty clinics.

## INTRODUCTION

Specialty medications, which are high-cost pharmaceuticals used to treat chronic medical conditions, require continuous monitoring and clinical oversight. They typically involve injectable or intravenous administration and may have complex storage requirements. In 2020, specialty medication expenditure in the United States was \$265.3 billion, which accounted for almost 50% of total pharmaceutical expenditure for that year.<sup>1</sup> Specialty pharmacist interventions have therefore become instrumental in medication optimization and cost avoidance.

Results of a study that evaluated pharmacist impact on the cost of specialty medications showed that 34% of pharmacist interventions could be directly associated with over \$1.5 million in cost savings over 5 months.<sup>2</sup> For example, intravenous immunoglobulin (IVIG), with a low volume of distribution, can be dosed utilizing ideal body weight (IBW) rather

**TABLE 1.** Cost Avoidance Initiatives, FY 2023 Through First Half of FY 2024

National initiatives		
	Preferred medication annual cost per veteran (US\$)	Nonpreferred medication(s) annual cost per veteran (US\$)
<b>Asthma</b>	Benralizumab: 15,437.50*	• Mepolizumab: 30,433.91
<b>Migraine</b>	Botulinum toxin Injections	
	AbobotulinumtoxinA: 1358.84	• OnabotulinumtoxinA: 2490.48
	CGRP mAb receptor antagonist (prevention)	
	Erenumab-aooe: 1560.72	• Fremanezumab-vfrm: 2,161.80 • Galcanezumab-gnlm: 5714.64 • Rimegepant ODT: 14,520.96 • Atogepant: 7,686.00
	CGRP receptor antagonist (abortive, as needed)	
	Ubrogepant: 7297.20	• Rimegepant ODT: 14,520.96
<b>Chronic idiopathic constipation</b>	lubiprostone: 1670.40	• Plecanatide: 1967.35 • Linaclotide (290 mcg): 3733.95
<b>Parathyroid in women</b>	Abaloparatide: 17,558.76**	• Teriparatide: 18,460.32**
<b>Psoriasis</b>	Ixekizumab: 17,184.00*	• Secukinumab: 25,512.00* • Risankizumab: 34,200.00* • Ustekinumab (90 mg): 52,696.00*
Local initiatives		
	Preferred dosing	Nonpreferred dosing
<b>IVIG***</b>	Based on IBW	Based on ABW
<b>Tafamidis</b>	20 mg daily	61 mg daily

ABW, actual body weight; CGRP, calcitonin gene-related peptide; FY, fiscal year; IBW, ideal body weight; IVIG, intravenous immunoglobulin; mAb, monoclonal antibody.

\*After completion of loading doses

\*\*Maximum treatment duration of 2 years

\*\*\*Dosage based on ABW if ABW < IBW

than actual body weight (ABW), and a 5-year retrospective analysis of 2564 patients receiving IVIG demonstrated \$3.9 million in annual medication cost avoidance.<sup>3</sup>

Implementation of infusion specialty clinics can improve patient outcomes and facilitate interdisciplinary collaboration, study results have shown.<sup>1</sup> In a 2022 American Society of Health-System Pharmacists (ASHP) survey, specialty providers reported that infusion and specialty clinical pharmacists (ISCPs) played an integral role in initial therapy selection, changes in therapy, and development of treatment algorithms.<sup>4,5</sup> Veteran satisfaction with specialty medication services has not been noted in the literature; however, results of an ASHP provider survey showed that 43% of providers frequently or always collaborated with an ISCP to discuss treatment selection.<sup>5</sup>

**METHODS**

The ISCP position at Veterans Affairs Maine Healthcare System (VAMHCS) was established in April 2022 to provide specialty medication management and recommendations in specialties such as rheumatology, dermatology, gastroenterology, pulmonology, neurology, and otolaryngology. The ISCP, with a scope of practice,

reviews all specialty medication nonformulary requests and provides initial education and follow-up visits at 1-, 3-, and 6-month intervals after therapy initiation. In addition, the ISCP tracks high-cost medication use and prescribing practices to make recommendations based on current clinical literature for conversion initiatives and dose optimizations. The ISCP also implemented process improvements utilizing Lean Six Sigma tools, which have helped prevent medication order entry and dispensing errors.

At VAMHCS, the ISCP closely collaborates with specialty providers, veterans, and the outpatient and inpatient pharmacy departments. Specialty medication education is essential because patients often have multiple associated comorbidities such as pain, disability, and fatigue.<sup>6</sup> Medication education is affiliated with increased adherence and improved treatment outcomes, which can prevent disease progression and the need for more costly alternatives.<sup>5</sup> The primary objective of this quality improvement (QI) project was to assess the impact of the ISCP at VAMHCS through analysis of cost avoidance and satisfaction of services. This QI project was approved by the VA’s Office of Research and Development and monitored by the VAMHCS Privacy Office.



**TABLE 2.** Completed Cost Avoidance Initiatives, FY 2023 Through First Half of FY 2024

National initiatives		
	Number of conversions	Projected total annual cost savings (US\$)
<b>Asthma</b>	19	284,931.79
<b>Migraine</b>	Botulinum toxin injections	
	77	87,136.28
	CGRP mAb receptor antagonist (prevention)	
	10	46,821.84
	CGRP receptor antagonist (abortive, as needed)	
	5	28,893.28
<b>Chronic idiopathic constipation</b>	15	30,953.25
<b>Parathyroid in women</b>	2	10,017.00
<b>Psoriasis</b>	20	458,150.00
<b>Total</b>	148	946,903.44
Local initiatives		
	Number of dose optimizations	Projected total annual cost savings (US\$)
<b>IVIG</b>	5	89,370.00
<b>Tafamidis</b>	2	290,955.00
<b>Total</b>	7	380,325.00

CGRP, calcitonin gene-related peptide; FY, fiscal year; IVIG, intravenous immunoglobulin; mAb, monoclonal antibody.

### Cost Avoidance: Conversions

The ISCP's impact on cost avoidance was evaluated by retroactively compiling completed local and national conversion initiatives and IVIG and tafamidis dose optimizations. To complete these conversions, the ISCP utilized the US Department of Veteran Affairs pharmacoeconomic dashboards, prescription dispensing reports, and pharmacy- and therapeutics committee-approved medication use evaluations to identify eligible veterans. Each veteran's electronic medical record (EMR) was reviewed to determine whether it was appropriate to convert to the preferred medication with a similar mechanism of action and safety profile (Table 1). They were excluded if found to have a contraindication to or prior trial of the preferred medication. Buy-in from both the providers and veterans was obtained, and veterans were educated on the change in medication by the ISCP and called for follow-up at 1- and 3-month intervals.

Specialty providers continued to monitor the veterans' disease state in addition to the ISCP's medication management. After successful conversion, the projected annual cost avoidance was retrospectively obtained using descriptive statistics by calculating the acquisition cost difference of the 2 specialty medications. The total number of conversions and associated cost avoidance were tracked for fiscal year (FY) 2023 (October 2022-September 2023) through the first half of FY 2024 (October 2023-March 2024) (Table 2).

### Cost Avoidance: Dose Optimizations

IVIG is used to treat a number of conditions including immune deficiency, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis and was identified as a potential medication for dose optimization due to its low volume of distribution and ability to be dosed based on IBW vs ABW.<sup>3</sup> ASHP conducted a retrospective study on the correlation of IVIG dose and serum immunoglobulin G (IgG) levels with 3 weight-based dosing methods, and the results determined that the dose of IVIG and the change in IgG levels correlated the strongest with IBW.<sup>7</sup>

Using ABW in patients with obesity or overweight can significantly increase the IVIG dose. In 2015, there was another retrospective study that determined patients with obesity (body mass index > 30) receiving IVIG could be dosed relative to their lean body equivalent without affecting outcomes.<sup>7,8</sup> These cost avoidance opportunities were again identified through prescription dispensing reports as well as review of the veteran's EMR (Table 2). For example, a veteran with an ABW of 70 kg and an IBW of 50 kg correlated to a 20-g dose difference and a \$1160 difference in cost per dose.

Tafamidis (Vyndamax; Pfizer) is a specialty oral medication approved to reduce cardiovascular mortality and related hospitalization in those with transthyretin-related familial amyloid cardiomyopathy. The phase 3 ATTR-ACT trial (NCT01994889) was a 30-month randomized control trial that compared the safety and

**TABLE 3.** Veteran Feedback on Clinical Attributes of ISCP

"What best described your experience with ISCP?"	N= 79	% of Respondents				
	No. of respondents	Very dissatisfied (%)	Somewhat dissatisfied (%)	Neither satisfied nor dissatisfied (%)	Somewhat satisfied (%)	Very satisfied (%)
Overall experience	74	3%	1%	1%	10%	85%
Accessibility	73	2%	0%	4%	10%	84%
Responsiveness to questions	71	3%	0%	1%	6%	90%
Professional demeanor	72	3%	0%	1%	3%	93%
Education about specialty medication	73	3%	0%	1%	7%	89%
Communication	73	3%	0%	3%	4%	90%
Effectiveness of follow-up calls	72	2%	0%	4%	6%	88%
			No (%)			Yes (%)
If a problem were to arise, I would feel comfortable contacting the clinical pharmacist.	72		0%			100%
I use my medications more appropriately after speaking with the infusion specialty pharmacist.	68		1%			99%

ISCP, infusion and specialty clinical pharmacist.

efficacy of both tafamidis 20 mg/day and tafamidis 80 mg/day vs placebo. Both treatment groups had significantly greater transthyretin stabilization compared with placebo. The 80-mg/day dose was associated with a higher mean transthyretin concentration than the 20-mg/day dose; however, the clinical significance of this is unknown. When compared with placebo, both treatment groups were found to significantly reduce all-cause mortality and cardiovascular-related hospitalizations.<sup>9</sup>

At VAMHCS, the ISCP informed eligible veterans of the dose decrease from tafamidis 61 mg or 80 mg daily to 20 mg daily; the veterans continued to be monitored by cardiology. The acquisition cost of the 20-mg capsule was approximately \$10,500 less per patient per 30-day supply than the 61-mg or 80-mg daily dose, and this was added to the direct cost avoidance associated with dose optimizations.

**Veteran Satisfaction**

Veterans who had face-to-face, phone, or video appointments with the ISCP from April 2022 through February 2024 also received the satisfaction questionnaire. Veterans must have been prescribed a specialty medication through at least 1 of the following specialties: dermatology, gastroenterology, neurology, pulmonology, rheumatology, or otolaryngology. Veterans were sent the questionnaire retrospectively, and the time between the initial appointment with the ISCP and when they received the questionnaire could have been as long as 22 months. In

total, 135 veterans were included to receive the satisfaction questionnaire; the Qualtrics platform was utilized for questionnaire distribution. Qualtrics is a customer experience management platform that focuses on collecting, organizing, and understanding important data relative to customers and employees. VA has a Qualtrics account that is validated by the VA’s privacy office and information technology support.

A 12-item questionnaire was developed to assess overall veteran satisfaction with their experience with the ISCP at VAMHCS. The questionnaire was carefully worded to avoid feedback on processes and policies, which was not the intent of the evaluation. At the beginning of the questionnaire, there was a disclaimer expressing that participation would not affect future care in any way. There were 7 Likert scale items, 2 yes/no responses, and 3 open-response questions. The 7 Likert scale items were ranked from very dissatisfied to very satisfied. Yes/no responses included: “If a problem were to arise, I would feel comfortable contacting the infusion and specialty clinical pharmacist,” and “I use my medication(s) more appropriately after speaking with the infusion and specialty clinical pharmacist.” Open-ended questions included: “What did the infusion and specialty clinical pharmacist do well?” “What can the infusion and specialty clinical pharmacist do to improve?” and “Please share any additional information about your experience.”

Eighty-four of the veterans received the questionnaire via email and the remaining veterans, who did not have

**TABLE 4.** Themes Reported in Open-Response Questions by Veterans Regarding ISCP

Theme	Attributes and number of responses where attribute was mentioned
Professionalism	<ul style="list-style-type: none"> <li>Professional (4)</li> <li>Respect (4)</li> <li>Knowledgeable (9)</li> </ul>
Communication	<ul style="list-style-type: none"> <li>Felt heard (8)</li> <li>Easily reachable (5)</li> </ul>
Education	<ul style="list-style-type: none"> <li>Spoke in a way that's easy to understand (10)</li> <li>Answered all questions (5)</li> </ul>
Medication support	<ul style="list-style-type: none"> <li>Injection technique (3)</li> <li>Explained what to expect regarding medications (9)</li> </ul>
Other	<ul style="list-style-type: none"> <li>Did "everything" well (11)</li> </ul>

ISCP, infusion specialty clinical pharmacist.

an email address readily available, were contacted via phone. Veterans' cell phone numbers and emails were extracted via chart review and tracked in a Microsoft Excel spreadsheet, which was imported into Qualtrics. Veterans received an initial email and cell phone text (if provided in the chart) from the Qualtrics platform inviting them to complete the online questionnaire. Reminder emails and texts were sent weekly for 3 weeks. Those who did not have an email or cell phone listed in their chart were contacted on their home phone. The questionnaire items were read verbatim and tracked via Microsoft Forms. There was 1 health care team member (not an ISCP) who collected verbal responses from

veterans via phone. Personal calls were made to veterans who had initially received the Qualtrics email and/or text message but had not responded. The questionnaire was open for response collection from veterans from November 30, 2023, to March 14, 2024.

**Provider Satisfaction**

The ISCP works closely with providers from multiple specialties at VAMHCS. To obtain provider feedback, an electronic questionnaire was developed using Microsoft Forms. The questionnaire consisted of 9 Likert scale items and 4 open-response questions. The wording was carefully selected to avoid feedback on processes and policies, which was not the intent of the evaluation. At the beginning of the questionnaire there was a disclaimer expressing that participation would not affect the professional relationship with the ISCP. Nineteen specialty providers were sent the questionnaire link via VA Microsoft email. The questionnaire was open for response collection from providers from November 30, 2023, to December 1, 2023.

**RESULTS**

**Cost Avoidance**

The ISCP's impact on direct cost avoidance was totaled from the cost conversion initiatives as well as IVIG and tafamidis dose optimizations. Four conversion groups had 1 preferred and 1 nonpreferred medication (asthma, parathyroid in women, migraines [Botox or tablets]). Two groups had a preferred, secondary preferred, and tertiary preferred option (chronic idiopathic constipation and

**TABLE 5.** Provider Feedback on Clinical Attributes of ISCP

"What best described your experience with ISCP?"	N = 17				
	Very dissatisfied (%)	Somewhat dissatisfied (%)	Neither satisfied nor dissatisfied (%)	Somewhat satisfied (%)	Very satisfied (%)
Overall experience	0%	0%	6%	0%	94%
Accessibility	0%	0%	6%	0%	94%
Responsiveness to inquiries	0%	0%	6%	0%	94%
Professionalism	0%	0%	6%	0%	94%
Clinical experience	0%	0%	6%	6%	88%
Communication	0%	0%	6%	0%	94%
Coordination of patient care	0%	0%	6%	0%	94%
	Very unlikely (%)	Somewhat unlikely (%)	Neither likely nor unlikely (%)	Somewhat likely (%)	Very likely (%)
I have made less errors in order entry due to assistance of clinical pharmacist.	0%	0%	12%	24%	64%
If a problem were to arise, I would feel comfortable contacting clinical pharmacist.	0%	0%	6%	0%	94%

ISCP, infusion specialty clinical pharmacist.

**TABLE 6.** Themes Reported in Open-Response Questions by Providers Regarding ISCP

Theme	Attributes and number of responses where attribute was mentioned
Communication	<ul style="list-style-type: none"> <li>• Communication liaison (7)</li> <li>• Resource for the specialty clinic (5)</li> <li>• Responsive (9)</li> </ul>
Responsibility	<ul style="list-style-type: none"> <li>• Asset to specialty clinic (7)</li> <li>• Allows providers more time for patient care (14)</li> <li>• Assists in placing medication orders (5)</li> </ul>
Patient care	<ul style="list-style-type: none"> <li>• Patient safety (4)</li> <li>• Patient education (3)</li> </ul>

ISCP, infusion specialty clinical pharmacist.

migraine injectables). Lastly, the psoriasis conversion had 4 therapeutic options (preferred, secondary preferred, tertiary preferred, and nonpreferred) (Table 1).

A total of 148 conversions were completed from FY 2023 through the first half of FY 2024, resulting in \$946,903 projected annual cost avoidance. Dose optimizations were completed for 5 IVIG and 2 tafamidis patients, adding \$380,325 to the projected annual cost avoidance. The total annual projected cost avoidance from conversion initiatives and dose optimizations was \$1,327,228.

### **Veteran Satisfaction**

The overall questionnaire response rate for veterans was 58.5% (79/135). Thirty-six responses were obtained via phone and 43 responses via Qualtrics (Table 3). Of the respondents, 89% reported that they were satisfied with the clinical attributes listed on the questionnaire (overall experience, accessibility, responsiveness to questions, professional demeanor, communication, and effectiveness of follow-up calls). There may have been a confounder as 1 veteran selected “very dissatisfied” for each clinical attribute. However, in the open-response section, the veteran noted that “she did great, much appreciated service, felt like she respected me!!”

Veterans (100%) reported they would feel comfortable contacting the ISCP if a problem were to arise. Nearly all (99%) reported using their specialty medications more appropriately after speaking with the ISCP. In the open-response section, veterans commented on respectful and professional communication with the ISCP and the effectiveness of medication education (Table 4).

### **Provider Satisfaction**

The overall response rate for specialty providers was 89.5% (17/19) (Table 5). Eighty-eight percent of providers reported being “very satisfied” with the clinical experience of the ISCP, and 94% of providers reported being “very satisfied” or “somewhat

satisfied” with the clinical experience. The majority of providers (94%) reported being “very satisfied” with the ISCP’s coordination of patient care, communication, professionalism, responsiveness to inquiries, accessibility, and overall experience. Providers reported being able to dedicate more time to veterans’ appointments and needs as a result of time saved from the ISCP services. Many providers commented on the importance of having an ISCP in the specialty clinic as part of the health care team (Table 6).

### **DISCUSSION**

There is an emerging role for pharmacists in specialty care to assist with medication management, given the complexity and cost of specialty medications. The ISCP at VAMHCS has had a significant impact on VA medication expenditure through cost avoidance and dose optimization initiatives, which have been associated with more than \$1.3 million in projected annual cost avoidance. In addition, there were opportunities for indirect cost avoidance identified over the course of this QI project, which were not able to be measured. These include process improvements such as creating medication order sets and calling veterans prior to shipment of costly refrigerated medications to avoid replacements. Order sets were created by the ISCP to streamline the medication ordering process for specialty providers to prevent potential dispensing errors.

An additional potential indirect cost avoidance was identified with the reduction in infusion time associated with IVIG dose optimizations. A retrospective analysis of 2564 patients receiving IVIG over 5 years estimated an annual infusion time savings of 1366 hours by dosing IVIG utilizing IBW.<sup>3</sup> Dosing IVIG by IBW decreases the amount of product in individuals with overweight or obesity, and it also decreases infusion time, therefore decreasing nurse labor and veterans’ time at appointments.

Of the specialty providers who completed the questionnaire, 94% reported being “very satisfied” with the ISCP’s coordination of patient care, communication, professionalism, responsiveness to inquiries, and accessibility. Many specialty medications have varying loading and maintenance dosing dependent on the indication, which can lead to order entry errors. The majority (88%) of providers self-reported that with the assistance of the ISCP they were somewhat or very likely to have made fewer order entry errors, which can be costly and impact patient safety and treatment outcomes. In addition, 99% of veterans self-reported that it was very likely that they used the specialty medication more appropriately after initial education with the ISCP. Questionnaire results highlighted the ISCP’s positive impact on patient care, including improved medication

safety, communication, and understanding of specialty medication therapy.

Cost avoidance results and positive feedback from both specialty providers and veterans support the value of ISCP positions at other VA health care systems as well as within private sector specialty clinics. Non-VA clinics could additionally benefit from collaboration with a specialty clinical pharmacist to assist with formulary management, prior authorizations, and pharmacogenomic interventions. Highlighting the impacts of the specialty clinical pharmacist will play a key role in future negotiations for reimbursement of pharmacist services and role classifications.

### Limitations

There were several limitations to this QI project, including the inability to quantify indirect cost avoidance due to lack of specific time-saving and error-avoiding metrics. In addition, the direct cost avoidance was expressed as projected annual cost avoidance. Actual cost avoidance would be dependent on veteran medication adherence in addition to veteran tolerability and clinical response to the converted medication.

Several factors may have contributed to the veteran questionnaire response rate of 58.5%, including extended length of time since the appointment with the ISCP (up to 22 months), potential phone call variance, and incomplete responses. Several veterans explained that they did not remember their experience with the ISCP and therefore did not complete the questionnaire. When veterans were contacted via telephone, some asked follow-up or clarifying questions, and others provided feedback based on their overall experience with the pharmacy, specialty clinic, or their personal success with the medication, all of which were not the intent of the questionnaire. Lastly, questions were asked on a Likert scale with only 5 options as well as yes/no responses, which both limited potential responses.

### CONCLUSION

This QI project illustrates that an ISCP can be a valued health care team member integrated into the specialty medication care provided to patients. This clinical pharmacist can assist in reducing overall health care burden by being a key collaborator in specialty treatment selection, education, and monitoring of specialty medications. The ISCP can also have a substantial impact on specialty medication expenditure by retroactively completing medication conversions and dose optimizations based on current clinical data and patient-specific appropriateness. 🌍

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# Enhancing Medication Safety Through USP Health Literacy Standards and Solutions

USP provides health literacy standards and solutions that enhance medication safety and improve patient outcomes.

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**M**edications safety is a critical concern in health care as medication errors can lead to adverse events (AEs), increased hospitalizations, and higher health care costs. At least 1.5 million people in the United States are harmed annually by medication errors, with associated costs exceeding \$3.5 billion per year.<sup>1</sup> Approximately one-third of AEs occur within the outpatient setting, and they are believed to be caused by patients not administering medicine as intended.<sup>2</sup>

In 2022, the IQVIA Institute for Human Data Science reported that more than 6.7 billion prescriptions were dispensed in the outpatient setting nationally.<sup>3</sup> This equates to approximately 19 prescriptions for every American.<sup>3</sup> Patients are dealing with chronic conditions and polypharmacy, defined as the regular use of 5 or more medications at the same time, which can be a contributing cause of errors during the prescribing, dispensing, and administering of medications. For this reason, the main sources of information on why, how, when, and what to look for when taking medication should be the prescription container label, medication information, and provider-patient communication.

Medication errors stemming from unclear or inaccurate labeling pose a significant risk to patient safety and health care outcomes. Clear labeling is of paramount importance in safe medication use. The United States Pharmacopeia (USP) established *USP* General Chapter <17> Prescription Container Labeling to provide a universal approach to labeling prescription medication.<sup>3</sup> This chapter includes guidance on the format, appearance, content, and language of medication instructions, directing health

care practitioners to utilize simple, concise language and provide explicit instructions that include the purpose for use and how to handle oral liquid medication dosing tools, if applicable.<sup>3</sup> The aim is to present the information on the label in a patient-centered manner that promotes patient understanding and helps mitigate medication errors.

Findings from studies have shown that variability in labeling and the use of certain terminology can adversely affect a patient's understanding of medication instructions.<sup>2</sup> Implementing *USP* General Chapter <17> Prescription Container Labeling addresses the need for using standardized, explicit instructions to improve patient understanding and promote safe medication use.<sup>4</sup> Furthermore, a lack of understanding about the drug product container label can lead to a higher risk of adverse medication use. To help ensure that product container labels are useful to health care providers in directing patients on their medications and treatments, *USP* General Chapter <7> Labeling emphasize the importance of cautionary statements to convey important safety messages, which should be simple, concise, and printed in a contrasting color to prevent imminent life-threatening situations for patients.<sup>5</sup> For example, this standard specifies that product labels and labeling for injectable products should include instructions or medication warnings, such as dilution instructions, storage conditions, and recommended dosage.<sup>5</sup>

Dispensing medications, a critical component of the pharmaceutical care process, can inadvertently lead to medication errors that jeopardize patient safety and undermine therapeutic outcomes.

# Individuals with low literacy or low English proficiency will greatly benefit from additional interventions, such as counseling and visual aids to mitigate the risk of misinterpretation.

The problems that can contribute to dispensing errors include the following<sup>6</sup>:

- Heavy health care practitioner workload
- Interruptions and distractions
- Illegible handwriting
- Similar drug names
- Failure to verify patient information
- Uncomfortable working conditions

USP General Chapter <1265> Written Drug Prescription Information Guidelines provides health care providers with information on how to utilize supplemental documentation, in a prescription drug leaflet format, to optimize the counseling of patients about their medicine. The chapter instructs that this documentation should provide details about the drug, including brand and generic names, pronunciation guides, and indications to ensure understanding of medication information.<sup>7</sup>

Individuals with low literacy or low English proficiency will greatly benefit from additional interventions, such as counseling and visual aids to mitigate the risk of misinterpretation.<sup>8</sup> Findings from studies show that patients with health literacy limitations are 3.4 times more likely to interpret prescription medication warning labels incorrectly.<sup>9</sup> Such interventions can significantly reduce medication errors and improve patient outcomes.

USP provides health care professionals access to a database of pictograms, which are standardized graphic images that help convey medication instructions, precautions, and/or warnings to patients. Data have shown that the USP pictograms have been of great value to pharmacists and pharmacy staff seeking to ensure that essential medical information is understood by patients with a lower reading level ability and patients for whom English is a second language.

As a standard-setting organization, USP is committed to improving global public health. The organization collaborates with key stakeholders to develop and refine standards and solutions to address health literacy challenges.<sup>7</sup> USP collaborates with health care

professionals by equipping them with the most up-to-date materials, guidance, and standards to assist them in delivering safe and efficient patient care. 🌐

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# Risks and Impacts of Cannabis Use During Pregnancy: A Growing Concern for Neonatal Health

Cannabis use during pregnancy may harm fetal development and long-term health.

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Cannabis use has increased over the past few years among the American population, and pregnant individuals are no exception. However, the use of cannabis in pregnant individuals has the potential to impact fetal development. In a study conducted by Young-Wolff et al, roughly 20% of the 279,457 pregnant women aged 24 or older studying in California between 2009 and 2016 tested positive for cannabis on a routine drug screen at a prenatal care appointment. The percentage of younger pregnant women using cannabis started at around 12.5% in 2009 and gradually increased to about 22% throughout the 7 years the study was conducted.<sup>1</sup> During this period, the use of cannabis in pregnant women aged 25 to 34 years remained relatively stagnant, likely due to cannabis use being most prevalent in women aged 18 to 25 years.<sup>2</sup>

However, Young-Wolff et al explain that self-reporting of cannabis use during pregnancy is also neither accurate nor reliable, as only 29.2% of the 54.9% of women who tested positive on drug screens reported their cannabis use. There are a variety of reasons why pregnant women may choose not to disclose their cannabis use, but one notable reason may be the stigma associated with substance use of any kind during pregnancy. However, it is important to address this stigma, specifically in relation to cannabis use, as cannabis can impact the health of neonates.

The impact of cannabis on neonates can be attributed to the variety of chemicals it contains, with the primary components being tetrahydrocannabinol (THC) and cannabidiol (CBD). Since the 1990s, the potency of THC found in forms of nonmedical cannabis has increased from approximately 4% to more than 15%.<sup>3</sup>

The chemical structure of THC is similar

to a chemical in the brain called anandamide. This similar structure allows THC to be recognized by the brain and alter brain communication.<sup>4</sup> THC, a psychoactive chemical, binds to our endogenous cannabinoid receptors, influencing areas of the brain that affect coordination, concentration, thinking, memory, and pleasure.<sup>4,6</sup>

CBD, on the other hand, is a nonpsychoactive chemical found in cannabis.<sup>7</sup> Medical formulations of CBD are not intended to contain THC. CBD alone is often well-tolerated by individuals but induces adverse effects such as dry mouth, drowsiness, changes in alertness, gastrointestinal distress, and changes in mood (eg, irritability and agitation).<sup>8</sup> The purity and dosage of CBD products are often unreliable, as many products contain lower amounts of CBD than indicated, or they potentially contain THC.<sup>8,9</sup>

One of the first steps to establish safety and toxicity limits of cannabis use in the general population—and specifically within the pregnant population—is stricter regulations with clear labeling of doses and ingredients. Similarly, long-term studies are needed to evaluate the lasting effects of in-utero cannabis exposure and whether there is a dose-dependent relationship with potential toxicities.

The main concern about cannabis use during pregnancy is that the chemicals in cannabis, such as THC, can pass to the baby through the placenta. A 2015 study published in *Frontiers of Human Neuroscience* scanned the brains of babies exposed to cannabis in utero, looking specifically at the caudate, insula, amygdala, and other regions of the brain.<sup>10</sup> These scans found that the neonates exposed to cannabis in utero had altered connectivity between certain areas of the brain compared with neonates who were not exposed. These alterations in

**TABLE 1.** Possible Negative Effects of Cannabis Exposure in Utero Over the Years<sup>11</sup>

Age	Effects
17-22 weeks gestation	Reduced foot length and body weight; decreased dopamine messenger RNA in amygdala of males only; decreased opioid peptide and receptor in caudal putamen and thalamus, respectively; increased opioid receptor in amygdala
Neonate	Decreased body length; increased tremors, exaggerated startles, and diminished responsiveness to light; more irritable; less responsive to calming; increased jitters and startles
9 months	Delayed mental development
1 year	Decreased motor scores; no effect on mental development
3 years	Lower sleep efficiency; more nocturnal arousals; more awake time after sleep onset
6 years	More impulsive and hyperactive; lower overall composite score (intelligence); reduced verbal reasoning, quantitative reasoning, and short-term memory
10 years	Increased inattention, hyperactivity, impulsivity, delinquent behavior, and externalizing problems; increased levels of depressive symptoms
13-16 years	Decreased stability of attention over time; lower scores in abstract designs and Peabody spelling test. <sup>a</sup>
18-22 years	Increased bilateral prefrontal cortex activity; increased right premotor cortex activity; decreased activity in left cerebellum; decreased activity in right brain regions

<sup>a</sup>Peabody spelling test: subsection of the Peabody Individual Achievement Test (PIAT) to assess spelling recognition abilities using unfamiliar words to measure the individual's understanding of spelling patterns and rules.<sup>15</sup>

brain function connectivity could contribute to deficits in the child's motor-spatial activity, attention, integration and coordination, and social-emotional stability.<sup>10</sup> Further, this is not the only study to raise concerns about the use of cannabis during pregnancy, as other studies have suggested similar warning signs of function and behavior in children exposed to cannabis in utero.<sup>11,12</sup>

*Future Neurology* published an article discussing the manifestations that cannabis use can have on a person in each stage of life after exposure to cannabis in utero.<sup>11</sup> In neonates, it was noted that a decrease in the dopamine receptor levels in the brain and a reduction in birth weight may occur. In early development, there have been observations of a reduction in verbal reasoning scores and short-term memory, as well as an increase in aggression, anxiety, and depression. Additionally, there have been links between prenatal cannabis exposure and impaired executive functions, such as impulse control, visual memory, and attention throughout the school year. There are also reports of young children experiencing an increase in impulsivity, inattention, and hyperactivity, which are all symptoms found in children with attention-deficit/hyperactivity disorder.<sup>11</sup> In adolescents, an increase in depressive symptoms,

delinquency, and antisocial behavior, and a reduction in abstract reasoning were found.<sup>13,14</sup> Even into adulthood, there are implications of an increased likelihood of drug-seeking behavior and a reduction of visuospatial memory in those exposed to cannabis in utero.<sup>11</sup> These articles do not include a specific statistical analysis of risk but rather emphasize the life-long possible risks associated with cannabis use in pregnant women (**Table 1**<sup>11</sup>). Additional human studies are needed to determine the definitive impact cannabis can have on this specific population.

Although the long-term effects of cannabis use on children in utero are still unclear due to the lack of human trials and research, preliminary findings suggest that prenatal cannabis use may impair fetal growth and development, which could increase the risk of stillbirths.<sup>1,16</sup> A study by Varner et al looked at the association between illicit drug use, smoking, and stillbirths. Results from the study showed that women with pregnancy potential with documented THC acid (THCA) levels had a 2-fold increase in the odds of stillbirth. THCA was the most common individual drug detected among pregnant women with stillbirth, with an odds ratio of 2.34 (95% CI, 1.13-4.81). This result indicates that pregnant women who are exposed to THCA are 2.34 times more likely to experience stillbirths than those who are not exposed to THCA.<sup>16</sup>

Small numbers of controlled substances, such as hydrocodone and morphine, also trended toward increased odds of stillbirth in another study.<sup>16</sup> This finding is particularly significant in light of the ongoing prescription opioid misuse crisis, emphasizing the potential risks associated with these medications during pregnancy.<sup>16</sup> However, there may be a confounding relationship between illicit drug use and stillbirth due to concomitant tobacco smoking, since those who were positive for both nicotine and substance drug use had an odds ratio for stillbirth at 3.86 (95% CI, 1.61-9.24).<sup>16</sup> Pregnant women who use both nicotine and illicit drugs had nearly 4 times (3.86 times) the odds of experiencing stillbirth compared with those who did not use either substance.

The growing use of cannabis during pregnancy may be attributed to the increasing legalization of recreational cannabis use across the country. California and Washington were the first 2 states to legalize the use of recreational cannabis in 2012. Over the next decade, 22 additional states and 2 U.S. territories followed suit, totaling 24 states to legalize the use of cannabis for non-medical purposes. Meanwhile, 47 states permit the use of medical cannabis, as well as three U.S. territories.<sup>17</sup> Due to the increasing number of states legalizing cannabis, the number of pregnant women using cannabis is likely to increase based on recent surveys conducted by the National Institute of Health.<sup>4,17</sup> To change the trajectory of these growing rates, health care professionals must acknowledge the issue and

**TABLE 2.** Possible Safe Alternatives to Cannabis During Pregnancy<sup>a</sup>

Condition	Pharmacologic	Nonpharmacologic
Nausea and vomiting	<ul style="list-style-type: none"> <li>Pyridoxine (vitamin B6) with or without doxylamine</li> <li>Ondansetron for persistent N/V (after the first trimester)<sup>18</sup></li> </ul>	<ul style="list-style-type: none"> <li>Prenatal vitamins 1 month prior to pregnancy</li> <li>Smaller meals</li> <li>Avoid spicy or fatty meals (try high-protein meals)</li> <li>Rest and avoid sensory stimuli (eg, odors, heat, noise, flickering lights)</li> <li>Ginger (may improve nausea)<sup>18</sup></li> </ul>
Major depressive disorder and/or anxiety	<ul style="list-style-type: none"> <li>SSRIs: citalopram (Celexa; Allergan, Inc), sertraline (Zoloft; Pfizer), escitalopram (Lexapro; Forest Laboratories, Inc), fluoxetine (Prozac; Eli Lilly and Company)</li> <li>SNRIs: venlafaxine (Effexor XR; Pfizer), duloxetine (Cymbalta; Eli Lilly and Company)</li> </ul>	<ul style="list-style-type: none"> <li>Psychotherapy</li> <li>Cognitive behavioral therapy<sup>19</sup></li> </ul>
Epilepsy	<ul style="list-style-type: none"> <li>Lamotrigine</li> <li>Levetiracetam</li> <li>Avoid polytherapy, if possible<sup>19</sup></li> </ul>	<ul style="list-style-type: none"> <li>Yoga</li> <li>Acupuncture<sup>21</sup></li> </ul>
Pain management	<ul style="list-style-type: none"> <li>Acetaminophen (OTC)</li> <li>NSAIDs (only for first 2 trimesters)<sup>22</sup></li> </ul>	<ul style="list-style-type: none"> <li>Acupuncture 22</li> <li>Neurostimulation (eg, TENS)</li> <li>Hypnosis</li> <li>Comfort therapy (eg, heat/cold application, companionship, massage)</li> <li>Physical/occupational therapy</li> <li>Psychosocial counseling<sup>23</sup></li> </ul>
Multiple sclerosis	<ul style="list-style-type: none"> <li>Glatiramer acetate</li> <li>All other medications should be discontinued at least 4 months before conception</li> </ul>	<ul style="list-style-type: none"> <li>Yoga and aerobic exercise</li> <li>Cognitive behavioral therapy<sup>24</sup></li> <li>Massage</li> <li>Healthy diet (eg, fruits, vegetables, whole grains, lean proteins)<sup>25,26</sup></li> </ul>


NSAID, nonsteroidal anti-inflammatory drug; N/V, nausea and vomiting; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TENS, transcutaneous electrical nerve stimulation.

<sup>a</sup>Discuss your treatment plan with your physician before stopping or starting any medication.

recommend alternatives to cannabis that take into account clinical indications, patient-specific factors, and particular circumstances (**Table 2**).

It is important to note that medical cannabis use has provided some benefits in pregnancy, despite the neonatal effects that were observed. There are a variety of clinical uses of cannabis, although the FDA-approved indications are few. For instance, Epidiolex (Jazz Pharmaceuticals), which contains pure forms of CBD, is FDA-approved for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.<sup>27-29</sup> Additionally, dronabinol (Marinol; Solvay Pharmaceuticals), which is a synthetic form of THC, is FDA-approved for the treatment of HIV/AIDS-induced anorexia as well as chemotherapy-induced nausea and vomiting in patients who failed antiemetics.<sup>11,30</sup> However, these FDA-approved forms of cannabis have been used off-label to help patients with various disease states, such as epilepsy, depression, anxiety, insomnia, multiple sclerosis, and pain management. Cannabis has also been used off-label to help with nausea and vomiting that pregnant women may

experience during their first trimester.<sup>5</sup> Based on a survey conducted by the *American Journal of Obstetrics and Gynecology*, 79% of 785 pregnant women surveyed between 2007 and 2012 reported perceiving little to no harm in the prenatal use of cannabis.<sup>31</sup> These survey results emphasize the need for public education of both benefits and risks (**Table 3**<sup>32</sup>).

In conclusion, the use of cannabis during pregnancy remains a contentious issue with potentially serious consequences for infants' development. While some studies suggest the potential benefits of cannabis use for certain medical conditions, the overall consensus is to be cautious and discourage cannabis use during pregnancy. The limited research available further raises concerns as there are currently many unknowns concerning risks. Additional research is needed to further elucidate the potential short- and long-term benefits and risks of prenatal cannabis use. 

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**TABLE 3.** Summarized Risks of Cannabis Use During Pregnancy<sup>32</sup>

<b>Studies show that the use of cannabis during pregnancy may:</b>
Increase risk of stillbirth
Increase risk of impulsivity, inattention, and hyperactivity, all of which are symptoms of attention-deficit/hyperactivity disorder
Increase children's depressive symptoms, delinquency, and antisocial behavior during their adolescent years
Increase likelihood of drug-seeking behavior in children exposed to cannabis in utero, even into adulthood

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## Tyler M. Kiles, PharmD, MPH, BC-ADM, Discusses Embracing Pharmacy Research and Shaping Health Equity in Practice

Kiles explores the impact of pharmacy research on health equity and education.

**P**harmacy Times interviewed Tyler M. Kiles, PharmD, MPH, BC-ADM, clinical assistant professor in the Pharmacy Practice Division at The University of Texas at Austin College of Pharmacy, on her journey into pharmacy research.

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

**Tyler M. Kiles, PharmD, BC-ADM:** I actually was never interested in research as a pharmacy student, but during my residency program I was really encouraged to develop a research project based on my interests, and I found the process really fun. I didn't realize how much I enjoyed reading literature about the things I was interested in, asking questions, and writing about the things I was passionate about until that point. This initial exposure really helped me see research as a potential part of my future career.

Research has also really shaped my work as an educator as there hasn't been much literature published about my areas of expertise, such as incorporating social determinants of health in pharmacy education and practice. It has been exciting to be at the forefront of advancement in this area, in the classroom as well as in pharmacy practice.

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

**Kiles:** I have had several roles in the research team, from initiating the project idea to collaborating with others to mentoring residents to develop their research ideas and projects. I primarily work with other pharmacists in my research, though I have collaborated with other PhD researchers with a specialization in qualitative or educational research.

**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?

**Kiles:** My first collaborators were other individuals within my institution; however, as my research portfolio has grown, I have found the majority of my research

collaborators through informal peer networks or professional organization opportunities. It has been exciting to find like-minded individuals with different areas of expertise. It has also been a joy to take the research mentorship I've received and pass it along to other junior faculty colleagues who are inspired to do work in similar areas.

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

**Kiles:** One of my greatest accomplishments as a researcher has been being invited to speak to the Joint Commission of Pharmacy Practitioners, a collaboration of the leaders of 13 national pharmacy associations, about the importance of incorporating SDOH in pharmacy education and practice. This opportunity was relatively early in my career, but it really made me feel like my research was meaningful and encouraged me to keep exploring this area. I have also been invited to present on numerous occasions about my research related to structural changes needed to diversify clinical pharmacy and pharmacy academia through the pharmacy residency pathway. These humbling opportunities make me feel like my perspective and experiences are valued within the academy. It's one thing to publish papers and hope that someone reads them, and it's another to share with people and have them imagine how they could apply your work to their sphere.

**Pharmacy Times:** What is a recent publication showcasing your research that you are proud of?

**Kiles:** A recent publication that I am proud of is "Following Your Dreams, and Not Killing Yourself to Do So": Black PharmD Student Perceptions of Pharmacy Residency," which was published in the *American Journal of Pharmaceutical Education*.<sup>1</sup> This qualitative project provided tangible recommendations for the pharmacy academy to support minoritized students with the goal of addressing health disparities through a diverse clinical pharmacy workforce and subsequently enhanced provision of clinical pharmacy services for minoritized patients. This paper ties together my interest in advancing health equity through pharmacy education. 🌱

# Understanding Gender-Affirmative Care Beyond Women's Health

Gender-affirming care and inclusive practices are essential for health equity.

Rachel Chandra, PharmD, MPH, FASHP

## ABOUT THE AUTHORS

**Rachel Chandra, PharmD, MPH, FASHP**, is a clinical pharmacist practitioner and PGY-1 program director at Dayton VA Medical Center in Ohio.

In recent years, there has been increasing awareness and understanding of gender as a fluid social construct that differs from biological sex. While sex is defined by physical characteristics, such as chromosomes and reproductive organs, gender refers to how individuals perceive and express themselves. Gender-affirmative care (GAC) is a holistic approach to health care that supports individuals' expressed gender identity. Understanding gender identity, implementing inclusive language, and creating welcoming health care environments are essential steps toward ensuring that all individuals, regardless of their gender, receive the care they need.

## Gender vs Sex

Gender is a social construct. As an expression of their gender identity, an individual may identify as cisgender, nonbinary, transgender male or female, genderfluid, or genderqueer.<sup>1,2</sup> Sex, on the other hand, is defined as biological characteristics at birth, such as reproductive, chromosomal, and hormonal characteristics. The sex of a baby at birth is often categorized as either male or female, although intersex is also a category.<sup>1</sup>

Further, gender identity pertains to a personal self-identity that may or may not align with a person's dress code, facial and body hair grooming, or how they speak. On the other hand, the manner with which a person externally expresses themselves, such as through their clothing, hairstyle, facial grooming, or behavior is called their gender expression.<sup>1</sup> The ideal way to know a person's gender is to ask them, while also keeping in mind that gender identity may not be permanent; basically, asking an individual about their gender identity at their first

appointment while establishing care may not be sufficient, as this question can remain a relevant component of care into the future.

## What Is GAC?

GAC is defined by the World Health Organization as a type of health care that includes one or a combination of social, psychological, behavioral, or medical interventions that are intended to support and affirm one's gender identity.<sup>3</sup> GAC is applicable for individuals of all ages (ie, children, adolescents, and adults).<sup>4</sup>

Transgender and nonbinary individuals often experience gender dysphoria, which the Human Rights Campaign defines as "clinically significant distress caused when a person's assigned birth gender is not the same as the one with which they identify."<sup>2,4,5</sup> When health care providers deliver GAC in a manner that is age-appropriate and evidence-based, individuals can interact with health care providers as their authentic and true selves, which supports trust within the relationship.

To understand GAC beyond women's health, a working knowledge of appropriate terminology is a crucial step (**Table**).<sup>2</sup> The 2021 edition of the "Inclusive Language Guide" by the American Psychological Association provides guidance that supports person-first language infused with cultural humility to promote gender-inclusive and affirming language for gender-diverse individuals.<sup>6</sup>

## What Does It Mean for Someone to Transition?

Gender transitioning is the process by which an individual (transgender or nonbinary) actively takes steps to live their authentic life in their true gender identity. The transition process is a personal



<b>TABLE. Terms and Definitions in Gender Identity<sup>2</sup></b>	
<b>Terminology</b>	<b>Definition</b>
Ally	An ally is an individual who is actively supportive of LGBTQ+ people. Allies may be straight and cisgender, as well as those within the LGBTQ+ community who support each other (eg, a lesbian who is an ally to the bisexual community).
Cisgender	An individual whose gender identity is the same as their sex assigned at birth.
Gender dysphoria	Clinically significant distress caused when a person's assigned birth gender is not the same as the one with which they identify.
Genderfluid	A person who does not identify with a single fixed gender or has a fluid or unfixed gender identity.
Genderqueer	Genderqueer people typically reject static categories of gender and embrace a fluidity of gender identity. People who identify as genderqueer may see themselves as being both male and female, neither male nor female, or as falling completely outside these categories.
Intersex	Intersex people are born with a variety of differences in their sex traits and reproductive anatomy, including differences in genitalia, chromosomes, gonads, internal sex organs, hormone production, hormone response, and/or secondary sex traits.
Lesbian	A lesbian is a woman who is emotionally, romantically, and/or sexually attracted to other women. Women and nonbinary people may use this term to describe themselves.
LGBTQ+	An acronym for lesbian, gay, bisexual, transgender, and queer with a plus sign to recognize the limitless sexual orientations and gender identities used by members of the Human Rights Campaign and their community.
Nonbinary	An individual who does not identify exclusively as a man or a woman.
Questioning	A term used to describe people who are in the process of exploring their sexual orientation or gender identity.
Sex assigned at birth	The sex (ie, male, female, or intersex) that a doctor or midwife uses to describe a child at birth based on their external anatomy.
Sexual orientation	An inherent or immutable enduring emotional, romantic, or sexual attraction to other people. Of note, an individual's sexual orientation is independent of their gender identity.
Transgender	An overarching term for people whose gender identity and/or expression is different from cultural expectations based on the sex they were assigned at birth.
Transitioning	A series of processes that some transgender people may undergo to live more fully as their true gender.

one and is different for each individual. Gender transitions may be social, medical, legal, or surgical.

Social transitioning refers to when a person uses reversible and nonmedical steps, such as adopting a new name and pronouns, a new hairstyle, different clothes, and/or sharing their gender identity. Medical transitioning is when individuals use sex hormones, such as androgen inhibitors or estrogen, to develop secondary sex characteristics. Legal transitioning involves elements of social transitioning and name change on legal documents such as driver's licenses. Surgical transitioning includes a broad range of procedures, such as plastic surgery to change features to appear either more masculine or feminine. Categories of surgeries may be referred to as top surgery or bottom surgery. Top surgery creates the desired gender chest or torso shape, and bottom surgery creates changes to the reproductive organs.<sup>5</sup>

### Does GAC Matter?

Outside of the relevance of GAC in health equity, decreasing disparities in care, and supporting patient trust in their health care providers and the health care system at large, Title VII of the Civil Rights Act of 1964 also prohibits discrimination in the workplace on the basis of sex. For this reason, there is a legal liability component to the importance of GAC.

#### *Bostock v Clayton County: A Landmark US Supreme Court Civil Rights Case*

In a case brought forward in Georgia, Gerald Bostock was fired for "conduct unbecoming of its employees" after he joined a gay softball league in 2013. Bostock sued because he alleged he was protected under Title VII on the basis of sexual orientation. Clayton County argued that Title VII does not prohibit such discrimination. It did not argue that sexual orientation

played any role in his being fired. In 2017, a decision in the federal appeals court in Georgia stated that Title VII did not protect LGBTQ workers and as such did not have a case in Georgia. The case was then taken up by the Supreme Court. In 2020, the Supreme Court's decision in *Bostock v Clayton County* ruled that Title VII of the Civil Rights Act of 1964 also extends to discrimination based on sexual orientation and gender identity because Title VII protects individuals, not populations.<sup>7,8</sup>

“The Supreme Court has made clear that people have a right not to be discriminated against on the basis of sex and receive equal treatment under the law, no matter their gender identity or sexual orientation. Fear of discrimination can lead individuals to forgo care, which can have serious negative health consequences,” said US Department of Health and Human Services (HHS) Secretary Xavier Becerra in an HHS statement. “It is the position of the Department of Health and Human Services that everyone—including LGBTQ people—should be able to access health care, free from discrimination or interference, period.”<sup>7</sup>

### GAC Beyond Women's Health

Traditionally, the term *women's health* has centered around the care of cisgender women (who are assigned the female sex at birth and identify as female). However, there are individuals of different genders, such as genderqueer, nonbinary, and others, who can and do carry pregnancies. A transgender woman and nonbinary individuals may require obstetric and gynecological services such as contraception, fertility care, estrogen treatment, and surgical care. When seeking appropriate care, these individuals often experience stigmatization, verbal harassment, fear of discrimination, and refusal of care, which contributes to social and health inequities in gender-diverse populations.<sup>9-11</sup>

### Overcoming Barriers to Care for All

Changes in language and environments can provide a welcoming and safe platform for the gender-diverse population in clinical settings. Further, some changes are simpler than others to achieve. To foster gender-diverse care that is psychologically safe, staff education is an important step in ensuring that everyone has a working knowledge of inclusive terminology and environmental considerations for gender-diverse individuals.

#### Language/Communication Considerations

- Changes in language is a simple way for all health care workers (including pharmacists and pharmacists' technicians) to be gender-inclusive in clinical care,

health policy, and patient advocacy. A shift to more gender-inclusive language among all health care workers can decrease stigmatization and fear, supporting a psychologically safe environment for gender-diverse individuals.

- All patients should be asked about their pronouns in a manner that makes them feel more comfortable. Pronouns can be stored in their medical record in areas visible and accessible to all staff (clinical and nonclinical) to foster appropriate communication.
- When working through insurance claims, both gender identity and gender at birth may be helpful components to note for benefits.
- Patient education materials should be created to include gender-diverse populations and language for all patients to feel a sense of belonging.
- Use gender-neutral terminology for examinations and procedures, such as *preventive care visits* instead of *well-woman visits*.

### Environmental Considerations

- Bathroom/changing room signage for a gender-specific bathroom creates an environment that is gender-inclusive. A transgender woman may be more inclined to get a mammogram screening at a facility where a gender-specific bathroom is available.
- Office color and decor may impact one's sense of belonging. For example, signage designating “women's space” using the color pink or lots of butterflies may be considered gender-exclusive. Office design schemes can be modified to be more gender-inclusive.
- Signage on rooms for infant feeding can be modified to say “infant feeding room” instead of “mothers' room” to foster inclusivity.

Fostering an inclusive and affirming health care environment for all individuals, regardless of their gender identity, is crucial for promoting health equity and reducing disparities. By understanding the differences between gender and sex, embracing GAC, and incorporating inclusive language and practices, health care providers can create spaces where individuals feel respected and supported, which can influence various aspects of health care outcomes. As society continues to evolve, it is essential that health care systems adapt to meet the needs of gender-diverse populations, ensuring everyone has access to compassionate and non-discriminatory care. Through education, understanding, and empathy, we can work toward a health care landscape where all individuals can thrive. 🌍

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# Strategies and Opportunities to Enhance Pharmacists' Role in Hyperkalemia Management

Pharmacists can improve hyperkalemia management through collaboration and innovation.

Alana Hippensteele, Lead Editor

**H**yperkalemia management is an area in which pharmacists can have a significant impact, particularly in ensuring that guideline-directed medical therapy (GDMT) is maintained while addressing elevated potassium levels. During a recent *Pharmacy Times* Clinical Forum discussion, Craig Beavers, PharmD, FACC, FAHA, FCCP, BCCP, BCPS-AQ Cardiology, CACP, vice president of professional services at Baptist Health Paducah in Kentucky, and a panel of pharmacists shared insights on the tools and strategies that may enhance the pharmacist's role in hyperkalemia care while addressing barriers and opportunities for improvement.

Danielle Garcia, PharmD, BCPS, a clinical pharmacy manager in transitional care excellence at Montefiore Health System in Bronx, New York, highlighted the complexity of finding tools that are both effective and well received by providers. She noted that although best practice alerts (BPAs) may seem like an ideal solution, they often lead to alert fatigue among providers, diminishing their efficacy. For example, Garcia noted that providers are more likely to ignore BPAs or override them during a busy shift. Garcia emphasized that the success of interventions such as BPAs often depends on ensuring they do not overwhelm the clinical workflow.

Tania Ahuja, PharmD, FACC, BCCP, BCPS, CACP, assistant director of clinical pharmacy services at NYU Langone Health in New York, New York, pointed out that the lack of robust national guidelines complicates the management of hyperkalemia, leaving health care providers to rely on inconsistent recommendations. This gap underscores the need for standardized pathways and protocols that integrate hyperkalemia management into broader GDMT frameworks. Similarly, Katherine E. Di Palo, PharmD, MBA, MS, an assistant professor in the Department of Medicine at the Albert Einstein College of Medicine at the Montefiore Health System, expressed frustration with the lack of pharmacy-driven guidelines. Specifically, Di Palo noted that pharmacists should take the lead in developing

hyperkalemia protocols tailored to pharmacotherapy.

“My key takeaways are that there's power in numbers and when it comes to pharmacotherapy, we are the key opinion leaders and we are the subject matter experts here. So why are we using other people's guidelines to figure out our algorithms, our pathways, and our protocols? It's because we don't have any of our own,” Di Palo said. “What would make sense to me as next steps and action items is for us to start to develop a compendium of tools [for] pharmacotherapy and clinical decision support and how we get to the right drugs if the laboratory can't suggest what's on the formulary.”

The discussion also explored the importance of incentivizing providers to adhere to GDMT. Garcia suggested that tying provider incentives to the prescription of GDMT could encourage the appropriate use of therapies rather than prematurely discontinuing agents such as renin-angiotensin system inhibitors due to mild hyperkalemia. Beavers elaborated on this point, sharing an example of a heart failure pathway implemented at Baptist Health Paducah. This pathway, developed collaboratively across multiple disciplines, includes decision points that require providers to justify deviations from the protocol, ensuring accountability and promoting adherence to evidence-based practices.

A consistent theme among the panelists was the importance of collaborative practice agreements (CPAs) and interdisciplinary protocols. Jenna Ingram, PharmD, BCACP, ambulatory clinical pharmacy manager in cardiology at Mount Sinai Health System in New York, New York, recognized an opportunity to incorporate hyperkalemia management into existing CPAs, ensuring pharmacists have a more defined role in addressing this condition. Similarly, Isha Rana, PharmD, associate director of ambulatory pharmacy at Mount Sinai Health System; Kaitlyn Pinkos, PharmD, BCCP, a cardiothoracic intensive care unit clinical pharmacy specialist at New York-Presbyterian; and Shanice Coriolan, PharmD, BCPS, BCACP, BC-ADM, an ambulatory care pharmacist at New York-Presbyterian

in New York, advocated for protocols to extend from inpatient to outpatient settings, where hyperkalemia management is often less structured.

“I would say we don’t have a formal [policy] for outpatient. But I think it’s because the [policies are] hybrid and they’re [using] an inpatient/outpatient protocol,” Coriolan said. “We have [sodium zirconium cyclosilicate (Lokelma; AstraZeneca)] on formulary, so outpatient is sending [sodium zirconium cyclosilicate] because that’s what they’re used to sending, and it only gets flipped if we get something back from the insurance. But I would say a lot of it comes from just [doing] what they’re used to.”

Ingram also emphasized the need to share expertise with other health care professionals on the team when discussing the treatment for hyperkalemia, which can foster a more unified approach. “On the inpatient side, [treatment approach] really depends on the patient and what they’re coming in for as well as their baseline renal function. I think there’s no specific approach that we take, but we all discuss it and take everything into consideration to make the best decision for the patient. So if it’s mild hyperkalemia, we get a baseline of what their potassium [level] may be at home and see if we can just change it with some of the medications or consider giving [sodium zirconium cyclosilicate] if needed,” Ingram said. “But because in the intensive care unit we have closer monitoring, if we see any electrocardiogram changes or more moderate to severe hyperkalemia, then we can act on it more quickly than other scenarios.”

Rebecca Chu, PharmD, BCPS, clinical pharmacy specialist at Northwell Health in New York, discussed challenges related to medication formulary management, particularly in settings with varying insurance coverage and socioeconomic factors. She proposed expanding pharmacists’ authority to interchange medications within the same therapeutic class to streamline patient care and minimize delays.

“When you have a patient who needs [potassium binders] urgently, the burden of a prior authorization stands in the way more than it does for [long-term] therapy,” Chu said.


Di Palo also highlighted the importance of the appropriate use of hyperkalemia therapies to avoid unnecessary interventions, such as the overuse of potassium binders. “There was a study published

at our institution that actually looked at potassium lowering in patiromer [Veltassa; Vifor Pharma, Inc] and also looked at the prescribing patterns, in terms of the thresholds for initiating a potassium binder as well as how quickly they would follow up,” Di Palo said. “Because you get the 5.5 [mEq/L], they throw in a binder. Some of them didn’t even check it. So that was an interesting thing for us.”

From the inpatient perspective, Juri Chung, PharmD, clinical pharmacy specialist at North Shore University Hospital in Manhasset, New York, and Abhishek Shah, PharmD, clinical pharmacy manager at Montefiore Medical Center, emphasized the role of education in optimizing hyperkalemia management. Chung noted that although order sets exist in many institutions, they are often underutilized due to workflow barriers or lack of awareness. Shah stressed the importance of proactive communication with providers to revisit decisions, such as discontinuing beneficial medications after a past episode of hyperkalemia.

Garcia and Di Palo also called for a broader focus on population health. Garcia suggested leveraging data to identify gaps in GDMT uptake and tailoring interventions to address systemic barriers. Di Palo reinforced the idea of creating pharmacist-led guidelines and decision-support tools, advocating for a more proactive approach to shaping hyperkalemia management.

As the discussion concluded, the panelists reflected on the need for creative solutions and pilot programs to address persistent challenges. Beavers underscored the value of data-driven initiatives to build consensus and foster collaboration among stakeholders. The session ended with a call to action for pharmacists to take ownership of hyperkalemia care by developing innovative models of care, advocating for policy changes, and leading efforts to standardize treatment pathways.

Overall, the pharmacist’s role in hyperkalemia care is multifaceted, requiring a balance of clinical expertise, collaboration, and innovation. By addressing barriers such as alert fatigue, inconsistent guidelines, and formulary restrictions, pharmacists can enhance patient outcomes and support the broader implementation of GDMT. With their unique position in the health care team, pharmacists are well equipped to lead efforts in advancing hyperkalemia management across inpatient and outpatient settings. 



# Pharmacists Are Key Partners in Navigating Treatment With B-Cell Therapies

Pharmacists bridge communication gaps and enhance shared decision-making.

Alana Hippensteele, Lead Editor

**P**harmacists play a crucial role in bridging communication gaps, supporting both patients and clinicians in navigating complex treatment decisions. In a *Pharmacy Times* Clinical Forum moderated by Jacci Bainbridge, PharmD, FCCP, MSCS, FAES, professor in the Department of Clinical Pharmacy and vice chair of research in the Department of Neurology at the University of Colorado Skaggs School of Pharmacy at the Anschutz Medical Campus in Aurora, panelists discussed the evolving role of pharmacists in shared decision-making (SDM) and the importance of collaboration in managing patients with relapsing multiple sclerosis (MS), particularly in relation to treatment with B-cell therapies.

Pharmacists are actively involved in SDM, a process that ensures patients feel empowered to participate in their treatment decisions. This approach improves patient satisfaction, health outcomes, and medication adherence.

“Once the patient is in the clinic and gets prescribed the medication, then we [as pharmacists] go over the medication with them. Oftentimes, we run into this problem where the patient would hear about the medication and be like, ‘Whoa, what if I don’t want to put myself at risk for infections, especially during the height of COVID-19? Maybe I need to go back to the doctor.’ And that creates delays,” Christian Sileo, PharmD, CSP, a clinical pharmacist at Ochsner Health in New Orleans, Louisiana, said during the Clinical Forum. “Specifically, within the neurology department, we established ambulatory care pharmacists within the clinic to work together with the physician and say [to the patient], ‘Hey, we’re going to assess your disease with the physician and nurse, and then we’re going to give you a few options to discuss with the pharmacist as far as what the adverse effect profile looks like.’”

Sileo noted that the pharmacist’s role in SDM becomes even more important when the treatment is highly complex with many considerations involved in treatment selection.

“[These treatments] have quite a few nuances as far as bradycardia monitoring or special genotype monitoring,” Sileo said. “So we are very involved with SDM because our physicians...are really putting a lot of effort into

making sure patients are informed and motivated to start therapy, because you really get people on board if you have them involved in the process.”

Despite the benefits, both clinicians and patients face various challenges when implementing SDM. For clinicians, long-standing traditions of physician-driven decision-making, concerns about patient litigation, and time constraints may hinder effective communication. Patients, on the other hand, may encounter health literacy issues or cultural barriers that affect their understanding and involvement in treatment discussions. To address these challenges, pharmacists play a vital role in ensuring that patients receive the information they need in a format that is accessible and comprehensible to them.

## Overcoming Barriers to SDM

Several panelists shared insights into methods they have found to be successful in overcoming common barriers to SDM. Jason Noel, PharmD, MPA, BCPP, associate professor at the University of Maryland School of Pharmacy in Baltimore, works with individuals with intellectual and developmental disabilities, and he emphasized the importance of educating patients in a way that accommodates potential cognitive limitations. Sileo and Millad J. Sobhanian, PharmD, BCPS, a clinical pharmacy specialist in neurology at the University of Maryland Medical System, discussed the role of pharmacists in clinical settings, particularly with B-cell therapies, noting the importance of collaborating closely with physicians to ensure patients understand their treatment options. Additionally, the panelists touched on the significance of laboratory monitoring to ensure patient safety, especially when dealing with complex therapies requiring ongoing assessment.

Barriers such as insurance coverage issues and step-therapy protocols were also addressed. The panelists noted that pharmacists are essential in helping patients navigate obstacles by advocating on their behalf and managing insurance requirements. Panelists also emphasized the importance of improving health literacy and cultural sensitivity to facilitate better communication and ensure patients fully understand their treatment choices.

## Patient-Centered Care in MS

Patient autonomy is very important in SDM, especially when family members are involved in treatment decisions, the panelists explained. For example, in one patient case where a patient's family members spoke English but the patient herself did not, the patient's health care team brought in an interpreter to ensure the patient was included in the decision-making process. Interpreter services can be critical to ensure the patient's voice is heard, even when the patient's family is able to translate. For example, if patients need to rely on family members for translation to health care professionals, unknown family dynamics could be at play and influence the information that is relayed, and family members may also have varying skill levels in translating accurately. For these reasons, an interpreter can ensure all necessary information is communicated to the health care team rather than relying solely on family members to translate.

## Treatment Options and Considerations in MS Care

The panel discussed various treatment options for MS, including subcutaneous vs oral therapies and newer medications such as ublituximab (Briumvi; TG Therapeutics). Whereas efficacy among B-cell-depleting therapies is generally similar, safety profiles can differ. For example, ofatumumab (Kesimpta; Novartis Pharmaceuticals) may have a gentler effect compared with ocrelizumab (Ocrevus; Genentech), potentially reducing the risk of adverse events (AEs). Regular monitoring, such as tracking IgG levels, is essential for ensuring patient safety and detecting signs of disease progression.

"Between the B-cell-depleting therapies, at our institution, basically it's ofatumumab or ocrelizumab, and sometimes rituximab [Rituxan; Biogen and Genentech]," Sobhanian said. "We are looking currently at subcutaneous ocrelizumab as well as ublituximab, which is the new kid on the block, so to speak, and from a safety standpoint and efficacy standpoint, they are fairly comparable. The nice thing with ublituximab is that it has a 1-hour infusion vs 4 to 6 hours with pretreatment and all that."

From an AE profile standpoint, Sobhanian noted that ofatumumab tends to be better tolerated because of the subcutaneous administration.

"Our patients seem to do a little bit better [with ofatumumab] because you're depleting a little bit more gently, I guess," Sobhanian said. "That's how I work it into the discussion with patients. I explain, 'With ocrelizumab, you're doing an IV and you're hitting all

the B cells and wiping them and then giving yourself time to recover. With ofatumumab, you're doing it more gently and letting it slide down and keeping them low, but perhaps that swing is what may lead to some of those AEs like the infectious risk, etc.' I also incorporate what we use for monitoring and how we can say maybe you're at an increased risk. We use IgG a lot to monitor. So that goes into part of the discussion, and we explain, 'If it stays above  $x$  number, you're probably OK.'"

Sobhanian explained further that in the University of Maryland Medical System, they have a specialty pharmacy that conducts regular check-ins and calls with patients to discuss questions and symptoms they might be having.

"We have our own templated notes that assess patients for the head-to-toe symptoms of MS. We get their baseline for cognitive issues, mood, fatigue, incontinence, etc, and we ask very basic questions," Sobhanian said. "Since we're pharmacists, we don't go into the weeds, but we assess the patients' symptoms with questions [such as], 'Compared with how you were before treatment, where are you in terms of these particular symptoms?'"

Sobhanian noted that these questions are looking to assess new or worsening symptoms that could be a sign of relapse.

"We don't really have any specific biomarkers for efficacy other than imaging, and that's handled by our providers, of course. We do ensure patients are keeping up with their monitoring and keeping up with their visits and their testing that's needed while they're on therapy," Sobhanian said. "I think therapy is very much patient centered in that way, where we're asking these more subjective questions, and that certainly is a helpful tool for us to pick up on some of those maybe subclinical symptoms and signs of progression that may not be as [clear as] an MRI finding, a hyperintensity, or a relapse but [may be signs of an] insidious progression that's ongoing that could be a sign that they're getting worse."

## Managing Multiple Conditions and Treatment Complexity

Managing patients with multiple autoimmune conditions, such as MS and type 1 diabetes, requires careful coordination between specialties. The panel discussed the importance of managing disease burden and activity when determining the most appropriate therapy. For some patients, treatment preferences, such as opting for infusions to accommodate travel schedules, must be considered. The need for close collaboration across specialties, including

neurology and endocrinology, is key to providing comprehensive care.

“I’ve seen quite a few of our patients [with MS] with multiple autoimmune conditions. They might have inflammatory bowel disease, arthritis, type 2 diabetes, or type 1 diabetes, and I think that really highlights the importance of making sure you have things in the [electronic medical record (EMR)], whether it’s Cerner or Epic. Seeing patients inside the same health system is a huge benefit [for that reason],” Sileo said.

Sileo explained further that treatment selection should also be assessed in relation to the other medications the patient may be on for other conditions.

“Ofatumumab on its own is probably not a huge immunosuppressant, but then once you’re adding in a JAK inhibitor, we really should carefully think about that,” Sileo said. “So just make sure you’re clearly communicating that plan. That way, if that endocrinologist wants to hop in, they can clearly see how long they’ve been on therapy, what the goals are, and why it’s important to continue.”

#### *Overcoming Administrative and Financial Barriers*

The discussion also touched on the financial and administrative challenges of MS treatment. Barriers such as formulary restrictions, prior authorizations (PAs), and the influence of pharmacy benefit managers often delay access to necessary therapies. Pharmacists play a crucial role in managing these challenges by facilitating insurance appeals and ensuring patients receive the treatments they need.

“We work with the physicians, and we were able to impact their behaviors, how they chart, what they document, and that’s really been a huge assistance on our end to help us get things approved, whether it’s through appeal or just PAs. Regardless, we need that,” Sapan Patel, PharmD, a specialty pharmacy manager at MedStar Health in Hanover, Maryland, said. “We really need it spelled out because that’s what helps get the insurance to pay for it.”

Sileo agreed with this sentiment, noting the importance of physician education to support this process.

“We’ve done a lot of provider education as far as if you don’t want to use this medication, tell us why in the chart, because we can write a paragraph in the PA, and who knows if they’ll actually read it,” Sileo said. “Also, sometimes we get denials and the doctor is like, ‘Oh, they can’t use that medication because x, or they already tried it,’ and it’s like, ‘Well, why wasn’t that in the EMR?’ So, definitely a lot of provider education is needed.”

Sileo noted that it’s also important to not lose momentum in the process of getting the authorization.

“If something’s denied, next step is message the

provider. I personally write in a field letter or medical letter of necessity and then send it over to the provider for notes,” Sileo said. “I’ve gotten so much great information. A lot of them have these studies just ready to go, but they don’t put them in the EMR, and how would you know? So communication is just really important.”

In this way, close collaboration with specialty pharmacies is essential for treating patients with MS effectively. The panel emphasized the importance of proactive steps, such as conducting formulary checks and quickly submitting appeals.


“When I see patients, I do put in my own note documenting if they had failed [therapy for] something in the past or a reason why they can’t be on a particular therapy. We do have the specialty pharmacy that we work very closely with, and I have a technician, and she does the PAs, so I make sure that she has my note in there. If she has the provider’s notes in there, they indicate if a particular therapy is preferred for whatever reason or others are contraindicated,” Sobhanian said. “Our administrative assistants have all these appeal templates for all the MS therapies that I’ve written up, and we’ve pulled in all the studies and the data, and they fill those in whenever they can, and we tweak it to match the patient.”

Sobhanian explained further that at the initial visit, her team begins the start forms.

“So when we get that denial back, they can just go straight into the free drug process to get set up... especially for Medicaid and Medicare patients,” Sobhanian said. “We can do a formulary check before we even start this, and I’ll say, ‘Hey, I want to start [fingolimod (Gilenya; Novartis Pharmaceuticals)] or [ozanimod (Zeposia; Bristol Myers Squibb)],’ and they can determine which one is going to go through more seamlessly, and that helps guide us too, and it works 7% of the time.”

## **Conclusion**

Pharmacists are essential in advancing SDM in the care of patients with MS, particularly in the context of complex therapies such as B-cell treatments. By serving as key communicators between patients and other clinicians, pharmacists help ensure that patients are informed and involved in their treatment choices, which enhances satisfaction, adherence, and overall health outcomes.

Through collaboration with physicians and other health care providers, pharmacists address barriers to care, including health literacy, cultural sensitivities, and administrative challenges. As MS care continues to evolve, the role of pharmacists will remain integral to improve treatment adherence, manage patient safety, and advocate for optimal patient care amid the complexities of multiple autoimmune conditions and insurance obstacles. 

# Redefining Relapsing Multiple Sclerosis Care With Shared Decision-Making and Pharmacist Innovation

Pharmacists play a key role in advancing care for this patient population.

Alana Hippensteele, Lead Editor

**A**dvancements in managing relapsing multiple sclerosis (RMS) have shined a spotlight on the importance of integrating shared decision-making (SDM) approaches into clinical practice.

In a *Pharmacy Times* Clinical Forum on RMS care, pharmacists from Mount Sinai, NYU Langone Health, Bellevue Hospital, and NewYork-Presbyterian Hospital, all in New York, New York, sat down with moderator Jacci Bainbridge, PharmD, FCCP, a professor in the Department of Clinical Pharmacy at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences in Aurora, to discuss how these advancements have affected clinical practice and transformed RMS care.

During the discussion, panelists emphasized the importance of empowering patients and fostering collaboration among health care teams to improve outcomes in RMS care. In traditional models, patient involvement in treatment decisions was limited, often relying on educational tools such as brochures or recordings, which did not require active participation, according to Bainbridge. Modern SDM models aim to shift this dynamic by engaging patients in meaningful discussions about their care, enabling them to feel more invested and informed about their treatment options.

Additionally, traditional models often did not place the pharmacist as a critical player involved in SDM. Bainbridge explained that when she first joined the Consortium of Multiple Sclerosis Centers (CMSC), pharmacists were not included in CMSC materials on SDM.

“When I first got involved with CMSC, the first thing that I noticed is there were all these pretty diagrams. They had the occupational therapist, they had the patient, they had the patient’s family, the physician, the nurses, the receptionist—everyone else—but they didn’t have the pharmacist on there,” Bainbridge said. “I was like, ‘Wait, wait, wait, wait, wait. Change this.’ So now you will see in those SDM models that the pharmacist has really been included, and quite honestly, we have a large role in SDM.”

Historically overlooked in multidisciplinary care models, pharmacists are now recognized as essential members of the RMS care team. They serve as accessible

touchpoints for patients, providing critical information about treatment options and adherence strategies. For example, pharmacists have been instrumental in managing the challenges associated with self-injected disease-modifying therapies, which often have resulted from poor adherence due to factors such as needle aversion, stigma, and travel-related difficulties, according to the panelists. By offering education, support, and tailored interventions, pharmacists help improve adherence and overall patient satisfaction.

The panelists also discussed barriers to effective SDM in RMS care, such as time constraints, limited training in SDM techniques, and concerns about potential litigation if patients make certain care or treatment decisions. These barriers can stem from a historically paternalistic approach to medicine, where clinicians believe their primary role is to make decisions for patients, Bainbridge explained.

Additionally, patients themselves encounter significant hurdles, including limited health literacy, cultural biases, cognitive impairments, and the burden of navigating complex health care systems. Social determinants of health (SDOH), such as unstable housing, language barriers, and socioeconomic disparities, further complicate the adoption of SDM practices. However, the panelists noted that pharmacists play a pivotal role in addressing these barriers and enhancing the effectiveness of SDM in RMS care.

“At NewYork-Presbyterian and in the pharmacy world, we do a lot of work around addressing health care disparities. SDOH is something that we’ve tried to integrate into our electronic health record to try to identify those issues early on and make sure that we are addressing them. But I’d say it’s definitely an ongoing challenge,” Krysta Shannon, PharmD, BCPS, BC-ADM, a clinical pharmacy manager at NewYork-Presbyterian Hospital, explained. “We have 10 different hospitals across the New York City metropolitan region, so every campus looks a little bit different with the type of patients we serve and the different backgrounds that they come from, so it’s definitely an ongoing challenge and is something we try to prioritize, which I think is important.”

Anthony Curraro, PharmD, RPh, system director of pharmacy operations at Icahn School of Medicine at

Mount Sinai, noted that his institution has a similar value system regarding equal care for all patients.

“I think health equity is so important. I think it’s especially a focus at Mount Sinai. Everybody who walks through the door gets the same care, no matter where they’re from or what they look like,” Curraro said. “It’s been proven that, depending on what your zip code is, your health care can be different, so I think it’s something we take very seriously—that everyone gets treated fairly. I think that having the patient feel like they’re part of the care team and having those discussions is showing them they are valuable [during treatment and care discussions].”

However, challenges remain when serving diverse patient populations with diverse needs because the needs for immigrants, non-native speakers, and individuals without stable housing may be quite different from other patient populations, requiring innovative approaches to provide care for each patient to appropriately meet their needs. “At Bellevue, when patients are homeless, they don’t have places to store drugs to self-inject...so sometimes the IV [intravenous] infusions are a lot better. These patients don’t have a place to even store oral drugs without them getting stolen,” Sarita Mohanty, PharmD, BCPS, a clinical oncology pharmacist manager at NYC Health + Hospitals/Bellevue Cancer Center, explained. “But we tried to figure out ways. Also, as a pharmacy, we can’t give a drug to a patient and then have them bring it back and have us store it, so it’s a challenge.”

Additionally, involving families in SDM for pediatric patients presents unique hurdles, especially when caregivers have conflicting priorities or limited availability due to work schedules.

“When working with kids, I think including family in SDM is very important,” Alisa Muckalli, PharmD, a pharmacist at NYU Langone Health’s Perlmutter Cancer Center, explained. “But it also can be a hurdle to involve them, making sure they’re all on the same page. We serve downtown Brooklyn, and the patient population we serve, a lot of them live in shelters, are immigrants, or are non-native speakers, which is a challenge as well.”


The panelists also highlighted the transformative potential of technology in advancing SDM. Artificial intelligence (AI)-driven decision aids and patient-specific digital tools have the potential to revolutionize how care is delivered and how patients engage with their treatment plans. These tools can be integrated into Epic to provide personalized recommendations based on individual patient needs, making SDM more efficient. For example, personalized digital aids could

tailor information to a patient’s specific circumstances, such as their treatment history, lifestyle preferences, and health literacy level. As technology continues to evolve, these innovations are anticipated to be further integrated into RMS care, Bainbridge noted.

Real-world evidence also underscores the value of SDM in improving patient outcomes, according to Bainbridge. Findings from recent studies have shown that patients involved in treatment decisions are more likely to choose therapies that align with their preferences and lifestyles, such as oral medications over injectable options. These patients also report improved perceptions of disease severity, better mental health outcomes, and greater confidence in discussing treatment changes with their health care providers. This sense of empowerment not only enhances patient satisfaction but also leads to improved adherence to prescribed therapies. For instance, results from a large trial evaluating the use of an MS-specific support tool found that patients in the intervention group were more likely to start and adhere to disease-modifying therapies within 6 months compared with those receiving standard care. Moreover, these patients reported fewer days of poor mental health and greater overall satisfaction with their care.

Despite these promising findings, the implementation of SDM tools and practices continues to have challenges. Integrating these tools into existing electronic health records can be particularly complex, as different systems have varying capabilities and levels of compatibility. Additionally, the timing and delivery of these aids can influence their effectiveness. For example, tools provided during a clinic visit may not be as impactful as those introduced beforehand, giving patients more time to reflect and prepare questions for their providers. Ensuring that these tools are accessible and usable for all patients, regardless of their socioeconomic or technological limitations, remains a critical area for improvement as well, Bainbridge explained.

When discussing the future of SDM in RMS care and the broader health care landscape, the panelists expressed optimism about the accelerating pace of innovation, particularly in the development of AI-driven technologies that can personalize and streamline patient engagement. These advancements are expected to further bridge gaps in care, reduce inequities, and enhance the role of pharmacists in therapy monitoring and education.

“As pharmacists, our role is transforming so much. Now you have a collaborative drug therapy management pharmacist who could actually end up being a prescriber,” Mohanty said. “I think that’s a really fun way our profession is changing.” 



# Optimizing Cholesterol Management: Incorporating Injectable Lipid-Lowering Therapies

Challenges include therapy gaps, nonadherence, and fragmented care.

Alana Hippensteele, Lead Editor

In 2019, 24 million people in the US had atherosclerotic cardiovascular disease (ASCVD), which is approximately 10% of the total adult population older than 21 years. Compared with 2014, in 2019 there was a significant increase in the use of lipid-lowering therapies (LLTs), especially of high-intensity statins, in patients with ASCVD: 3.8% of patients on ezetimibe (Zetia; Merck), less than 1% on PCSK9 inhibitors, and more than 40% on no LLTs. Among patients with ASCVD, 31.2% are at very high risk for recurrent events. Further, the majority of patients with ASCVD are not at the guideline-recommended low-density lipoprotein cholesterol (LDL-C) goal.<sup>1</sup>

## Unmet Needs in Managing Cholesterol in Very High-Risk Patients With ASCVD

In a *Pharmacy Times* Clinical Forum in Chicago, Illinois, moderated by Craig Beavers, PharmD, FAHA, BCPS-AQ Cardiology, CACP, vice president of operations and a cardiovascular clinical pharmacist at Baptist Health Paducah in Paducah, Kentucky, the panelists discussed gaps and challenges in the management of cholesterol, particularly among very high-risk patients with ASCVD. According to the panelists, these challenges are compounded in rural and regional health care systems, where resources such as pharmacy services or structured lipid management programs are often lacking. The conversation underscored the importance of ensuring adequate follow-up, adherence, and appropriate escalation of therapy to achieve guideline-directed LDL-C targets.

Pharmacists in rural settings who participated in the panel discussion noted difficulties in maintaining continuity of care for patients after discharge or referral. Pharmacy services, which play a critical role in optimizing therapy, are often unavailable where patients transition, highlighting the need for a structured plan to ensure long-term follow-up and adherence to therapy goals.

“I’ll tell you, in Kentucky, where we live, and you guys probably deal with this too—so not just saying it’s a rural issue because even in a city, it can be a challenge—but we actually use a lot of inclisiran [Leqvio; Novartis

Pharmaceuticals] because it is hard for our patients to get back [to our clinic] to do things, or to even get to pick certain prescriptions up,” Beavers said during the Clinical Forum.

Nonadherence remains a widespread issue, often stemming from adverse effects (AEs), lack of understanding, or insufficient follow-up, according to Beavers. Outpatient PCSK9 consult services have reported identifying significant adherence problems during chart reviews, for example. Moreover, chart reviews can help to uncover which patients are not adequately escalated to the next line of therapy (eg, ezetimibe or PCSK9 inhibitors), despite failing to meet LDL targets.

“From the outpatient perspective, at least from our PCSK9 consult service, typically the providers will put in a consult and essentially say, ‘We need to do something. We need to escalate therapy,’ but often when we do a chart review or we call the patients, we identify a ton of nonadherence for any number of reasons, whether [they have adverse] effects or they just didn’t really understand the therapies or the need for them,” explained panelist Erika Hellenbart, PharmD, BCPS, a clinical pharmacist and clinical assistant professor at University of Illinois at Chicago, during the Clinical Forum.

## Inpatient vs Outpatient Gaps

According to the panelists, on the inpatient side, cholesterol management tends to focus on “checking the box” for statin therapy initiation. Augmentation of therapy—such as adding nonstatin agents such as ezetimibe or PCSK9 inhibitors—is often overlooked, especially if patients are already on a high-intensity statin. Further, physicians frequently defer lipid optimization to outpatient care without clear ownership of the transition process.

On the outpatient side, pharmacists in ambulatory care practices play a pivotal role in addressing gaps in outpatient care. With greater autonomy and the ability to provide close follow-up, pharmacists ensure appropriate escalation of therapy, improve adherence, and educate patients. However, gaps remain for patients not referred to these services, according to the panelists.

The discussion also revealed that many institutions lack

robust data tracking systems or dashboards to measure how well high-risk patients with ASCVD meet LDL-C targets. During retrospective reviews, these low rates of therapy escalation can be uncovered. For instance, one center learned during a retrospective review that fewer than 50% of eligible patients received therapy intensification postevent. Without these data, it becomes challenging to identify gaps, hold the appropriate health care professionals accountable, and implement practice improvements.

## Shared Decision-Making in Lipid Management

In clinical practice, shared decision-making is a vital framework for aligning treatment strategies with patient preferences, especially when considering LLTs. Panelists in the Clinical Forum emphasized the importance of treating patients holistically, which requires engaging them as individuals. While conversations about therapies can sometimes be complex, panelists shared practical approaches that facilitate patient understanding and promote informed decision-making.

For example, visual aids and simplified tools play a significant role in these educational discussions. Handouts, written explanations, and dummy pens are often employed to break down treatment plans, according to the panelists. Patients are encouraged to verbalize their understanding, ensuring clarity in navigating options such as oral medications, PCSK9 inhibitors, or emerging therapies. Despite such efforts, the panelists acknowledged that patients may retain only a fraction of the information provided, reinforcing the need for repeated engagement and simplified education.

When evaluating treatment pathways, the panelists explained that they assess the magnitude of LDL reduction required and individual preferences regarding treatment modalities, such as home-based or in-clinic injections. Although PCSK9 inhibitors (eg, evolocumab [Repatha; Amgen] and alirocumab [Praluent; Regeneron Pharmaceuticals, Inc and Sanofi]) have become more accessible, insurance requirements—such as mandatory clinical trials of ezetimibe—remain a barrier. Bempedoic acid (Nexletol; Esperion Therapeutics, Inc) was also briefly discussed as an alternative, but its approval process and formulary challenges limit widespread use, according to the panelists.

Fragmentation of care emerged as a recurring challenge as well. Physicians frequently defer responsibility among specialists, leading to missed opportunities for optimal therapy initiation and follow-up. Pharmacists, however, are uniquely positioned to bridge these gaps. Their expertise in prior authorizations (PAs), formulary navigation, and patient counseling has proven invaluable for optimizing therapy, particularly in advanced or high-risk patients with ASCVD.

Increased pharmacist involvement—both in the clinic and during care transitions—was highlighted as a significant opportunity for improvement.

However, the panelists noted several barriers to expanding pharmacist engagement, such as resource limitations, lack of provider time, and fragmented systems. Panelists suggested leveraging informatics and clinical decision support tools to drive standardization. Algorithm-based prompts, tied to LDL thresholds, could facilitate earlier pharmacy involvement and ensure therapy optimization. However, prioritizing informatics solutions often requires physician champions to advocate for systemic change.

## Injectable LLTs

For the selection and implementation of injectable LLTs, particularly inclisiran and PCSK9 inhibitors (eg, evolocumab and alirocumab), in clinical practice, panelists explored decision-making factors such as safety, efficacy, and logistical considerations in managing these therapies for patients with persistent hyperlipidemia despite maximally tolerated statins.

### *Efficacy and Safety*

Most panelists acknowledged the similarities between inclisiran and PCSK9 inhibitors in mechanism and LDL-lowering efficacy. However, the panelists noted some concerns about inclisiran, primarily stemming from its lack of extensive long-term cardiovascular outcomes data (beyond 2 to 3 years), though mechanistic similarities with PCSK9 inhibitors provided a degree of reassurance.

### *Patient Preferences and Accessibility*

The group emphasized that therapy selection of injectable LLTs often depends on patient characteristics, preferences, and logistics. For example, patients who find frequent medication administration to be a challenge might benefit from inclisiran's biannual dosing schedule. Conversely, those comfortable with self-administration at home often preferred PCSK9 inhibitors due to their flexibility. Additionally, rural or underserved populations face unique challenges, and inclisiran's less frequent administration was seen as advantageous for patients with limited access to health care facilities.

### *Barriers and Implementation Challenges*

PA processes emerged as a significant barrier during the discussion, especially in ambulatory settings where physicians balance multiple responsibilities. Some clinicians proactively document PA details, while others rely on dedicated teams or drug manufacturer programs to streamline renewals. Effective systems, such as automatic work queues and reminders, were highlighted as beneficial when managing ongoing therapy.

### Cost and Bias Considerations

Cost remains a crucial factor in decision-making, particularly when evaluating inclisiran vs PCSK9 inhibitors under medical (buy-and-bill) or pharmacy benefits. Participants acknowledged that their own biases, such as familiarity with existing therapies or concerns about newer mechanisms such as RNA therapeutics, may unconsciously influence patient discussions. Additionally, transparency about drug mechanisms and clinical data was considered vital for patient education and decision-making.

### Patient Case: JB

A case-based discussion highlighted considerations for selecting adjunctive therapy for a 64-year-old man named JB with a history of coronary artery disease, status post-myocardial infarction and stent placement 3 years ago. JB is maintained on atorvastatin (Lipitor; Pfizer) 80 mg daily. He also takes metoprolol succinate XL (Toprol XL; Melinta Therapeutics) 50 mg daily, lisinopril (Prinivil; Merck) 10 mg daily, aspirin 81 mg daily, and metformin 1000 mg twice a day. However, JB continues to have an LDL-C of 120 mg/dL and feels overwhelmed by the number of pills he's already taking. His past medical history includes hyperlipidemia, hypertension, and type 2 diabetes (T2D). JB is physically active, and his tobacco use is 43 pack-years; he continues to smoke.

For JB, the panelists explained that they favored injectable therapies but stressed assessing patient adherence, cost, and lifestyle factors (eg, smoking cessation, diet, and exercise) before deciding. While PCSK9 inhibitors are often the default due to their robust safety data, the panelists noted that inclisiran remains an option for patients seeking less frequent dosing or with barriers to self-injection.

The panelists also generally accepted the safety and efficacy of both inclisiran and PCSK9 inhibitors while recognizing the importance of tailoring the therapy to the patient's preferences, logistical constraints, and cost considerations.

### Patient Case: DJ

The discussion also centered on optimizing the treatment of DJ, a 68-year-old female patient with multiple comorbidities, including hyperlipidemia, hypertension, T2D, stage 3 chronic kidney disease, arthritis, and limited mobility. DJ is a complex patient with coronary artery disease poststent placement 2 years ago. Six months ago, she experienced a non-ST segment elevation myocardial infarction, requiring additional stent placement. She has been maximized on rosuvastatin (Crestor; AstraZeneca) 40 mg daily. She also takes valsartan (Diovan; Novartis Pharmaceuticals) 160 mg daily, metformin 1000 mg twice a day, empagliflozin (Jardiance; Boehringer Ingelheim)


25 mg daily, aspirin 81 mg daily, and metoprolol succinate XL 50 mg daily. However, DJ continues to have an LDL cholesterol level of 110 mg/dL, blood pressure at 140/90, and hemoglobin A<sub>1c</sub> at 8.2%.

When discussing this patient case, the group emphasized the importance of first assessing medication adherence, including the use of refill histories and detailed questioning to confirm patient compliance and identify potential AEs or intolerance to statins. Addressing barriers such as perceived AEs, patient pushback, and misinformation—particularly from social media—was highlighted as a major challenge, with some patients expressing fears related to dementia or diabetes onset due to statin use.

### Moving Forward: The Role of Pharmacists

The panelists concluded that pharmacists, particularly in ambulatory care and specialty roles, are key to addressing unmet needs for very high-risk patients with ASCVD. Strategies for pharmacists to address these needs include establishing lipid management consult services to streamline therapy optimization, improving transitions of care through structured handoffs, leveraging data and dashboards to measure outcomes and identify gaps, and educating providers on guideline-directed therapy escalation. Ultimately, addressing these gaps requires a concerted effort to measure performance, address gaps presented in data, and implement systems that ensure very high-risk patients with ASCVD achieve optimal cholesterol control.

The panelists also noted that pharmacists should evaluate the full medication list for deprescribing opportunities or consolidating therapies to enhance adherence. The team also discussed alternative therapies, particularly for statin-intolerant patients, and the need for robust patient follow-up and monitoring to mitigate concerns about new treatments.

System-level barriers, such as time and resource limitations and clinical inertia, were identified as key challenges by the panelists. Participants noted the importance of integrating pharmacists into specialty and primary care clinics, emphasizing comprehensive medication management protocols that address multiple chronic conditions simultaneously. The conversation highlighted the need for sustainable solutions, such as building referral pathways, improving clinic workflows, and using informatics to streamline care. Ultimately, the group underscored the pharmacist's unique role in managing cardiovascular risks within a broader framework of chronic disease management. 

### REFERENCE

Gu J, Sanchez R, Chauhan A, Fazio S, Wong N. Lipid treatment status and goal attainment among patients with atherosclerotic cardiovascular disease in the United States: a 2019 update. *Am J Prev Cardiol.* 2022;10:100336. doi:10.1016/j.ajpc.2022.100336

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