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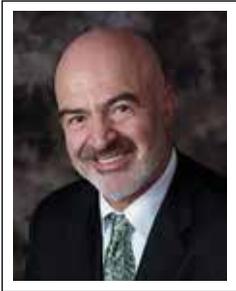
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A SPECIAL SUPPLEMENT ON Hot Topics in Primary Care

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Stephen A. Brunton, MD, FAAFP
Executive Vice President
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Introduction

Family physicians conduct approximately 1 in 5 medical office visits. That's 192 million appointments annually, 48% percent more than the next most visited specialty.¹ Because of this reality, it is incumbent upon us as family physicians to manage common conditions uncommonly well.

Our core precepts, encompassed by the 4 C's: first Contact, Continuity, Comprehensiveness, and Coordination of care, are explicated throughout the supplement. Because clinical content in primary care is diverse, in this third annual Hot Topics Supplement, we cover 13 different areas that are particularly relevant to your daily practice.

This supplement addresses developments and new considerations in therapy, as well as provides a review of diagnostic criteria. We trust that you will find this special issue contains useful and practical information that will assist in the daily management of your patients.

Another supplement to the journal will be developed next year, and we welcome your input and suggestions of areas that we should cover. Your input this year was invaluable, and we thank you. ●

Stephen A. Brunton, MD, FAAFP
Executive Vice President
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REFERENCE

1. American Academy of Family Physicians. Family medicine specialty. Published 2018. <https://www.aafp.org/about/the-aafp/family-medicine-specialty.html>. Accessed June 16, 2018.

On the Front Lines: Hepatitis C Infection in Primary Care

George P. Kent, MD; Christopher McGowan, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify patients who should be screened for HCV infection
- Identify patients with HCV infection who may be considered for referral
- Initiate and modify pharmacologic therapy based on stage of infection and to meet individual needs
- Implement a follow-up care plan to improve long-term treatment and adherence

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of hepatitis C infection.

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INTRODUCTION

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States, with an estimated incidence of 33,900 acute cases in 2015—nearly a 100% increase from 2011 and a 250% increase from 2010.^{1,2} The largest increase has been among persons 20 to 39 years of age, with three quarters of cases occurring in persons who use illicit injection drugs.^{1,3} Other groups at increasingly high risk of acute HCV infection are men who have sex with men and newborns of infected mothers, as well as reproductive-age and pregnant women (the latter for unclear reasons).⁴⁻⁶

Approximately 75% to 85% of newly infected persons develop chronic HCV infection.^{7,8} An estimated 3.5 million persons are chronically infected in the United States; three quarters were born between 1945 and 1965.^{9,10} Among people with chronic HCV infection, approximately 20% develop cirrhosis and 10% develop end-stage liver disease or liver cancer; 3% to 4% will require a liver transplant or will die of an HCV-related cause.^{10,11} In 2014, 19,659 persons died of HCV infection, a 20% increase from 2010.¹⁰

There is, however, a real opportunity to change the story line for HCV, due to the advent of direct-acting antivirals (DAAs). With DAAs, safety and tolerability are much improved over previous treatments. In addition, nearly all persons with chronic HCV infection should be treated, because >90% of patients treated with DAA therapy in clinical trials are cured.^{10,12,13} Of course, this requires that infected patients be identified, appropriate treatment with DAAs be initiated, and treatment adherence be maintained. Regrettably, nearly 50% of people who are infected with HCV are unaware that they are infected.^{2,14,15} Yet screening is cost-effective, particularly in populations with a high prevalence of illicit injection drug use.^{16,17} However, evidence indicates that only 9% to 24% of persons diagnosed with HCV infection are treated, due to issues such as medication cost, need for an office visit for drug administration (with injectables), and patients' concern about adverse events.^{10,18-20} Treatment with DAAs has been shown to be cost-effective in the vast majority of treatment-naïve and treatment-experienced patients across all HCV genotypes.²¹⁻²⁷

In addition to the efficacy of DAAs, their safety and oral administration mean that the majority of patients with HCV infection can be successfully managed in the primary care setting, if desired, with limited referral to subspecialists.²⁸ This requires the primary care provider (PCP) to acquire the knowledge and skills for providing comprehensive care. A notable educational resource for PCPs is Project ECHO (<https://echo.unm.edu>), a learning community that links PCPs with expert specialist teams at an academic hub, who mentor and provide feedback to the PCP. Additionally, the Centers for Disease Control and Prevention has supported development of a comprehensive resource (www.hepatitisc.uw.edu). Similarly, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America maintain an online, continually updated resource for HCV management (www.hcvguidelines.org).¹³

SCREENING AND FURTHER EVALUATION

Most people with chronic HCV infection are asymptomatic or have nonspecific symptoms, such as chronic fatigue and depression. Many eventually develop chronic liver disease, which can range from mild to severe, including cirrhosis

and liver cancer. Chronic liver disease in HCV-infected people is usually insidious, progressing slowly without signs or symptoms for several decades. In fact, HCV infection is often not recognized until asymptomatic people are identified as HCV-positive when screened for blood donation or when elevated liver enzyme levels are detected during routine examination.²⁸

Screening tests

One-time HCV testing is recommended in select populations, based on demographics, possible exposures, high-risk behaviors, and medical conditions (**TABLE 1**).¹³ For persons who illicitly inject drugs and for human immunodeficiency virus (HIV)-infected men who have unprotected sex with men, annual or more frequent testing is recommended.¹³

Screening for HCV infection should begin by testing for HCV antibody, using a laboratory-based or point-of-care assay approved by the US Food and Drug Administration (**FIGURE**).²⁹ HCV can be detected 4 to 10 weeks after infection, using an enzyme immunoassay, and 2 to 3 weeks after infection using HCV ribonucleic acid (RNA) testing.³⁰⁻³² A positive test for HCV antibody indicates (1) current (active) HCV infection (acute or chronic); (2) past infection that has resolved; or (3) a false-positive result. A false-positive result is more likely in a population with low prevalence of HCV infection; one nationally representative study with an HCV infection prevalence of 1% showed a false positive rate of at least 22%.³³

Consequently, if the HCV antibody test is positive, an HCV RNA test is necessary to detect viremia and confirm active HCV infection. An HCV RNA test is also recommended in persons with a negative HCV antibody test who are either immunocompromised or who might have been exposed to HCV within the past 6 months. If HCV RNA is detected, active HCV infection is confirmed. If HCV RNA is not detected, past or resolved HCV infection or a false-positive result is demonstrated.²⁹

Further evaluation

Assessing the extent of liver damage due to chronic HCV infection is critically important in guiding the treatment plan. Liver fibrosis is most commonly described using the METAVIR score, which ranges from F0 (no fibrosis) to F4 (cirrhosis). The METAVIR score is based on standard histopathological features identified on biopsy; however, noninvasive tests can be used to approximate the METAVIR score. Liver biopsy is limited by cost, risk of complications, and sampling error, and is rarely necessary. Noninvasive methods to assess the extent of liver damage include a liver-directed physical examination, although findings are generally unremarkable. Routine blood tests—alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin, inter-

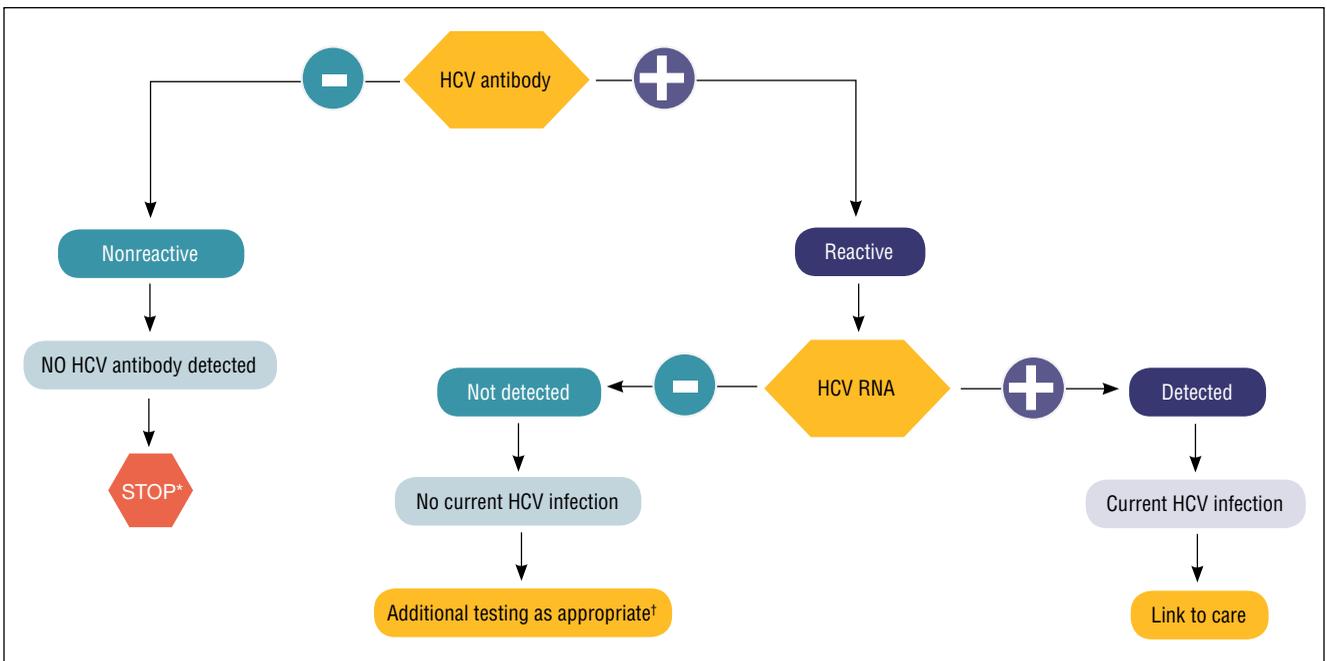
TABLE 1 People for whom one-time hepatitis C testing is recommended¹³

Birth year	Born from 1945 through 1965, regardless of country of birth, without prior ascertainment of risk
Risk behaviors	Illicit injection drug use (current or ever, including persons who injected only once) Illicit intranasal drug use
Risk exposures	Long-term hemodialysis (ever) Percutaneous or parenteral exposure in an unregulated setting Needle-stick, sharps, or mucosal exposure to HCV-infected blood (in health care, emergency medical, and public safety workers) Children born to HCV-infected women Prior recipient of transfusion or an organ transplant, including persons who: <ul style="list-style-type: none"> • were notified that they received blood from a donor who later tested positive for HCV • received a transfusion of blood or blood components or who underwent organ transplantation, before July 1992 • received clotting factor concentrate produced before 1987 Incarcerated (ever)
Other conditions and circumstances	HIV infection Sexually active, about to start pre-exposure prophylaxis for HIV Unexplained chronic liver disease and/or chronic hepatitis, including an elevated ALT level Solid-organ donor (deceased or living)

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

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FIGURE Recommended testing sequence for identifying current HCV infection²⁹



Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid.

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

national normalized ratio (INR), and a complete blood count (CBC), including platelet count—may be useful.¹³

It is important to note that it is common for liver enzyme levels to go up and down in HCV infection, with periodic return to a normal or near-normal level. Direct biomarker profiles, such as Hepatitis C Virus (HCV) FibroSURE and the FibroTest-ActiTest Panel, are useful noninvasive tests to assess the degree of liver fibrosis.^{34,35} Ultrasonography or computed tomography can be used to assess liver surface nodularity and spleen size, identify occult portal hypertension, and screen for hepatocellular carcinoma (HCC). Liver elastography, widely used by gastroenterologists, is useful to determine the extent of liver stiffness, as well as to distinguish patients with a high versus low likelihood of cirrhosis.³⁶ Vibration-controlled transient elastography has superior sensitivity and specificity to the AST-to-platelet ratio index (APRI) or the fibrosis-4 (FIB-4) index (**TABLE 2**).³⁷ Because no single test alone has high accuracy for staging the degree of fibrosis, the most efficient approach is to combine direct biomarkers with vibration-controlled transient elastography.¹³

Biopsy can be considered for any patient who has discordant results between the 2 modalities (direct biomarkers and vibration-controlled transient elastography) that would affect clinical decision making (eg, one shows cirrhosis, the other does not). With this approach, the need for liver biopsy is markedly reduced. Alternatively, if direct biomarkers or vibration-controlled transient elastography are not available, APRI or the FIB-4 index can prove helpful.³⁸⁻⁴⁰

CONSIDERATIONS FOR REFERRAL

Primary care providers can increasingly provide much of the management needed by patients with HCV infection. For PCPs with limited experience, it is recommended to start by managing treatment-naïve patients without cirrhosis or with well-compensated cirrhosis, but referring other patients to a liver or infectious disease specialist.

EVIDENCE-BASED TREATMENT

Goal

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related adverse health consequences, including end-stage liver disease and hepatocellular carcinoma.^{10,13} A key objective is to achieve virologic cure—that is, sustained virologic response (SVR),¹³ defined as continued absence of detectable (≤ 25 IU/mL) HCV RNA for ≥ 12 weeks after completion of therapy (HCV antibodies remain). All patients with chronic HCV infection should be treated, except those whose life expectancy would be < 12 months despite treatment.

Benefits

Benefits of virologic cure include decreased liver inflammation (improved ALT and AST levels) and slowed progression of liver fibrosis and necrosis.⁴¹ Some patients experience resolution of cirrhosis; other manifestations of advanced liver disease, such as portal hypertension and splenomegaly, often improve.⁴¹ The risk of liver cancer may be reduced by 70% and liver-related mortality and transplantation, by 90%.⁴²⁻⁴⁴ Extrahepatic manifestations, such as cryoglobulinemic vasculitis and lymphoproliferative disorders, often improve as well.^{45,46} For these reasons, all-cause mortality is dramatically reduced.^{17,43,47,48} Last, patients typically experience considerable improvement in quality of life.^{49,50}

Prior to initiating antiviral therapy

Quantitative HCV RNA testing is recommended prior to initiation of antiviral therapy to determine the baseline viral load, because this may impact treatment duration with certain DAA regimens. Testing for HCV genotype and the absence or presence of cirrhosis helps guide selection of the most appropriate antiviral regimen. Other laboratory tests previously identified (see “Further Evaluation,” above) that have not been performed within 12 weeks prior to initiating antiviral therapy should be done.¹³ Additional pretreatment assessments include hepatitis A or B virus coinfection or past infection, as well as resistance-associated substitutions. Last, the patient’s medication regimen, including nonprescription and complementary or alternative medicines, should be evaluated for potential drug interactions because certain DAAs can interact with many commonly prescribed medications, including statins, proton-pump inhibitors, benzodiazepines, and anticonvulsants.¹³

Direct-acting antivirals available in the United States

Traditional antivirals—peginterferon alfa-2a, peginterferon alfa-2b, and ribavirin—have been used to treat HCV infection for more than a decade, but their role in 2018 is limited due to the availability of DAAs. There are 3 subtypes of DAAs:

- NS3/4A serine protease (glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir)
- Nonstructural protein 5A (NS5A) (daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir)
- Nonstructural protein 5B (NS5B) polymerase (dasabuvir, sofosbuvir).

Initial DAA therapy in treatment-naïve people with HCV

The selection of initial antiviral therapy in a patient with treatment-naïve chronic HCV must be individualized based on genotype, the presence or absence of compensated cir-

TABLE 2 Calculated measures of liver fibrosis³⁷

Test	Calculation	Interpretation
APRI	$[(AST/AST\ ULN)/platelets^a] \times 100$	>0.7 ($\geq F2^c$): significant fibrosis likely >2 (F4 ^c): probable cirrhosis
FIB-4	$(Age^b)(AST)/(Platelets^a)(\sqrt{ALT})$	<1.45 (<F2 ^c): excludes fibrosis >3.25: cirrhosis highly likely

Abbreviations: $\sqrt{}$, square root; ALT, alanine aminotransferase [U/L]; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase [U/L]; AST ULN, aspartate aminotransferase upper limit of normal; FIB-4, fibrosis-4 index.

^a $\times 10^9/L$.

^bIn years.

^cThe METAVIR fibrosis score.

rhosis, comorbidities, and concomitant medications. Certain treatment recommendations require testing for the presence or absence of NS5A resistance-associated substitutions, but there are fixed-dosage regimens available that are pan-genotypic and do not require baseline resistance testing for non-cirrhotic treatment-naïve patients. Recommended regimens for initial therapy in treatment-naïve patients with the most common genotypes of HCV infection are listed in **TABLE 3**.^{13,51} These DAA regimens are appropriate for most patients within the group based on efficacy, tolerability and toxicity profiles, and treatment duration—the latter of which may depend on patient characteristics such as race, HIV status, and viral load. Some of these regimens may not be appropriate in children, HIV/HCV coinfection, decompensated cirrhosis, Child-Turcotte-Pugh prognosis class B or C, HCV infection post-organ transplantation, and severe renal impairment, as well as post-kidney transplantation.

Monitoring for treatment response and safety is important, much of which can be done by telephone, texting, or e-mail.¹³ However, quantitative HCV RNA testing is recommended after 4 weeks of therapy to assess initial response. An undetectable HCV RNA level is observed by Week 4 in most patients who do not have cirrhosis, but may take longer in those with cirrhosis. Repeat viral load testing ≥ 12 weeks after treatment completion is essential to assess cure. Virologic relapse after 12 weeks is rare. Last, working with a specialty pharmacy that offers hepatitis services is recommended to facilitate prior authorization and medication delivery, as well as to assist with patient education, drug selection based on insurance requirements, and avoidance of drug interactions.

Counseling people with active HCV infection

A key component of treatment is preventing further liver damage. Therefore, patients with current HCV infection should be educated about interventions to reduce the progression of liver disease and to prevent HCV transmission.^{13,28} Education about preventing HCV transmission is especially important for per-

sons who illicitly inject drugs, are HIV-infected, or have multiple sex partners or a sexually transmitted infection.

Patients should be advised to abstain from alcohol, because daily consumption of >50 g of alcohol has a high likelihood of accelerating fibrosis; this equates to approximately 4.5 oz of 40% hard liquor or 3.5 servings of 12 oz of beer or 5 oz of wine.^{7,13,28} Other conditions that accelerate liver fibrosis, such as overweight or obesity, hyperlipidemia, and cardiovascular comorbidities, should be managed. Hepatotoxic drugs (such as acetaminophen, >2 g/d; amoxicillin-clavulanate; and isoniazid) and nephrotoxic drugs (such as acyclovir, nonsteroidal anti-inflammatory drugs, and rifampin) should be avoided.²⁸

Several vaccinations are particularly important for persons with HCV infection, including against hepatitis A and hepatitis B. In patients with HCV infection and cirrhosis, vaccination against pneumococcal infection is important.^{13,28}

FOLLOW-UP

Patients who do not achieve SVR retain the possibility of continued liver injury and the potential to transmit HCV. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available.¹³

All patients who achieve SVR should clearly understand that they are not immune to HCV and can become reinfected. Specific liver follow-up for patients who achieve SVR is based on the degree of underlying liver fibrosis.¹³ Patients with F0-F2 fibrosis do not need further liver monitoring or follow-up, as achievement of SVR halts progression of HCV-related liver disease. Patients with advanced fibrosis (F3 or F4) may experience improvement in fibrosis, but they are considered to be at persistent risk of developing HCC.⁵² Accordingly, these patients should have surveillance for HCC with hepatic ultrasonography every 6 months. Patients with confirmed cirrhosis (F4) require a baseline upper endoscopy to screen for varices. Last, patients at ongoing risk of HCV infec-

TABLE 3 Recommended antiviral therapy for treatment-naïve people¹³

Group	Fixed-dosage combination direct-acting antiviral regimens	
	8 weeks	12 weeks
Genotype 1a without cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg ^b	Elbasvir 50 mg/grazoprevir 100 mg ^c Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 1a with compensated cirrhosis		Elbasvir 50 mg/grazoprevir 100 mg ^c Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 1b without cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg ^b	Elbasvir 50 mg/grazoprevir 100 mg Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 1b with compensated cirrhosis		Elbasvir 50 mg/grazoprevir 100 mg Glecaprevir 300 mg/pibrentasvir 120 mg ^a Ledipasvir 90 mg/sofosbuvir 400 mg Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 3 without cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg ^a	Sofosbuvir 400 mg/velpatasvir 100 mg
Genotype 3 with compensated cirrhosis		Glecaprevir 300 mg/pibrentasvir 120 mg ^a Sofosbuvir 400 mg/velpatasvir 100 mg ^d

(Regularly updated treatment recommendations may be found at <https://www.hcvguidelines.org>.)

^aThis is a 3-tablet coformulation. Please refer to prescribing information.

^bNon-black, HIV-uninfected, HCV RNA <6 million IU/mL.

^cWithout baseline NS5A resistance-associated substitution (RAS) testing for elbasvir (Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93, known to confer antiviral resistance).

^dRAS testing for the Y93H resistant variant is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered.

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tion should have periodic reassessment for HCV reinfection with HCV RNA testing (not testing for HCV antibody, which will likely remain positive), and counseling on prevention of reinfection. Additionally, any flare in liver enzymes should prompt evaluation for reinfection.

SUMMARY

Chronic HCV infection is a common, yet often asymptomatic, infection that can be successfully managed in the primary care setting. To achieve this, screening—particularly of high-risk groups—is an essential first step in a comprehensive management plan that is linked to individualized antiviral therapy with DAAs, based on genotype, stage of disease, comorbidity, and other patient variables. ●

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Approach to the Identification and Differentiation of Migraine

Merle L. Diamond, MD; Susan Hutchinson, MD

CASE SCENARIO

Elise is a 43-year-old woman who presents for a 6-month follow-up for type 2 diabetes mellitus. Although her diabetes is well-controlled, Elise's primary care physician (PCP) notices numerous gaps in blood glucose levels when reviewing Elise's diabetes log. The PCP also notes that Elise is tired and in some distress. Upon questioning, Elise indicates that she was awake most of the night because of throbbing headache pain.

Nearly one in four US households includes a person with migraine.¹ Approximately 18% of women and 9% of men in the US experience migraine during their lifetime.²

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Dr. Diamond discloses that she is on advisory boards and a consultant for Alder BioPharmaceuticals Inc.; Amgen Inc.; Promius Pharma, LLC; and Teva Pharmaceutical Industries Ltd. She is on the speakers' bureaus for Amgen Inc.; Avanir Pharmaceuticals, Inc.; Depomed, Inc.; Pernix Therapeutics; Supernus Pharmaceuticals, Inc.; and Teva Pharmaceutical Industries Ltd. She is on the advisory boards for Avanir Pharmaceuticals, Inc.; Depomed, Inc.; Eli Lilly and Company; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories. Dr. Diamond is on the Board of Directors for the National Headache Foundation and the Diamond Headache Clinic Research and Educational Foundation.

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IMPROVING THE DIAGNOSIS OF MIGRAINE IN PRIMARY CARE: WHY IT'S IMPORTANT

Why is improving the diagnosis of migraine important? Consider these facts.

- Migraine is the second leading cause of disability worldwide.³
- Migraine morbidity is not limited to attacks; between attacks, one-quarter of people with migraine reported symptoms such as anxiety, lack of freedom from headache symptoms, and avoidance of any activities.⁴
- Some of the more prevalent comorbidities with migraine include ischemic stroke, myocardial infarction, depression, anxiety, bipolar disorder, panic disorder, chronic pain, hypertension, and hyperlipidemia.⁴⁻⁹
- Approximately 1 in 8 people with migraine report they have done less well in their education because of their headaches.⁴
- Children of parents with migraine report a significant impact on their lives, including reverse caregiving, moderate-to-severe anxiety, and moderate-to-severe depression.¹⁰
- Patients with chronic migraine commonly report the belief that nothing can control migraine onset and course.⁷

These findings make it clear that people with migraine experience significant morbidity, which also affects families and employers, yet a high proportion don't seek medical care.¹¹ An early, accurate diagnosis of migraine may lead to better medical management and improved patient outcomes.

CASE SCENARIO (CONT)

Elise further reports that she has experienced similar headaches since her twenties. The headaches became more frequent and painful when she became a supervisor at a local factory about 5 years ago. She doesn't experience any visual or auditory sensations before or during the attack, but she generally experiences nausea. In addition, pain is worsened with routine activity such that she finds it difficult to function during an attack. She has tried various OTC analgesics.

DIAGNOSIS

An important first step in headache diagnosis is to determine if the headache is a primary or secondary headache.¹² For primary headaches, eg, migraine, cluster, and tension-type, the headache is the disease. In contrast, secondary headaches are caused by something else (eg, infection, trauma, mass, vascular abnormality).¹³

Differentiating secondary from primary headaches

Differentiating primary from secondary headaches begins with the search for “red flags” that might suggest a secondary headache. Several tools are available to clinicians for identifying red flags; one helpful mnemonic is SNOOP4 (FIGURE).¹⁴ The presence of a red flag does not confirm a secondary headache.¹²

The assessment for red flags begins with a detailed history and physical and neurological examination.¹⁴ Although the majority of patients with headache will have normal examinations, those with an abnormality may warrant imaging or other studies to rule out secondary headache.^{15,16} In the primary care setting, the need for imaging is limited. Findings from the pertinent medical history suggesting a need for imaging or other studies include change in headache pattern, frequency, severity; abnormal neurological signs or symptoms; headaches associated with trauma or new onset seizures; or headaches in patients with a history of cancer, human immunodeficiency virus, or active infection.^{15,16} Magnetic resonance imaging is the preferred method of imaging in nonacute headache.¹⁶ In the emergency department setting, imaging should be considered if red flags are present. When they are encountered, computed tomography is useful to assess for subarachnoid hemorrhage, head trauma, and bony abnormalities.¹⁶ If a secondary headache can be excluded by history, physical and neurological examination, or appropriate testing, the next step is to identify the primary headache disorder.

Identifying the type of primary headache

As in identifying patients with secondary headache, the history is vitally important in the diagnosis of primary headache, including migraine. Consequently, patients should be provided adequate time to fully describe the headaches and how they have been self-managing, including the use of complementary and alternative therapies. Issues to explore are listed in TABLE 1.¹⁷

The patient’s medical history, including associated disorders, and social history should be reviewed or, if unknown, investigated in detail. When it comes time to develop the treatment plan, addressing associated disorders that may be modifiable should be considered as this may be helpful in improving patient outcomes.¹⁸

FIGURE Ruling out secondary causes of headache: SNOOP4¹⁴

S	ystemic symptoms/signs/disease
N	eurologic symptoms or signs
O	nset sudden
O	nset after age 50 years
P	attern change (if previous history) <ul style="list-style-type: none"> • Progressive headache with loss of headache-free periods • Precipitated by Valsalva maneuver • Postural aggravation • Papilledema

Figure: © Georg Thieme Verlag KG.

Patients may have more than one type of primary headache.¹³ Therefore, to simplify the diagnostic evaluation, the most severe headache should be the initial focus. This can be facilitated by asking the patient to describe the headache that causes them the greatest disability. To assess disability, validated questionnaires such as the Headache Impact Test (HIT-6) or the Migraine Disability Assessment Questionnaire (MIDAS) may be used.

Migraine is a neurologic disease that includes headache characterized by a unilateral, throbbing pain with concurrent nausea and/or vomiting. Migraine symptoms can vary in patients with migraine. The aforementioned are some of the characteristics that may be experienced by patients with migraine, but may not always be present (TABLE 2).¹³

For example, migraine is unilateral in approximately 54% to 67% of patients.¹⁹ Similarly, only about 13% to 41% of patients with migraine experience aura.¹⁹ When nausea is present $\geq 50\%$ of the time with headache, it has been shown to be associated with a two-fold increased risk of progression from episodic to chronic migraine over 2 years of follow up compared to those with no or low frequency of nausea.²⁰

Symptoms occurring hours or days before and/or during the migraine attack appear to be common. These commonly include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue, neck stiffness, and/or pain. Patients may find it difficult to provide all of the needed information during the history.¹³

If so, the use of a headache diary may be considered. Identifying patients with migraine can be challenging. One reason is that patients may experience one or more types of headache.¹³ In addition, the frequency, signs and symptoms, and associated disability of migraine may vary over time, even within the same day.¹³

TABLE 1 Important characteristics to assess as part of the headache history¹⁷

Pattern—when and how it begins; continuous, episodic, or both
Triggers
Duration
Nature—location, character, severity
Premonitory symptoms, eg, excessive tiredness; yawning; excessive urination; neck stiffness; vertigo; visual/auditory
Symptoms accompanying attack, eg, nausea, sensitivity to lights, noises, smells, touch, movement
Treatments—current and previous; when taken; if effective or abandoned
Previous medical history—depression; sleep disorders; allergies
Current medications
Family history, especially of headache
Social history—occupation; smoking; alcohol and tobacco consumption
Previous medical consultation

As with some other types of headache, migraine is often classified as either episodic or chronic, the only difference is in their frequency. Migraine is considered chronic if headache occurs on ≥ 15 days/month for >3 months, which, on ≥ 8 days/month, has the features of migraine headache.¹³ Migraine headache on ≤ 14 days per month is referred to as episodic migraine in migraine research; the International Classification of Headache Disorders, 3rd edition (ICHD-3) does not have a category specifically for episodic migraine. Although disability due to chronic migraine is greater, patients with episodic migraine may also experience substantial disability.^{21,22}

The American Migraine Prevalence and Prevention (AMPP) study was conducted from 2004 to 2009 to describe migraine prevalence, sociodemographic profiles, burden, comorbidity patterns, prognosis, and health-related outcomes.²¹ Results from 5681 eligible study respondents with episodic migraine in 2006 revealed that patients who received inadequate efficacy from their acute treatment were at increased risk of new-onset chronic migraine.¹¹ Over a one-year period, progression of migraine from episodic to chronic was assessed based on 4 defined categories of migraine treatment efficacy. Increasing progression with decreased treatment efficacy was a key finding: maximum efficacy (1.9%), moderate efficacy (2.7%), poor efficacy (4.4%), and very poor efficacy (6.8%).²³ Triptan use was highest in the maximum efficacy group, while opioid or barbiturate use was highest in the moderate and poor efficacy groups.²³

Despite thorough assessment, it may not be appropriate to make a definitive diagnosis of migraine. In fact, current

TABLE 2 ICHD-3 diagnostic criteria for: 1.1 migraine without aura headache¹³

A	≥ 5 attacks ^a fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated) ^{b,c}
C	Headache has ≥ 2 of the following 4 characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by, or causing avoidance of, routine physical activity, eg, walking or climbing stairs
D	During headache ≥ 1 of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis

Abbreviations: ICHD-3, International Classification of Headache Disorders, 3rd edition.

^aOne or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least 5 attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without Aura but have had fewer than 5 attacks should be coded 1.5.1 Probable Migraine without Aura.

^bWhen the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.

^cIn children and adolescents (age <18 years), attacks may last 2-72 hours (the evidence for untreated durations of <2 hours in children has not been substantiated).

Table 2: International Headache Society, *Cephalalgia* 38(1), pp 1-211, copyright © 2018 by International Headache Society. Reprinted by Permission of SAGE Publications, Ltd.

ICHD-3 classification schema includes categories of “probable migraine” and “headache unspecified.”¹³ The updated ICHD-3 was developed by the International Headache Society to guide classification of headache disorders using evidence-based diagnostic criteria. Even so, in the absence of a definitive diagnosis of other primary or secondary headache, if the patient experiences substantial disability, migraine may be the likely diagnosis.²⁴ Finally, it should be remembered that patients often have more than one type of headache, often with overlapping and/or fluctuating symptoms. Consequently, it is important to periodically reassess the diagnosis to ensure that the patient is receiving optimal care.

COMMON QUESTIONS

Is there a quick way to diagnose migraine?

Although the diagnosis of migraine is generally based on the history and physical examination, the use of a validated screener such as ID Migraine may be useful once a secondary headache has been ruled out. Development of the ID Migraine screener was based on the existing 1988 ICHD criteria using 9 screening questions.²⁵ Among these, a three-item subset assessing disability, nausea, and photophobia

TABLE 3 ID Migraine Test²⁵

_____	You felt nauseated or sick to your stomach
_____	How many days did your headache limit you from working, studying, or doing what you needed to do?
_____	Light bothered you (a lot more than when you don't have headaches)

(TABLE 3) provided optimum performance in the primary care setting. Testing showed that the optimal total score in the primary care setting was any combination using 2 of the 3 questions with a sensitivity of 81% (95% confidence interval (CI) 77%-85%) and specificity of 75% (95% CI 64%-84%). Using all three questions provided a positive predictive value of 93% (95% CI 89.9%-95.8%) and good test-retest reliability (kappa 0.68, 95% CI 0.54-0.82). The sensitivity and specificity were similar regardless of age, presence of comorbid headaches, or previous diagnostic status; the sensitivity was slightly lower and the specificity higher in men than women.

What kind of information should be captured using a headache diary?

Patients' headache diaries can be used to provide information assessed during history taking (TABLE 1). It can be very helpful in identifying and modifying factors that influence a patient's headaches, including triggers. This information can be useful to differentiate modifiable (eg, light, stress, caffeine, alcohol) from nonmodifiable (menstruation for females, environmental) factors, targeting treatment at those that are modifiable. Diaries are available from several sources:

- American Academy of Family Physicians (<https://www.aafp.org/fpm/2013/0500/fpm20130500p24-rt1.pdf>)
- Migraine Trust (<https://www.migrainetrust.org/wp-content/uploads/2015/11/FS05aMigraineDiaries.pdf>)
- National Headache Foundation (<https://headaches.org/wp-content/uploads/2018/02/Diary2.pdf>) ●

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Addressing Unmet Needs with Prandial Insulin: A Focus on Orally Inhaled Human Insulin

John E. Anderson, MD

ROLE OF INSULIN IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

Patients with type 1 diabetes mellitus (T1DM) require insulin therapy because their bodies are unable to produce insulin.¹ Although patients with type 2 diabetes mellitus (T2DM) might be able to produce insulin, they may not be able to use it efficiently and suffer defects in glucose metabolism. Insulin therapy can be used across the spectrum of T2DM and the American Diabetes Association recommends initiation of insulin therapy (with or without additional agents) in patients newly diagnosed with T2DM who have symptoms of hyperglycemia (ie, polyuria, polydipsia), glycated hemoglobin (HbA_{1c}) ≥10%, and/or blood glucose levels ≥300 mg/dL. Insulin also is recommended in patients who are not achieving glycemic goals with lifestyle changes and oral antihyperglycemic agents.¹ The 2018 American Association of Clinical Endocrinologists/American College of Endocrinology algorithm suggests insulin be used alone or with other glucose-lowering agents in patients with an initial HbA_{1c} >9.0% or as part of dual or triple therapy for patients with HbA_{1c} ≥7.5%.²

All patients with T1DM and approximately 40% of patients with T2DM require both basal and prandial insulin.¹⁻³ Insulin historically has been administered as a series of daily subcutaneous (SC) injections or by continuous (SC) insulin infusion using an insulin pump.

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UNMET NEEDS WITH INJECTABLE INSULINS

Although injectable insulin has been the standard of care for >90 years, challenges remain.⁴⁻⁶ These include patient concerns about their ability to self-administer injections, pain associated with injections, general uneasiness about injection, and social discomfort related to using syringes in public.⁵⁻⁷ Hypoglycemia, weight gain, the need for multiple daily injections, and the need to carry the dosing equipment and glucose monitor are widely recognized as barriers to effective insulin therapy.

A great deal of complexity is associated with coordinating the timing of prandial doses with meals, monitoring blood glucose, and determining the proper dose based on the size and composition of the meal and current blood glucose concentration.⁴⁻⁷ Patients might experience anxiety related to the timing of mealtime insulin injections. Subcutaneously injected insulin, even the rapid-acting insulin analogs (insulin aspart, insulin glulisine, and insulin lispro), are absorbed slowly enough into systemic circulation that the insulin concentration can remain elevated up to 6 hours after dosing. As a consequence, the time-action profiles of injectable prandial insulins do not match the absorption of prandial glucose and can put patients at risk of postprandial hypoglycemia, especially 2 to 5 hours after the meal (late postprandial hypoglycemia).^{8,9}

Several approaches have been taken to simplify insulin therapy. The most straightforward is to make it easier for patients to self-administer the dose. For example, mechanical, tubeless, disposable patch pumps can be affixed to the skin to deliver insulin via cannula or small needle from a reservoir that is changed every 1 to 3 days. One product, V-Go (Valeritas, Inc.), provides rapid-acting insulin at a basal rate, with the ability to deliver discrete mealtime or correctional doses.^{10,11} Another product, OneTouch Via by Calibra Medical, delivers 2 units of rapid-acting insulin with each actuation of the 2 buttons on the device but does not provide basal insulin coverage.^{12,13}

Other routes of administration also have been explored. Oral administration of insulin has been studied for decades, with no success to date. The obstacles to oral delivery include: (1) degradation of insulin in the stomach; (2) limited diffu-

sion through intestinal mucosa into the bloodstream, and (3) variable absorption rates due to meal effects and other factors affecting gastrointestinal motility.¹⁴

Inhaled insulin, another route of administration, has been investigated for >80 years.¹⁵ In 2006, the US Food and Drug Administration (FDA) approved Exubera (Nektar Therapeutics/Pfizer) as the first inhaled insulin for patients with T1DM or T2DM.¹⁶ Exubera was withdrawn from the market several months after its release because of limited commercial success. The lack of success was attributed to: (1) a large, bulky, complicated inhaler; (2) the cumbersome administration process; (3) Exubera doses were labeled in milligrams rather than units, making the conversion difficult; and (4) requirement for full pulmonary function tests because of small pulmonary function changes associated with the drug. After patients overcame these hurdles, the pharmacokinetics (PK)/pharmacodynamic (PD) of Exubera was so similar to SC administration of rapid-acting insulin analogs that Exubera was considered a “convenience” product. Finally, a small potential lung cancer signal was seen in former heavy smokers.^{17,18}

ORALLY INHALED INSULIN

Notwithstanding the limitations observed with Exubera, pulmonary delivery of insulin remains a viable route for administration. In contrast to SC insulin that is absorbed from a localized region around the injection site, pulmonary delivery exploits the large area of the alveoli for absorption into the systemic circulation.¹⁹ In addition, oral inhalation avoids physiologic barriers such as peptidases in the GI tract and first-pass metabolism.¹⁶

Afrezza (MannKind) is a rapid-acting, orally inhaled insulin approved by the FDA in 2014 to improve glycemic control in adults with T1DM or T2DM.²⁰ It is composed of Technosphere® insulin inhalation powder, a dry powder formulation of recombinant human insulin adsorbed onto carrier Technosphere microparticles (median diameter 2.0 to 2.5 µm) that are within the optimal size range for delivery deep into the lung.^{8,20} Inhaled Afrezza is delivered using cartridges that are loaded into a thumb-sized delivery device. The current Afrezza inhaler is smaller and more efficient than the MedTone delivery system used in clinical development through 2010.^{8,16}

PHARMACOKINETICS/PHARMACODYNAMICS

Inhaled Afrezza is characterized by a rapid onset and short duration of action.^{8,21} Upon inhalation, Afrezza particles dissolve in the neutral pH of the lung and insulin is rapidly absorbed into the circulation.^{8,16} Afrezza exhibits a linear, dose-related response. Time to maximum plasma drug concentration (10 to 15 minutes) and peak glucose-lowering effect (approximately 45 minutes) for Afrezza are shorter

than with regular human insulin or insulin lispro.^{8,21,22} This has been demonstrated repeatedly in crossover, hyperinsulinemic, euglycemic glucose clamp studies. The most recent was a study in 30 patients with T1DM in which the onset of metabolic activity for Afrezza occurred earlier than for insulin lispro (15 to 19 minutes vs 45 to 52 minutes), and the duration of action for Afrezza was approximately 2 to 3 hours shorter than equivalent doses of insulin lispro (1.8 to 6.4 hours vs 5.0 to 9.8 hours).²³ Afrezza’s glucose disposal effect occurs earlier than that of SC insulin. For example, the rate of glucose disposal over the first 60 minutes after administration is 34% greater for Afrezza than SC regular human insulin ($P < .05$) and 4% less for Afrezza than SC insulin lispro ($P = \text{NS}$).²⁴

Because Afrezza is administered by oral inhalation, the potential effects of an acute upper respiratory tract infection (URTI) on the PK/PD profile were investigated.²⁵ No significant impact was observed among patients with T1DM or T2DM who developed an URTI while being treated with Afrezza. Similarly, the PK profile is not significantly different in persons with mild-to-moderate chronic obstructive pulmonary disease (COPD) compared with healthy controls.²⁶

EFFICACY OF AFREZZA INHALED INSULIN

Clinical studies from 2010 and earlier used the MedTone inhalation device, while more recent phase 3 trials (Affinity 1 and Affinity 2) used the currently available Afrezza inhaler in patients with T1DM or T2DM, respectively.^{16,27-29} Efficacy results from the Affinity 1 and 2 trials are summarized in **TABLE 1**.^{27,28} The results from Affinity 1 and 2 generally were consistent with those of a meta-analysis of 12 earlier clinical trials vs SC insulin or SC rapid-acting analog in T1DM and T2DM. The meta-analysis showed a mean HbA_{1c} reduction from baseline of 0.55% with Afrezza (95% confidence interval [CI], 0.34%-0.78%). The mean reduction in HbA_{1c} was slightly larger in patients receiving SC insulin (net treatment difference was 0.13% in T1DM and 0.19% in T2DM), but the difference was not statistically significant.³⁰

Afrezza has demonstrated effective control of postprandial hyperglycemia in clinical trials.²⁷⁻²⁹ In the Affinity 2 trial of insulin-naïve patients with T2DM, Afrezza produced clinically meaningful reductions in postprandial glucose (PPG) levels at weeks 12 and 24 compared with baseline as demonstrated by less variability in the 7-point glucose profile (based on self-monitored blood glucose values taken immediately before every meal, 90 minutes after the meal, and at bedtime) compared with placebo.²⁸ These findings were consistent with those of an earlier trial in patients with T2DM that was poorly controlled with basal insulin with or without oral antihyperglycemic agents.²⁹ In that study, patients receiving Afrezza plus insulin glargine had significantly lower 1 hour

TABLE 1 Efficacy of Afrezza

	Affinity 1 ²⁷		Affinity 2 ²⁸	
Methods				
Design	Randomized, open-label, 24 week		Randomized, double-blind, placebo-controlled, 24-week	
Type of diabetes	Type 1		Type 2	
Intervention	Afrezza (n = 174) vs prandial aspart (n = 170)		Afrezza (n = 177) vs placebo (n = 177)	
Adjunctive therapy	Basal insulin (NPH or detemir, or glargine)		Oral antihyperglycemic agents	
Mean HbA _{1c} levels at baseline (TI/comparator)	Afrezza 7.94%	Aspart 7.92%	Afrezza 8.35%	Placebo 8.35%
Results				
	Afrezza	Aspart	Afrezza	Placebo
Reduction in HbA _{1c} vs baseline	−0.21%	−0.40%	−0.82%	−0.42%
Treatment difference Afrezza-comparator	0.19% vs aspart (95% CI, 0.02 to 0.36) met criteria for noninferiority		−0.40% vs placebo (95% CI, −0.57 to −0.23)	
Proportions of patients reaching HbA _{1c} ≤ 7%	18%	31%	38%	19%
Changes in 7-point glucose profiles	Lower fasting glucose	Lower glucose concentrations at other time points	Clinically meaningful reductions in postmeal glucose values	—

Abbreviations: CI, confidence interval; HbA_{1c}, glycated hemoglobin; NPH, neutral protamine Hagedorn; TI: technosphere insulin.

PPG levels than those receiving biaspart insulin (171 mg/dL vs 209 mg/dL; $P = .0001$), while 2-hour PPG levels were similar between groups (213 mg/dL in both groups). Consistent with its short duration of action, glucose excursions—ie, fluctuations in blood glucose either above or below the normal range—at 2 hours were higher among patients receiving Afrezza than those receiving biaspart.

The PK/PD profile of Afrezza provides excellent glucose control in the early postprandial period, but its duration of action might be too short to cover meals that are absorbed over longer times.^{29,31} The short duration of action, however, also suggests a second dose could be administered with minimal risk of hypoglycemia. This hypothesis was tested in several pilot studies.^{31,32} In a single-arm, 45-day study of patients with T1DM (N = 15), a second dose (administered if the 2-hour PPG level was ≥ 180 mg/dL) was used 38% of the time and reduced mean HbA_{1c} from 7.86% to 7.47% with no increase in the time spent with blood glucose < 60 mg/dL.³² In a T2DM study of SC rapid-acting insulin in patients with inadequate glycemic control with optimized basal insulin and oral agents, 21% of patients (n = 19) receiving Afrezza took a second dose (administered if the 90- to 120-minute PPG level was > 140 mg/dL).³¹ The reduction in HbA_{1c} levels over 16 weeks was similar in the 2 groups, while the Afrezza group did not experience higher incidences of hypoglycemia and adverse events than those on SC therapy.

SAFETY OF TECHNOSPHERE INHALED INSULIN

As with other insulin products, the most common adverse event associated with Afrezza is hypoglycemia. The incidences of hypoglycemia and severe hypoglycemia occurring in the Affinity 1 and 2 trials are summarized in **TABLE 2**. A meta-analysis of 5 studies in patients with T1DM or T2DM found similar results; severe hypoglycemia was reported less frequently with Afrezza (12% of patients) than with SC insulin (19% of patients; odds ratio [OR] 0.61; 95% CI, 0.35-0.92).³⁰ Furthermore, the timing of hypoglycemic events with Afrezza reflects its rapid onset and short duration of action. As evidenced by results of the Affinity 1 study, hypoglycemic event rates within 2 hours after meals were similar among the treatment groups, but were 2 to 3 times less frequent 2 to 5 hours after meals in patients randomized to Afrezza.²⁷

Cough is the most common nonhypoglycemic adverse effect (**TABLE 2**), reported by 29% of patients receiving Afrezza in a meta-analysis of 7 studies.²⁷⁻³⁰ Cough induced by Afrezza is generally mild, transient, occurring within 10 minutes of inhalation, typically occurs within the first month of treatment, and decreases over time with continued use.³⁰ Patients with persistent or recurring cough require close monitoring of lung function and, if necessary, treatment discontinuation.²⁰ Although cough is the most common adverse event leading to discontinuation (2.8% of patients discontinued

TABLE 2 Safety of Afrezza

	Affinity 1 ²⁷		Affinity 2 ²⁸	
	Afrezza	Aspart	Afrezza	Placebo
Proportions of patients reporting adverse effects	58%	43%	61%	51.1%
Withdrawal due to adverse effects	9.2%	0%	4%	5.1%
Proportions of patients reporting hypoglycemia ^a	96%	99.4%	67.8%	30.7% (<i>P</i> < .0001)
Proportions of patients reporting severe hypoglycemia ^b	18.4%	29.2% (<i>P</i> = .0156)	5.7%	1.7%
Proportions of patients reporting cough	31.6%	2.3% (<i>P</i> < .05)	23.7%	19.9%
Withdrawal due to cough	5.7%	0%	1.1%	3.4%
Change in mean weight	-0.4 kg	+0.9 kg (<i>P</i> = .01)	+0.5 kg	-1.1 kg (<i>P</i> < .0001)
Change in mean FEV ₁ (L)	-0.07 L	-0.04 L	-0.13 L	-0.04 L

Abbreviations: FEV₁, forced expiratory volume in 1 second.

^aSelf-monitored blood glucose <70 mg/dL and/or presence of symptoms of hypoglycemia.

^bEvent requiring third-party assistance.

due to cough), it is reversible and resolves within 1 to 2 days after drug discontinuation.^{28,30}

Patients on Afrezza lost more weight or gained less weight than those on SC prandial insulin (TABLE 2).^{27,28} A meta-analysis of 3 studies reported significantly less weight gain compared with SC prandial insulin (net difference -1.1 kg).³⁰

Given the concerns about earlier inhaled insulin products, the potential impact of Afrezza on lung function has been investigated closely. One such investigation was a 2-year, phase 3 clinical study comparing patients on Afrezza with patients receiving usual care and a cohort of healthy volunteers as a reference group to characterize normal changes in pulmonary function.³³ Small declines from baseline in forced expiratory volume in 1 second (FEV₁) were observed in all 3 groups, with the smallest change occurring in those without diabetes. The mean change in FEV₁ at 24 months was -0.09 L in healthy volunteers, -0.11 L in patients receiving usual care, and -0.15 L in patients receiving Afrezza. The net difference between the Afrezza and usual care groups was 0.037 L (95% CI 0.014-0.06 L). For reference, baseline FEV₁ was approximately 3.1 L in patients with diabetes. The decline was significantly greater for Afrezza at 3 months; thereafter through 24 months, the rate of change in FEV₁ and forced vital capacity (FVC) was not significantly different between groups. The small, non-progressive decline in lung function was considered by investigators to not be clinically meaningful.³³ In Affinity 1 and Affinity 2, slight declines in FEV₁ also were observed in the Technosphere insulin (TI) groups relative to comparators, were not associated with cough status, and were judged as unlikely to be clinically

meaningful.^{27,28} In Affinity 2, for example, the FEV₁ declined 4.5% for TI vs 1.4% for placebo at 24 weeks (end of treatment difference -0.09 L; 95% CI, -0.12 to -0.05).

Acute bronchospasm and wheezing were observed after inhalation of Afrezza in 29% (5 of 17) of patients with asthma who did not take their usual bronchodilator; no bronchospasm was observed in 13 individuals without asthma.²⁰ This was accompanied by a substantial mean reduction in FEV₁ of 400 mL at 15 minutes after a single dose of Afrezza. Similarly, in a small group of patients with COPD (n = 8), a mean decline in FEV₁ of 200 mL was observed 18 minutes after Afrezza inhalation.²⁰ Therefore, Afrezza is contraindicated in patients with chronic lung disease such as asthma or COPD.

Two cases of lung cancer, 1 in controlled trials and 1 in uncontrolled trials (2 cases in 2,750 patient-years of exposure), were observed in participants exposed to Afrezza.²⁰ In both cases, a history of heavy tobacco use was identified. Two additional cases of lung cancer in non-smokers exposed to Afrezza were reported several years after clinical trials were completed. Minimal information was available regarding interim medical issues and these data are insufficient to determine whether Afrezza has an effect on lung or respiratory tract tumors.²⁰

Afrezza is not contraindicated in patients with cancer. Rather, a risk-benefit analysis should be performed for each patient.

PATIENT SELECTION

Several of the key features and benefits of Afrezza suggest it could address some unmet needs encountered with SC

TABLE 3 Patient education checklist

✓	Adherence/self-management	Instruct on self-management procedures and verify at each visit (eg, dosing with meal, glucose monitoring, handling special situations [eg, intercurrent illness]); review key aspects of Technosphere insulin handling and storage and verify administration technique at each visit
✓	Hypoglycemia risk and monitoring	Reinforce signs/symptoms of hypoglycemia; provide written action plan
✓	Cough	Occurs in 24% to 33% of patients within 10 minutes of inhalation; mild, typically subsides after first month
✓	Change in lung function (FEV ₁)	Evaluate with spirometry; a small change is generally not considered clinically relevant
✓	Lung cancer	Conduct risk-benefit analysis
✓	Diabetic ketoacidosis	Monitor blood glucose and maintain dosing during illness, infection, and other risk situations
✓	Drug interactions	Certain drugs may increase the risk of hypoglycemia; increase or decrease the blood-glucose-lowering affect; or affect the signs and symptoms of hypoglycemia. Dosing adjustments and increased glucose monitoring may be warranted
✓	Dosing	Increase dose or add second mealtime dose if glucose not well controlled and hypoglycemia not an issue
✓	Storage/handling	Refrigerate cartridges; dispose of inhaler after 15 days; video demonstration of dose administration technique: https://www.afrezza.com/hcp/afrezza-steps
✓	Affordability	Verify insurance coverage

Abbreviations: FEV₁, forced expiratory volume in 1 second.

prandial insulin. The rapid onset of TI provides easier and more flexible mealtime dosing because it is administered at the beginning of a meal rather than 15 to 30 minutes prior as required with rapid-acting SC insulin analogs. This might be of particular benefit to patients with unpredictable or erratic meal schedules. The shorter duration of action reduces the incidence of late postprandial hypoglycemia, which could be especially important in patients with hypoglycemia unawareness. Afrezza also circumvents the need to use a syringe in public and patients' dislike of injections. Additionally, Afrezza eliminates the need for any injection beyond basal insulin. This might be particularly beneficial for the 37% to 64% of patients who experience lipohypertrophy from injecting insulin and its associated increase in variability of effect.³⁴⁻³⁶ Finally, Afrezza is associated with slightly less weight gain, which may help allay this common concern among patients.

When considering Afrezza for a patient, the absence of chronic lung disease must be confirmed through medical history, physical examination, and spirometry evaluation (FEV₁) before treatment.²⁰ Afrezza is not appropriate for patients with chronic lung disease such as COPD and asthma because of the risk of acute bronchospasm.²⁰ Spirometry should be repeated at 6 months and annually thereafter to monitor for small decreases in FEV₁, even in the absence of pulmonary symptoms. If lung function decreases by $\geq 20\%$, consider discontinuing TI.²⁰ A Risk Evaluation and Mitigation Strategy to mitigate the risk of acute bronchospasm associ-

ated with TI has been developed by the manufacturer (www.AfrezzaREMS.com).³⁷

Afrezza has not been studied in all populations. There are limited data in pregnant women or lactating mothers.²⁰ Based on animal studies, it is likely that the insulin and carrier in Afrezza are excreted in human breast-milk, but there is insufficient information to determine the risk for adverse developmental outcomes.²⁰ Afrezza has not been studied in patients under the age of 18 years or in patients with renal or hepatic impairment.²⁰

ADMINISTRATION AND DOSING CONSIDERATIONS

Administration

The Afrezza delivery system is composed of a small, thumb-sized inhaler and single-use cartridges containing 4 units, 8 units, or 12 units of Afrezza. Only 1 inhalation per cartridge is required. If the prescribed dose is >12 units, >1 cartridge is needed. This is accomplished by loading, administering, and removing 1 cartridge, then repeating with a second cartridge.²⁰ A video demonstration of the process is available at <https://www.afrezza.com/hcp/afrezza-steps>. Afrezza cartridges should be refrigerated until opened. Unopened foil package or blister cards not refrigerated must be used within 10 days; opened blister cards must be used within 3 days.²⁰ The patient does not need to clean the inhaler; it is replaced with a new one every 15 days.

Dosing

Insulin naïve patients should be started on 4 units of Afrezza at each meal. Individuals using SC mealtime insulin should be converted to TI based on a conversion chart in the product labeling. For individuals using SC premixed insulin, one half of the total daily insulin dose is given as basal insulin and the other half as TI prandial insulin, given in one-third increments at each meal. The dose is calculated using the same conversion for individuals using mealtime insulin.²⁰ Subsequent dosing should be adjusted based on the individual's metabolic needs, blood glucose monitoring results (via self-monitoring of blood glucose, continuous glucose monitoring, or flash glucose monitoring) and glycemic control goal.²⁰

It is important to note that patients might require doses that seem high compared with SC insulin, perhaps 1.5 to 2-fold. This is a normal consequence of Afrezza's unique PK/PD profile and is not an indication of lack of effect. As with any insulin, the dose should be titrated to achieve and maintain glycemic control.

PATIENT EDUCATION

Educating patients about Afrezza includes several topics appropriate for any patient treated with insulin, as well as some specific subjects (TABLE 3). All these topics, particularly hypoglycemia and adherence/self-management, should be reviewed with the patient at every visit.

CONCLUSIONS

Prandial insulin analogs are improvements over earlier products, and yet there are still unmet needs for optimal treatment of patients with diabetes. These include a mismatch between onset and duration of action and PPG levels, concern for hypoglycemia, dose timing, needle phobia, and treatment complexity. Compared with SC prandial insulin, the rapid-acting inhaled insulin of Afrezza leads to better control of early PPG with less weight gain and less frequent hypoglycemia, although control of late PPG remains suboptimal in some patients. Together with the ease of use of the TI inhaler, the convenience of administering the dose at the beginning of a meal, and non-injectable administration make TI a useful option for select patients who require prandial insulin. TI is contraindicated in patients with chronic lung disease such as asthma or COPD. ●

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Long-term Treatment of Gout: New Opportunities for Improved Outcomes

Paul P. Doghramji, MD, FAAFP

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Make a presumptive diagnosis of gout based on history and physical examination
- Individualize and modify urate-lowering therapy based on best evidence to achieve treatment goals

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Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of the long-term treatment of gout.

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WHAT DO THE 3 FOLLOWING REAL-LIFE CASES HAVE IN COMMON?

1. An adult male presenting with pain in the foot and instep
2. A postmenopausal female presenting with wrist pain and stiffness
3. A young, thin male presenting with severe pain in the mid-foot, similar to what his father and brother experience.

The underlying cause of pain in all 3 of these patients is undiagnosed gout, demonstrating different presentations of gout.

This article will discuss some of the key questions and clinical challenges encountered in the long-term primary care management of patients with gout.

ARE THERE CONSEQUENCES OF GOUT BEYOND IMPAIRED FUNCTIONING AND QUALITY OF LIFE?

Gout is an independent predictor of premature death and is associated with a high frequency of comorbidities, many with a prevalence 2 to 3 times higher than among people without gout: hypertension, chronic kidney disease (CKD), obesity, type 2 diabetes, nephrolithiasis, cardiac disease (including coronary artery disease, heart failure, and atrial fibrillation), dyslipidemia, stroke, peripheral arterial disease, and sleep apnea.¹⁻³

DO ALL PATIENTS WITH HYPERURICEMIA DEVELOP GOUT?

Based on an estimated prevalence of gout of 3.9% (8.3 million) and hyperuricemia (ie, serum uric acid [sUA] level >7.0 mg/dL in men and >5.7 mg/dL in women) of 21.4% (43.3 million) among US adults, approximately 1 in 5 people with hyperuricemia develop symptoms of gout.⁴ Although the prevalence of hyperuricemia is similar among men (21.2%) and women (21.6%), the prevalence of gout is approximately 3 times higher in men than in women (5.9% and 2% of adults in the United States, respectively); the disparity between sexes lessens after menopause.⁵ The overall prevalence of gout increases with age, from 3.3% in adults over the age of 40 years to 9.3% in adults over the age of 70 years.⁴ Family history may also play a small role.

CASE STUDY, STEVE:

A 37-year-old male with obesity (body mass index, 33 kg/m²) presents with a painful, swollen big toe. He has a family history of gout (father, brother). sUA is 7.3 mg/dL.

WHAT ARE THE COMMON FINDINGS ON HISTORY AND PHYSICAL EXAMINATION THAT SUGGEST GOUT?

An acute gout attack (flare) is typically monoarthritic early in the disease and peaks within hours, manifesting as a severely inflamed joint that is red, hot, swollen, and tender to the touch or movement.⁶ The attack is self-limiting, with symptoms resolving within about 2 weeks, although ongoing joint damage during intercritical asymptomatic periods usually occurs due to continuing monosodium urate (MSU) crystal deposition and inflammation.⁷ An acute attack most commonly manifests in the lower extremities, particularly the first metatarsophalangeal joint (podagra) in men, whereas the elbow, wrist, and hands are more likely to be affected in women.^{6,8} The reduced solubility of urate at lower temperatures may account for the occurrence of gout at peripheral joints, which are cooler than central-axis

joints.⁹ Involvement of more than 1 joint is more common as disease progresses.⁶

WHAT, IF ANY, FURTHER ASSESSMENT IS NEEDED BEYOND THE HISTORY AND PHYSICAL EXAMINATION TO CONFIRM THE DIAGNOSIS OF GOUT?

The most important component of the differential diagnosis of acute gout is septic arthritis, although the incidence of septic arthritis is much lower. In addition, the onset of septic arthritis is more insidious, and patients with septic arthritis tend to be quite sick with fever, rash, or other signs of systemic illness, and typically require hospitalization.^{8,10}

Synovial fluid aspiration and identification of MSU crystals by polarized light microscopy is the gold standard of gout diagnosis.⁶ However, an adequate clinical analysis is sufficient for diagnosis in most cases, so this test is often not required.¹¹ Combined with intra-articular corticosteroid injection, joint aspiration provides immediate and lasting pain relief for many patients.^{6,8} Radiography is not useful in early gout because small erosions and tophi are difficult to detect, but such lesions are detectable in chronic gout.⁶ Although not commonly done, ultrasonography is useful in early gout to distinguish between active and inactive tophi.⁶

The absence of hyperuricemia is inadequate alone to rule out a gout diagnosis because the sUA level may drop to normal during a gout attack. Therefore, even though it is reasonable to measure sUA during an attack, the sUA level should be measured again several weeks after the flare has resolved.¹⁰ It should be kept in mind that each laboratory calculates its own sUA threshold for hyperuricemia, so a “normal” sUA level may, nevertheless, reflect levels in joint tissues that are above ~6.8 mg/dL necessary for MSU crystal deposition.⁷ Most labs these days will also list, “sUA desirable level for gout treatment: <6.0 mg/dL.”

Hyperuricemia and gout should be considered red flags for metabolic syndrome and cardiovascular disease. Therefore, additional evaluation includes a comprehensive metabolic panel (eg, blood glucose and hemoglobin A1c levels and kidney and liver function) and a lipid panel, as well as clinical screening for associated comorbidities and cardiovascular risk factors (eg, obesity, hypertension, smoking).^{12,13}

CASE STUDY, STEVE (CONTINUED)

A diagnosis of gout is confirmed. A plan is developed to begin a nonsteroidal anti-inflammatory drug for acute treatment for the flare. Once the flare has resolved, urate-lowering therapy will be initiated.

WHAT ARE THE OBJECTIVES OF LONG-TERM GOUT MANAGEMENT?

Monosodium urate crystal formation is reversible, and crystals will dissolve when the sUA level drops below the limit of solubility (~6.8 mg/dL). This will result in the disappearance of gout flares and a reduction in the size and number of tophi.^{12,14} The lower the sUA level, the faster the crystal deposits (and tophi) resolve. Therefore, the goal of long-term gout management is to lower the sUA level below the limit of solubility.¹⁴ In addition, the management of patients with gout should include prevention and treatment of associated cardiovascular and other diseases.³

WHAT IS THE TARGET SUA GOAL?

According to both the American College of Rheumatology (ACR) guidelines and the European League Against Rheumatism (EULAR) recommendations, the target sUA goal for urate-lowering therapy (ULT) is <6 mg/dL for all gout patients. A lower sUA target (<5 mg/dL) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout are achieved.^{12,15}

Appropriately treated gout, with maintenance of sUA below target levels, markedly reduces the frequency of gout flares and the size and number of tophi and improves quality of life (QoL).¹² Inadequate treatment that fails to maintain sUA below target levels is associated with recurrent flares, further joint damage, and subsequent loss of mobility, functional impairment, and decreased QoL.¹¹

HOW OFTEN SHOULD SUA BE MONITORED?

The American College of Radiology guidelines recommend monitoring sUA every 2 to 5 weeks during ULT titration (see “How is each of the approved ULTs initiated and titrated?” on page S23), then every 6 months once the sUA target level is achieved.¹⁵

DOES LIFESTYLE MANAGEMENT HAVE A ROLE?

Evidence from randomized, blinded studies is lacking regarding alteration of lifestyle factors translating into improved outcomes in patients with gout. However, diet, exercise, and weight loss have been associated with a modest reduction in the sUA level in some clinical trials; therefore, every patient should be encouraged to make such changes as best as possible.^{12,15} Lifestyle management (eg, reducing excess body weight, regular exercise, smoking cessation, and avoiding excessive alcohol and sugar-sweetened drinks) has a greater role in reducing the risk and optimizing management of life-threatening comorbidities in patients with gout.^{12,13,15}

WHAT MEDICATIONS ARE APPROVED IN THE UNITED STATES AS ULT? WHAT IS THE MECHANISM OF ACTION OF EACH MEDICATION?

Available US Food and Drug Administration (FDA)-approved options for lowering sUA include xanthine oxidase inhibitors (allopurinol and febuxostat) that prevent production of uric acid; a uricosuric agent (probenecid) that increases uric acid output in urine; and a uric acid-specific enzyme (pegloticase) that converts uric acid to allantoin. Another recently approved uricosuric agent, lesinurad, inhibits the function of transporter proteins (urate transporter 1 and organic anion transporter 4) involved in uric acid reabsorption in the kidney.^{6,16}

Fenofibrate, losartan, and atorvastatin are not FDA-approved for gout but act as uricosurics and can therefore be used to treat gout comorbidities or in association with xanthine oxidase inhibitors.⁶ There has been limited study of rasburicase, an injectable approved for tumor lysis, in the treatment of tophaceous gout.¹⁶

CASE STUDY, HARRIET:

In a patient diagnosed with gout (and who has normal renal function), allopurinol, 300 mg daily, is initiated after resolution of an acute flare. sUA is reduced from 8.6 mg/dL to 7.2 mg/dL after 9 months of treatment. Clinical decision points:

- Should the dosage of allopurinol be increased or should a non-xanthine oxidase inhibitor be initiated?
- If the patient's estimated glomerular filtration rate is 35 mL/min/1.73 kg/m², would this impact the decision between uptitrating and adding a second agent?

WHAT ARE THE RECOMMENDATIONS AND EVIDENCE FOR EACH ULT?

Guidelines recommend a xanthine oxidase inhibitor as first-line therapy.¹⁵ Allopurinol is most commonly used due to its low cost, extensive clinical experience, and relatively good safety and efficacy profile.^{8,13}

For patients who do not achieve the target sUA level with optimized allopurinol therapy, the next-step choice is primarily a consideration of patient-specific factors, physician and patient choice, and cost. In the author's experience, a good option is using medications with different mechanisms of action because this provides further lowering of sUA while enabling the use of lower dosages of individual medications, thereby reducing the incidence and severity of dosage-related adverse events.

The xanthine oxidase inhibitor febuxostat, 80 mg/d or 120 mg/d (the latter an investigational dose but recommended by ACR and EULAR when needed) has demonstrated superior urate-lowering efficacy compared with allo-

TABLE Key studies of urate-lowering therapy^{18,19,22-25}

• Study/author • Baseline sUA level • Prior treatment	Treatment	Primary efficacy result
<ul style="list-style-type: none"> FACT/Becker¹⁸ Mean sUA, 9.8-9.9 mg/dL ALP (44% of subjects) 	52 weeks ALP 300 mg/d (n=253) FBX 80 mg/d (n=256) FBX 120 mg/d (n=251)	<i>Percentage of patients with sUA <6 mg/dL at last 3 monthly measurements</i> ALP 300 mg/d: 21% FBX 80 mg/d: 53% ($P<.001$) ^a FBX 120 mg/d: 62% ($P<.001$) ^a
<ul style="list-style-type: none"> APEX/Schumacher¹⁹ Mean sUA, 9.85 mg/dL ALP (~1/3 of subjects) 	28 weeks ALP 300 mg/d (n=268) ^b FBX 80 mg/d (n=267) FBX 120 mg/d (n=269) FBX 240 mg/d (n=134) PBO (n=134)	<i>Percentage of patients with sUA <6 mg/dL at last 3 monthly measurements</i> ALP 300 mg/d: 22% FBX 80 mg/d: 48% ($P<.05$) ^a FBX 120 mg/d: 65% ($P<.05$) ^a FBX 240 mg/d: 69% ($P<.05$) ^a PBO: 0%
<ul style="list-style-type: none"> CLEAR 1/Saag²³ sUA, ≥ 6.5 mg/dL ALP ≥ 300 mg/d (≥ 200 mg/d in patients with moderate renal impairment) and ≥ 2 gout flares during the previous year 	12 months PBO/ALP (n=201) LSN 200 mg/d + ALP (n=201) LSN 400 mg/d + ALP (n=201)	<i>Percentage of patients with sUA <6 mg/dL at 6 months</i> PBO/ALP: 27.9% LSN 200 mg/d + ALP: 54.2% ($P<.0001$) ^a LSN 400 mg/d + ALP: 59.2% ($P<.0001$) ^a
<ul style="list-style-type: none"> CRYSTAL/Dalbeth²² ULT-naïve: sUA, ≥ 8 mg/dL; ULT treated: sUA, ≥ 6 mg/dL 	12 months PBO/FBX 80 mg/d (n=109) LSN 200 mg/d + FBX 80 mg/d (n=106) LSN 400 mg/d + FBX 80 mg/d (n=109)	<i>Percentage of patients with sUA <5 mg/dL by month 6</i> PBO/FBX 80 mg/d: 46.8% LSN 200 mg/d + FBX 80 mg/d: 56.6% ($P=.13$) ^a LSN 400 mg/d + FBX 80 mg/d: 76.1% ($P<.0001$) ^a
<ul style="list-style-type: none"> Open label study/Reinders²⁴ N/A Benzbromarone 	Stage 1: 2 months ALP 200-300 mg/d (based on renal function) (n=32) Stage 2: >2 months Probenecid 1000 mg/d, added to ALP in patients failing to attain sUA <0.3 mmol/L ^c (n=14)	<i>Percentage of patients attaining sUA <0.3 mmol/L^c</i> Stage 1 ALP monotherapy: 25% Stage 2 ALP plus probenecid: 86%
<ul style="list-style-type: none"> CO405/Sundy²⁵ sUA, 9.4-10.4 mg/dL Intolerant or refractory to ALP 	6 months Group 1: Pegloticase 8 mg biweekly (n=43) Group 2: Pegloticase 8 mg monthly (n=41) Group 3: PBO (n=20)	<i>Percentage of patients with sUA <6 mg/dL $\geq 80\%$ of the time at Month 3 and Month 6</i> Group 1: 47% (95% CI, 31%-62%) Group 2: 20% (95% CI, 9%-35%) Group 3: 0
<ul style="list-style-type: none"> CO406/Sundy²⁵ sUA, 9.5-9.8 mg/dL Intolerant or refractory to ALP 	6 months Group 1: Pegloticase 8 mg biweekly (n=42) Group 2: Pegloticase 8 mg monthly (n=43) Group 3: PBO (n=23)	<i>Percentage of patients achieving sUA <6 mg/dL $\geq 80\%$ of the time at Month 3 and Month 6</i> Group 1: 38% (95% CI, 24%-54%) Group 2: 49% (95% CI, 33%-65%) Group 3: 0

^aCompared with allopurinol-based arm.^b10 subjects received 100 mg/d and 258 subjects received 300 mg/d, based on renal function.^csUA, 0.3 mmol/L = ~5.0 mg/dL.**Abbreviations:** ALP, allopurinol; CI, confidence interval; FBX, febuxostat; LSN, lesinurad; PBO, placebo; sUA, serum uric acid.

purinol at a fixed dosage of 300 mg/d (**TABLE**).^{12,17-19} Although ACR guidelines do not give preference to allopurinol or febuxostat, EULAR and other international guidelines recommend that febuxostat be used in patients who are intolerant of, or do not respond to, an adequate dosage of allopurinol.^{12,13,15} Febuxostat has been associated with cutaneous reactions, but data do not support any cross-reactivity with allopurinol.¹² Liver function abnormalities and a slightly higher incidence of cardiovascular thromboembolic events may occur.²⁰

Guidelines also recommend adding a uricosuric agent (lesinurad or probenecid) or switching to a uricosuric agent (probenecid) if the sUA target level cannot be reached by an appropriate dosage of a xanthine oxidase inhibitor or when a xanthine oxidase inhibitor is not tolerated.^{12,13,15} The efficacy of probenecid in combination with allopurinol in such patients has been demonstrated in a few small trials.²¹ However, probenecid is not recommended in patients with a creatinine clearance <50 mL/minute or uric acid urolithiasis.¹⁵

Lesinurad is approved only as add-on therapy to a xanthine oxidase inhibitor.¹⁶ In large, randomized clinical trials, lesinurad in combination with either allopurinol or febuxostat has demonstrated greater efficacy than either of the xanthine oxidase inhibitors as monotherapy (**TABLE**).^{18,19,22-25} Lesinurad has been associated with a transient elevation of serum creatinine and kidney stones, the incidence of which is higher if taken without a xanthine oxidase inhibitor.

Pegloticase can be considered in patients with crystal-proven severe, debilitating chronic tophaceous gout and poor QoL, in whom the sUA target level cannot be reached with any other available drug at the maximal dosage (including combination therapy).¹² Pegloticase is an IV medication that must be given at an appropriately trained infusion center because there is a risk of anaphylaxis.

The **TABLE** summarizes results of key clinical trials for ULT agents approved in the United States.^{18,19,22-25}

HOW IS EACH OF THE APPROVED URATE-LOWERING MEDICATIONS INITIATED AND TITRATED?

A treat-to-target approach should be utilized, whereby ULT is initiated and intensified as needed to achieve and maintain the target sUA level <6 mg/dL, or ≤5 mg/dL in certain patients (eg, those with tophi), as discussed.^{12,15} Because initiation of ULT is associated with gout flares for approximately the first 6 months, prophylactic use of anti-inflammatory therapy (eg, colchicine or a nonsteroidal anti-inflammatory drug) is recommended during that time frame.¹³

Allopurinol

In patients with normal kidney function, allopurinol is initi-

ated at a low dosage (100 mg/d) and increased by 100 mg/d increments every 2 to 4 weeks if required, to reach the uricemic target.¹² A reduced initial dose, eg, 50 mg/d, and a daily dose of 200 mg is suggested in patients with a creatinine clearance of 10 to 20 mL/minute. This approach can minimize the risk of a severe cutaneous hypersensitivity reaction (eg, Stevens-Johnson syndrome) as well as an acute gout flare.¹² In approximately 30% to 50% of patients with normal kidney function, 300 mg/d is the most commonly used dosage of allopurinol. Because 300 mg/d does not achieve the target sUA level of <6 mg/dL in more than 50% of patients with gout, guidelines recommend dosage escalation when needed to reach the sUA target.¹⁵ Dosages of 600 to 800 mg/d have a 75% to 80% success rate in achieving an sUA level <6 mg/dL.¹² Dosages >300 mg/d are given in divided doses to avoid gastrointestinal side effects. In patients with renal impairment, EULAR guidelines recommend adjusting the allopurinol dosage downward due to the risk of serious cutaneous adverse events.¹² ACR guidelines, however, recommend increasing allopurinol until the sUA target level is reached in these patients, while monitoring for drug toxicity.¹⁵ The ACR recommendation is based on several small series of patients in which no increased incidence of severe reactions was demonstrated in patients whose allopurinol dosages were progressively titrated above those recommended, based on creatinine clearance and the level of renal impairment.^{6,18,19,26-28}

Febuxostat

Febuxostat is approved by the FDA at a starting dosage of 40 mg/d, uptitrated to 80 mg/d if patients do not achieve an sUA level <6 mg/dL after 2 weeks.²⁰ ACR guidelines suggest uptitration to as much as 120 mg/d (an investigational dosage) if necessary to achieve the target sUA level.¹⁵

Probenecid

The initial dosage of probenecid is 250 mg twice daily, uptitrated weekly to 1 g twice daily, based on the sUA level.⁶ Patients must be counseled to hydrate well due to the risk of urolithiasis.¹⁵ Probenecid is not recommended for patients with a creatinine clearance <50 mL/min, due to lack of data on long-term safety and efficacy in stage 3 CKD.¹⁵

Lesinurad

Lesinurad is indicated at a dosage of 200 mg/d as add-on therapy to allopurinol or febuxostat.¹⁶ Lesinurad should not be initiated in patients with a creatinine clearance <45 mL/min; renal function should be evaluated prior to initiation and periodically thereafter.¹⁶ Lesinurad is available as a 200 mg tablet and as a combination tablet of

200 mg of lesinurad with either 200 mg or 300 mg of allopurinol, which may improve patient adherence and lessen the risk of lesinurad being inadvertently taken without allopurinol.^{16,29}

Pegloticase

Pegloticase must be administered under supervision at an infusion center, due to the high risk of serious allergic reaction, including anaphylaxis.³⁰ Pegloticase is administered as an 8-mg IV infusion every 2 weeks, and should not be combined with other urate-lowering medications.³⁰

CASE STUDY, HARRIET (CONTINUED)

Because Harriet has not reached the sUA target of <6.0 mg/dL and she is tolerating allopurinol, the decision is made to increase the dosage of allopurinol to 200 mg twice daily and recheck the sUA level in 2 weeks.

SUMMARY

Gout is a common disorder that is associated with significant patient morbidity, as well as with comorbidities such as CKD, diabetes, and various cardiovascular disorders. Diagnosis is often based on history and physical examination, with confirmation by joint aspiration when necessary. Lifestyle management generally provides modest reduction of the sUA level. Several urate-lowering medications have been approved for chronic therapy. Allopurinol is typically used as first-line therapy. When combination therapy is required to achieve the target sUA level, the choice is generally based on patient-specific factors, physician and patient choice, and cost. ●

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Recognition and Management of Orthostatic Hypotension in Primary Care

Jennifer Jones, MD; Louis Kuritzky, MD

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- Classify patients by type of orthostatic hypotension
- Assess patients to arrive at a firm diagnosis
- Implement evidence-based treatment to alleviate symptoms, prevent complications, and improve quality of life

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INTRODUCTION

Orthostatic hypotension (OH) is associated with significant morbidity and potential loss of autonomy. In addition to increased risk of falls, OH is associated with an increased risk of heart failure, atrial fibrillation, kidney failure, hospitalization, stroke, cognitive impairment, and death.¹⁻⁶ The prevalence of chronic OH is underestimated and OH often is overlooked in common disorders, such as Parkinson's disease (PD) and diabetes mellitus.⁷ Fortunately, there are effective nonpharmacologic and pharmacologic interventions

available to improve quality of life and reduce the risk for devastating consequences, such as a fall or hip fracture. However, many clinicians neglect to screen for OH, missing the opportunity to treat.

DEFINITION AND EPIDEMIOLOGY

Maintenance of blood pressure (BP) upon standing requires a complex interaction between baroreceptors, the sympathetic nervous system, and the cardiovascular system. Defective compensatory responses can result from cardiac dysfunction, reduced intravascular volume, excessive vasodilation, baroreceptor dysfunction, autonomic nervous system impairment, or as a result of medications.^{8,9}

OH generally has been defined as a sustained reduction of systolic BP (SBP) of 20 mm Hg or diastolic BP (DBP) of 10 mm Hg within 3 minutes of standing from a supine or seated position, or a tilt table head-up tilt of ≥ 60 degrees.¹⁰ The authors do not suggest that tilt table testing be performed routinely; rather, OH should be a straightforward clinical diagnosis. Tilt testing could produce significant false positive results because the support of lower extremity musculature critical for maintaining normotension in the erect posture is eliminated during tilt table testing.

OH sometimes is comorbid with postural orthostatic tachycardia syndrome (POTS). POTS, which also causes lightheadedness or fainting as the primary symptom, is a condition in which an excessively reduced volume of blood returns to the heart when moving from the supine to the standing position. POTS is accompanied by a rapid increase in heart rate of ≥ 30 beats per minute (bpm). Most people who experience POTS are women between the ages of 15 and 50 years.¹¹

Neurogenic OH (NOH), a commonly overlooked subtype of OH, is associated with nervous system impairment, and is predominantly seen in neurodegenerative disorders such as PD, multiple system atrophy (MSA), and pure autonomic failure (PAF).¹⁰ NOH also might accompany peripheral and autonomic neuropathies associated with diabetes, amyloidosis, and immune-mediated neuropathies.¹² In primary or secondary diseases of the autonomic nervous system, NOH often is accompanied by supine hypertension. The prevalence of NOH is approximately 50% among patients with PD, and approximately 33% among those with diabetes, amyloidosis, or spinal cord injury.^{1,13,14} Fortunately, only a portion of these patients are symptomatic at the time of OH diagnosis.

Patients at increased risk for OH should be screened even in the absence of symptoms; this includes those with PD, MSA, PAF, dementia with Lewy bodies, and peripheral neuropathies associated with autonomic dysfunction (eg, diabetes, amyloidosis, HIV). Patients with an unexplained fall or syncopal episode,

elderly patients (age >70 years), and those on multiple medications that affect intravascular volume, vascular tone, sympathetic activity, or cardiac function also warrant screening.¹⁵

DIAGNOSIS

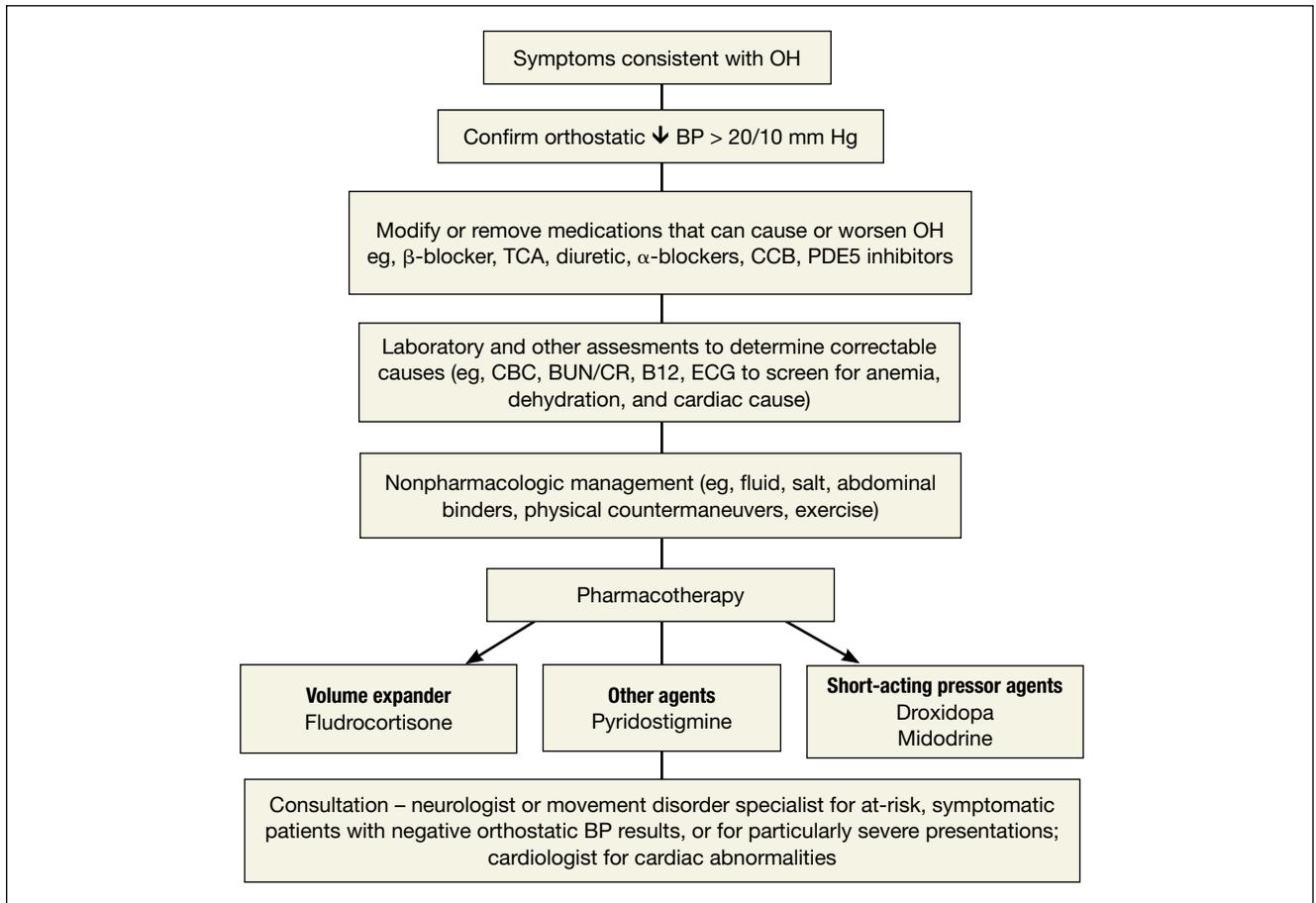
Typical OH symptoms, which occur when standing, less frequently when sitting, and abate when lying down, include dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache. Less common symptoms include syncope, dyspnea, chest pain, and neck and shoulder “coat hanger” pain.^{16,17} Heat exposure, large or carbohydrate-dense meals, alcohol, dehydration, and medications with potential for vasodilation, volume depletion, bradycardia, or sympatholytic medications (eg, antihypertensives, tricyclic antidepressants, diuretics, dopaminergic anti-parkinsonian agents, and phosphodiesterase inhibitors) could exacerbate OH symptoms.^{10,13,16} Nocturnal diuresis results in peak symptoms in the morning.^{12,17} Among patients with autonomic dysfunction, supine hypertension commonly co-exists with NOH, and might exaggerate this overnight diuresis.¹⁶

The diagnosis of OH requires measuring BP in both the supine and upright positions.¹⁰ To establish a baseline, BP and heart rate are measured after 5 minutes of rest in the supine or seated position. Ideally, standing BP and heart rate are measured at 30 seconds, 60 seconds, 2 minutes, and 3 minutes; however, for practicality, some experts advocate using the 3-minute reading as the primary discriminator.¹³ In situations where a supine to standing diagnostic assessment cannot be performed easily, a sit-to-stand procedure could be used.¹⁸ Patients sit for at least 5 minutes and then stand for 3 minutes, with BP measured just before standing and at 1 and 3 minutes upon standing.¹⁵ One investigation showed a decrease in SBP >15 mm Hg or DBP >7 mm Hg to yield the highest sensitivity and specificity for the diagnosis of OH.¹⁸ Note that these criteria differ slightly from the criteria included in the definition of OH.

An increase in heart rate >15 bpm within 3 minutes of standing is consistent with non-neurogenic OH (eg, volume depletion).¹⁵ An increase in heart rate <15 bpm on standing is suggestive of NOH caused by reduced sympathetic response.^{15,17} Medications that impede an appropriate heart rate response and cardiac arrhythmias must be taken into account.

If standard orthostatic BP testing (including extended at-home BP monitoring or 24-hour ambulatory monitoring) does not reveal OH in an at-risk individual with unexplained postural symptoms, referral to a movement disorder specialist is necessary.¹⁵ Presence of a potential cardiac etiology warrants referral to a cardiologist.¹⁹

History and physical examination are key to differentiating between NOH and non-neurogenic OH. Laboratory,

FIGURE Diagnostic and treatment algorithm for orthostatic hypotension^{1,8,12,15}

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; CCB, calcium channel blocker; ECG: electrocardiogram; OH, orthostatic hypotension; PDE5, phosphodiesterase inhibitor; SCR, serum creatinine; TCA, tricyclic antidepressant.

electrocardiogram, and imaging assessments further aid in ruling out non-neurogenic causes such as dehydration, acute blood loss, cardiovascular disorders (eg, constrictive pericarditis, cardiomyopathy, aortic stenosis), endocrine disorders (eg, adrenal insufficiency, diabetes), and excessive vasodilatation (eg, systemic mastocytosis, carcinoid syndrome) (FIGURE).^{1,8,12,15} Patients should be queried about exacerbating factors that suggest an autonomic cause, eg, prolonged standing, cardiovascular exercise, heat exposure, alcohol, morning time, or large meals.¹⁶ Laboratory evaluations could include basic metabolic panel, complete blood count, morning cortisol level, vitamin B12, folic acid (peripheral neuropathy), and fasting plasma glucose or glycated hemoglobin.^{15,20}

TREATMENT

There is insufficient evidence to support intervention for asymptomatic OH. The goal of treatment in symptomatic OH is not to normalize standing BP, but rather to alleviate symp-

toms, prevent falls, and improve standing time to allow for activities of daily living. Additionally, in patients with NOH, the goal is to minimize comorbid supine hypertension.²¹ Management of OH addresses modifiable contributing factors (eg, medications, dehydration, anemia), and employs nonpharmacologic strategies, and, if necessary, pharmacologic treatment (FIGURE).^{1,8,12,15} Because orthostatic stress varies with circumstances during the day, a patient-oriented approach that emphasizes education and nonpharmacologic strategies to minimize orthostatic stress is vital.⁹

Nonpharmacologic strategies

Patients should be counseled to avoid situations that could exacerbate symptoms associated with OH such as prolonged or motionless standing, alcohol, large or carbohydrate-dense meals, physical activity sufficient to cause muscle vasodilation, heat exposure (eg, hot weather, hot bath), sudden postural changes, and Valsalva maneuvers.^{9,17}

TABLE Nonpharmacologic interventions for treating orthostatic hypotension^{1,9,12,16,17,21-27}

Intervention	Specific Instructions	Comments
Dietary counseling and recommendations	2 to 2.5 liters of fluid/d 10 g/d sodium intake (1-2 teaspoons of added salt to a healthy diet; 0.5-1 g salt tablets) Avoid diuretics, including coffee Avoid high glycemic index meals/beverages	Clear urine provides patient with a visual target for maintaining adequate hydration Benefits of salt loading can be seen as early as 3 days after initiation 24-hour urinary sodium excretion ≥ 170 mmol and 24-hour urine output of 1.5 liters are indicative of adequate salt loading and plasma volume
Water bolus	Drink 500 mL of water over 3 to 4 minutes	Raises SBP ≥ 20 mm Hg within 5-15 minutes; peaks at 20-30 minutes; lasts for 1-2 hours Anticipatory management (eg, prolonged standing, hot weather, preprandial, upon awakening)
Physical counter-maneuvers and exercise	Perform physical counter-maneuvers, eg, crossing legs, trunk bending, squatting, knee flexing, toe raises, tensing muscles (contract a group of muscles bilaterally for 30 seconds, relax, and then repeat) Gradual staged movements with postural changes Elevate head of the bed 6-9 inches Avoid daytime recumbency Avoid Valsalva maneuvers Isotonic exercises	Counter-maneuvers can be done to attenuate OH symptoms at onset Rise gradually from lying to sitting to standing, especially in the morning when orthostatic tolerance is lower or after meals or straining with defecation Exercise in a recumbent or seated position or in a pool to attenuate exercise-induced hypotension, which accompanies deconditioned states
Compression garments	Abdominal binder and/or custom-fitted thigh or waist high compression stockings	Splanchnic-mesenteric venous bed compression reduces venous pooling and drop in SBP after postural changes Should be tight enough to exert gentle pressure Place before rising from bed in the morning, and take off when lying supine May use as needed during times of orthostatic stress More effective than lower extremity compression Might be difficult for patients to put on, uncomfortable, and cosmetically unappealing

Abbreviations: OH, orthostatic hypotension; SBP, systolic blood pressure.

Evidence-based nonpharmacologic strategies can be employed to expand blood volume (increased fluid and salt intake), decrease nocturnal diuresis (raise the head of the bed), decrease venous pooling (abdominal binder, physical counter maneuvers [see online video demonstration at: <https://www.youtube.com/watch?v=1Lq0AN9AJ0A&t=352s>]), or induce a pressor response (water bolus intake).⁹ These strategies, and the evidence supporting them, are further detailed in the **TABLE**.^{1,9,12,16,17,21-27}

Pharmacologic strategies

Pharmacologic intervention is indicated when nonpharmacologic strategies and lifestyle modification do not sufficiently resolve OH symptoms. Pharmacologic strategies aim to expand intravascular volume (fludrocortisone) or increase

peripheral vascular resistance with the pressor agents midodrine or droxidopa.¹⁷ Because of the prevalence of supine hypertension among patients with OH (up to 50%), slow titration and frequent monitoring is advised.^{12,16} Home BP monitoring is recommended for several days after starting or changing therapy.¹⁵

Fludrocortisone

Fludrocortisone, a synthetic mineralocorticoid, is an aldosterone receptor agonist. It increases plasma volume by increasing renal sodium and water reabsorption and improves vascular alpha-adrenoreceptor sensitivity to circulating catecholamines. Fludrocortisone monotherapy could be considered for patients who do not adequately raise plasma volume with fluid and salt supplementation.

Fludrocortisone may also be added to midodrine in patients with persistent OH symptoms.^{9,12}

The initial dose of fludrocortisone is 0.1 mg/d, which can be titrated to 0.2 mg/d. Daily dosages >0.2 mg rarely are more effective and amplify side effects.¹⁷ A weight gain of 3 to 5 pounds and mild dependent edema is indicative of adequate plasma volume expansion.^{9,19} The onset of action typically is 3 to 7 days, but may require up to 2 weeks.^{15,17} Because hypokalemia can develop in nearly 50% of patients and hypomagnesemia in 5%, electrolyte monitoring is required, and patients should be counseled to increase dietary potassium. Other common adverse events include supine hypertension, nausea, peripheral edema, and headache.^{1,16}

Midodrine

Midodrine is a peripherally selective alpha-1-adrenoreceptor agonist that constricts arteriolar and venous vasculature resulting in supine, sitting, and standing SBP and DBP increases.¹⁷ Double-blind multicenter placebo-controlled trials have shown midodrine to increase standing BP and improve OH symptoms.^{28,29} In dose-response trials, midodrine, 10 mg, compared with placebo produced an average 1-minute standing SBP increase at 1 hour of 15 mm Hg.³⁰ This drug is approved for treating symptomatic OH.³⁰

Midodrine is dosed in 4-hour intervals 3 times a day; eg, shortly before or upon arising in the morning, midday, and late afternoon before 6 PM. Dosages are titrated to clinical response or maximum daily dosage of 30 mg. The evening dose should be taken 3-4 hours before bedtime because of risk of supine hypertension in up to 25% of patients.¹⁹ The medication should be discontinued in patients who do not have significant symptomatic improvement.^{13,16} Midodrine can be used as monotherapy or in combination with fludrocortisone or, in low dosages, with pyridostigmine.^{19,31} Adverse events include urinary urgency or retention (6%), piloerection (13%), pruritus/tingling (mostly of scalp; 9% to 10%), and chills (5%).¹⁹

Droxidopa

Droxidopa is a prodrug converted to norepinephrine in the central nervous system and peripheral tissues, including sympathetic peripheral nerve endings. Droxidopa is approved for treatment of symptomatic NOH caused by primary autonomic failure (PD, MSA, PAF), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy.³² Droxidopa is only available through specialty pharmacies and requires that the prescriber submits a treatment form indicating primary diagnosis, symptomatic condition, treatment history, and patient clinical notes.³³

An integrated efficacy analysis of 3 clinical trials com-

paring droxidopa with placebo in patients with a primary neurodegenerative disease and symptomatic NOH (N=460) showed significant reduction in most NOH symptom scores: Orthostatic Hypotension Questionnaire composite score, dizziness/lightheadedness, visual disturbances, weakness, and fatigue.³⁴ Droxidopa also significantly improved 3 of 4 patient-oriented measures and significantly increased upright SBP (11.5 ± 20.5 vs 4.8 ± 21 mm Hg; $P < .001$) and DBP (8 ± 15.55 vs 1.8 ± 17.3 mm Hg; $P < .001$).³⁴ A lower incidence of falls was observed in the droxidopa group.³⁴

The starting dosage of droxidopa is 100 mg three times daily, titrated by 100 mg three times daily to a maximum dosage of 600 mg three times daily. The last daily dose should be at least 3 hours before bedtime and the head of bed should be elevated to minimize supine hypertension.³² The rates of supine hypertension (SBP >180 mm Hg) in clinical trials were $\leq 7.9\%$ with droxidopa vs $\leq 4.6\%$ with placebo.³⁴ Adverse effects include hypertension, headache, dizziness, and nausea.¹⁴

Pyridostigmine

Pyridostigmine, an acetylcholinesterase inhibitor that potentiates neurotransmission in autonomic ganglia, amplifies sympathetic activation in response to orthostatic stress. Pyridostigmine has been used off-label as monotherapy in patients with mild symptoms, and as an adjunct to low-dose midodrine (2.5 mg once or twice daily).^{15,31} In a double-blind, 4-way crossover study in patients with NOH (n=58), pyridostigmine, 60 mg either alone or with 2.5 mg, or midodrine, 5 mg, produced smaller reductions in standing DBP vs placebo with no effect on supine SBP or DBP.³¹ Because pyridostigmine is not associated with worsening supine hypertension, it could be considered when supine hypertension becomes problematic.³¹ The starting dosage of pyridostigmine is 30 mg two or three times daily, and can be increased to 60 mg three times daily.⁹ Adverse effects include diaphoresis, hypersalivation, diarrhea, muscle cramping, and urinary incontinence.^{15,16}

SPECIAL CONSIDERATIONS

Supine and nocturnal hypertension

Although most patients with essential hypertension experience BP elevation throughout the day and night—albeit to a lesser degree at night by 10% to 20%—patients with supine HTN experience HTN *only* at night. Although the potential long-term effects of supine HTN should not be minimized, it should be recognized that the risks of supine HTN remain uncertain with no clinical trials documenting benefit from treating supine HTN. The short-term risks associated with NOH (ie, falls and hip fractures) could take precedence over

the longer-term theoretical risks associated with supine HTN (ie, cerebrovascular and cardiovascular events).³⁵ Paradoxically, untreated supine HTN can worsen OH by causing pressure natriuresis and diuresis, resulting in volume depletion.³⁵ To minimize episodes of supine HTN, patients should avoid recumbency during the day, raise the head of the bed, and avoid fluids within 1 hour of bedtime.¹³ If these measures are insufficient, a short-acting antihypertensive at bedtime could be considered (eg, angiotensin II receptor blocker, short-acting angiotensin-converting enzyme inhibitor, nifedipine, clonidine, or a nitrate patch [removed 1 hour before rising]).¹³

Postprandial hypotension

Among patients with autonomic dysfunction, 40% to 80% of patients also have postprandial hypotension.³⁶ This is commonly defined as a decline in SBP ≥ 20 mm Hg within 2 hours of consuming a meal or decline of SBP to < 90 mm Hg when preprandial SBP is > 100 mm Hg.³⁷ Large and carbohydrate-heavy meals induce splanchnic vasodilation and redistribution of blood flow to the digestive system.¹⁶ Patients are advised to avoid carbohydrate-heavy meals, alcohol, and sudden standing or physical activity after a meal.¹² Treatment with the alpha-glucosidase inhibitor acarbose could be considered because it delays intestinal glucose absorption by inhibiting complex carbohydrate breakdown, thereby delaying release of vasodilatory gut hormones.^{35,38}

SUMMARY

A fall of SBP ≥ 20 mm Hg or in DBP ≥ 10 mm Hg within 3 minutes of standing is diagnostic of OH. History and physical examination are key to differentiating between neurogenic and non-neurogenic OH. To achieve the primary goals of reducing symptoms and preventing falls, treatment of OH is directed at increasing blood volume, decreasing venous pooling, and increasing vasoconstriction. Reversible causes of OH (dehydration, hypotensive medications) should be investigated. Patient education and nonpharmacologic strategies alone can be effective in mild cases of OH. If symptoms persist, consider low-dosage fludrocortisone. Other pharmacologic options include droxidopa, pyridostigmine, or an α -adrenoreceptor agonist such as midodrine. For patients with NOH, worsening of supine HTN should be evaluated and proactively managed. Because OH can have devastating consequences for some patients, identifying persons at increased risk is imperative. Avoiding falls by successfully managing OH has the potential to reduce morbidity and mortality. ●

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Practical Evaluation and Management of Irritable Bowel Syndrome with Diarrhea: A Case Study Approach

Brian E. Lacy, MD, PhD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify patients who are appropriately diagnosed based on history and symptoms
- Describe the roles of the Rome-IV criteria, colonoscopy, and other tests in the diagnosis of irritable bowel syndrome (IBS)
- Differentiate subtypes of IBS
- Characterize the benefits and limitations of currently available prescription medications for IBS
- Individualize treatment for IBS based on current evidence-based guidelines

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of IBS-D.

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CASE STUDY

A 32-year-old science teacher is referred for further management of abdominal symptoms. His symptoms started after a trip to Mexico 1 year ago where he and his wife both developed severe food poisoning. Since then he has had daily loose, watery, non-bloody, urgent bowel movements. He says he feels somewhat bloated and distended. He reports daily pain in his lower abdomen that worsens

just before a bowel movement and improves after having urgent diarrhea.

His weight has remained stable. He does not report fevers, chills, rashes, oral ulcers, myalgia, or arthralgia. He does not take any medications or use complementary or alternative therapies. Past medical and surgical history are unremarkable. He does not have a family history of irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), celiac disease, or colorectal cancer.

He went to an urgent care clinic 3 months after his symptoms began. A complete blood count (CBC), complete metabolic panel, celiac serology cascade, and stool studies were all within normal limits. His wife's symptoms resolved completely. A 2-week trial of a lactose-free diet did not help. Loperamide taken as needed has not helped his abdominal pain, bloating, or diarrhea.

The patient has done some research and brings several questions to the visit, which are listed below. The discussion in response to his questions serves as the basis for this article.

WHAT IS MY DIAGNOSIS?

IBS is a common functional bowel disorder characterized by recurrent abdominal pain associated with altered bowel habits (diarrhea, constipation, or both).¹ Abdominal bloating and distension also often are present, but neither is required to make an IBS diagnosis.¹ IBS is classified according to the type of bowel habit alteration (based on stool form only on days with at least 1 abnormal bowel movement): diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or mixed-type IBS (IBS-M). IBS-M has alternating periods of diarrhea and constipation.¹ IBS-D is the most common subtype, affecting approximately 40% of IBS patients, and is the focus of this discussion.²

Diagnosing IBS can be challenging because the symptoms can mimic other disorders (eg, lactose or fructose intolerance, small intestine bacterial overgrowth, celiac disease, IBD, microscopic colitis, or functional diarrhea) and could fluctuate over time. Moreover, there is no precise biomarker for IBS.^{3,4} The Rome IV criteria (**TABLE 1**) are intended to facilitate making a positive diagnosis of IBS, rather than making an IBS diagnosis only after a battery of tests has been performed (ie, a diagnosis of exclusion).^{1,5} A key difference from Rome III is that the ROME IV criteria classifies IBS subtypes by the proportion of days with symptomatic bowel movements rather than measuring all days.

The diagnosis of IBS is based on a thoughtful history and a limited physical examination to assess the presence of the distinguishing symptom of IBS, which is abdominal pain in association with: 1) defecation, 2) change in stool frequency, and/or 3) change in stool form or appearance. Limited diagnostic tests to confirm the diagnosis and exclude other dis-

TABLE 1 Rome IV Irritable Bowel Syndrome Diagnostic Criteria^{a1,5}

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in the frequency of stool
- Associated with a change in the form (appearance) of stool

^aThese criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

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TABLE 2 Alarm signs/symptoms that warrant further investigation^{3,8}

- Age >50 years without prior colon cancer screening
- Presence of overt gastrointestinal bleeding
- Nocturnal passage of stool
- Unintentional weight loss
- Family history of inflammatory bowel disease or colorectal cancer
- Recent changes in bowel habits
- Presence of a palpable abdominal mass or lymphadenopathy

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orders, eg, IBD, are recommended.^{1,5} This approach is supported by several practice guidelines.^{6,7}

IS THERE ANYTHING WORRISOME IN MY HISTORY? DO I NEED ANY FURTHER TESTS?

Alarm symptoms or warning signs ("red flags") discovered on history and physical examination that warrant further evaluation are listed in **TABLE 2**.^{3,8}

In patients without alarm symptoms, extensive diagnostic testing to rule out other disorders is unlikely to yield a new diagnosis in those with IBS symptoms who meet Rome IV criteria.^{4,8,9} New to Rome IV criteria is the use of limited testing to consider in patients without alarm symptoms, which includes CBC to ensure the patient is not anemic, C-reactive protein (CRP) or fecal calprotectin to lower suspicion for IBD and prevent indiscriminate use of colonoscopy, and celiac serologic testing because IBS-D can mimic this disorder.⁹

CASE STUDY (CONTINUED)

A detailed history ruled out warning signs for other organic diseases. Further information to quantify the duration and frequency of symptoms, the proportion of days with symptomatic stools,

the association of abdominal pain with bowel habits, and a benign physical examination confirmed he met Rome IV criteria for IBS-D. A CBC was normal without evidence of anemia; CRP and celiac serum tests were both negative, effectively excluding IBD and celiac disease. Examination of the eyes, mouth, skin, extremities, and perianal area did not show evidence of IBD.

WHY DID MY SYMPTOMS DEVELOP?

The pathophysiology of IBS is complex, multifactorial, and not completely understood. It involves genetic predisposition, visceral hypersensitivity, abnormalities in GI motility, secretory function and permeability, immune activation, and autonomic nervous system dysregulation.^{10,11}

IBS traditionally has been thought of as a brain-gut disorder because of the high frequency of coexisting conditions such as anxiety and depression.⁹ It has been postulated that among individuals with a genetic predisposition or exposure to environmental factors, an abnormal stress response combined with psychological distress and an infectious or inflammatory response could alter intestinal permeability and trigger a cascade of events (eg, infiltration of inflammatory cells, localized edema, and release of cytokines or chemokines) that results in development of IBS symptoms.⁹

There is a growing body of evidence implicating the gastrointestinal microbiota—the complex ecosystem of microorganisms inhabiting the intestine—and alterations in its composition and function (dysbiosis) as important components in the pathogenesis of IBS.^{12,13} The intestinal microbiota in patients with IBS is altered compared with healthy controls in terms of both a general decrease in diversity, and more specifically, decreases in *Bifidobacterium* and *Lactobacillus* species, and an increase in *Gammaproteobacterium* species.^{12,14} Among risk factors for IBS, infectious gastroenteritis (IGE) is the strongest, with 3% to 36% of individuals who have experienced IGE developing IBS-D (referred to as post-infectious IBS) with symptoms lasting months to years.^{15,16} IGE is the likely cause of IBS in this patient, especially because of the temporal relationship of symptom onset after an episode of food poisoning. Emerging evidence also suggests that changes in the gut microbiome and the release of inflammatory mediators could modulate the gut-brain axis.^{17,18} In up to one-half of patients with IBS, gastrointestinal symptoms appear before development of mood disorders.¹⁹

WILL MY SYMPTOMS GO AWAY?

Treatment of IBS-D is directed at decreasing abdominal pain, bloating, and diarrhea. Treatment should be individualized in a stepwise manner according to disease symptoms

FIGURE 1 Treatment guided by severity of IBS-D

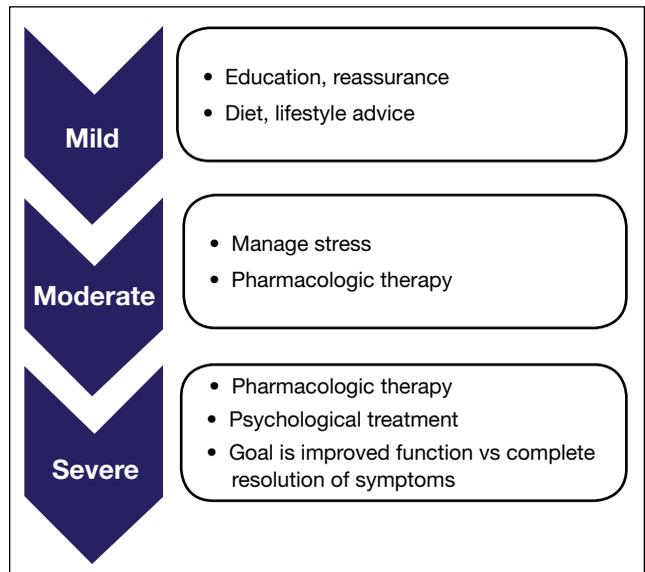


FIGURE 2 Therapies for IBS-D by symptom

Abdominal pain/ discomfort	Bloating/ distension	Diarrhea
<ul style="list-style-type: none"> • Alosetron • Rifaximin • Antidepressants (TCA, SSRI)^a • Smooth muscle antispasmodics (dicyclomine, hyoscyamine^a) • Low FODMAP diet^a 	<ul style="list-style-type: none"> • Rifaximin • Probiotics^a • Diet^a 	<ul style="list-style-type: none"> • Alosetron • Eluxadolone • Rifaximin • Cholestyramine^a • Diphenoxylate-atropine^a • Loperamide^a

^aNot approved for IBS-D by the US Food and Drug Administration

Abbreviations: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-D, diarrhea-predominant irritable bowel syndrome; SSRI, serotonin selective reuptake inhibitor; TCA, tricyclic antidepressant

and severity because symptom severity can impact realistic expectations for treatment outcomes. (FIGURES 1 and 2).^{1,20}

Mild symptoms of IBS-D that the patient considers a nuisance, but that don't significantly impact daily life, often are effectively managed with diet and lifestyle modifications (see below) and loperamide as needed. Moderate symptoms that affect patients' home, social, and professional life likely will require scheduled pharmacologic treatment with ≥ 1 medication options. In patients with more severe disease, symptoms could resolve after months or years, but achieving improved symptom management and daily functioning might be a more attainable goal.²¹ For patients with severe symptoms, consider referral to a gastroenterologist for specialty care or combination therapy. An additional option is referral for psy-

chological or behavioral intervention (eg, cognitive-behavioral therapy, hypnosis, or relaxation methods).^{1,22,23}

Evidence-based treatment guidelines for IBS are available from the American Gastroenterological Association (AGA) ([http://www.gastrojournal.org/article/S0016-5085\(14\)01089-0/pdf](http://www.gastrojournal.org/article/S0016-5085(14)01089-0/pdf)) and the American College of Gastroenterology (ACG) (http://gi.org/wp-content/uploads/2014/08/IBS_CIC_Monograph_AJG_Aug_2014.pdf).^{7,24} This review article includes updated information on options for managing patients with IBS-D that were released after publication of the guidelines in 2014, including eluxadolone and rifaximin for IBS-D.

ARE THERE ANY DIETARY INTERVENTIONS THAT MIGHT HELP? DOES EXERCISE HELP?

Lifestyle and dietary modifications are reasonable first-line approaches that could provide adequate relief for many patients with mild IBS symptoms.²³ These include exercise, stress reduction (eg, meditation, counseling), and attention to impaired sleep.^{1,20,25,26} Healthy eating habits include limiting intake of potential dietary triggers, such as alcohol, caffeine, spicy foods, fat, and gas-producing foods.²³

The role of fiber in IBS remains subject to debate because of contradictory data, but recent studies suggest that soluble fiber with a low rate of fermentation (eg, psyllium) might have some benefit in addressing diarrhea and constipation in IBS patients.^{7,23}

For patients in whom symptoms persist despite following general diet and lifestyle advice, a growing body of evidence supports the efficacy of the low FODMAP diet (approximately 70% response rate) to reduce gastrointestinal symptoms such as abdominal pain, bloating, diarrhea, abdominal distention, and flatulence.²⁷⁻³¹ The FODMAP diet restricts short-chain carbohydrates known collectively as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) found in such foods as wheat, broccoli, legumes, dairy, apples, and stone fruits.²⁸ A low FODMAP diet should be guided by a dietitian because of its complexity and potential risks for inadequate nutritional intake. Observational studies suggest durable efficacy even with reintroduction of FODMAPs, as recommended.²⁹

Although limited data suggest a gluten-free diet could be helpful in reducing global symptoms, abdominal pain, and bloating, at least 1 randomized trial demonstrated no additive effect of a gluten-free diet over a low-FODMAP diet alone.⁹

WILL PROBIOTICS HELP?

Probiotics, composed of live microorganisms that are beneficial to human health when ingested, have been studied extensively to treat IBS.¹¹ Their role in treating IBS is supported

by generally beneficial effects and a benign adverse event profile in >80 trials consisting of >10,000 patients, including several meta-analyses.³²⁻³⁵ Interpretation of results is difficult because of heterogeneity of populations (ie, IBS subtype) and the myriad of probiotics (variety of single and multi-strain products and dosages) studied. The most convincing data are derived from multi-strain probiotics containing both *Lactobacillus* and *Bifidobacteria* with a concentration of 200 million to 10 billion colony-forming units/d.^{14,34} ACG guidelines indicate that probiotics improve global symptoms, bloating, and flatulence, but make a weak recommendation for their use based on the low quality of evidence.⁷

WILL AN ANTIBIOTIC HELP?

Neomycin, the first nonabsorbable antibiotic investigated for IBS, produced a 50% improvement in global IBS symptoms compared with placebo, but also showed rapid bacterial resistance.³⁶ Rifaximin, an oral, nonsystemic antibiotic with a low bacterial-resistance profile and a favorable side-effect profile, was approved in May 2015 for treating adults with nonconstipation IBS, including IBS-D.^{37,38}

A combined analysis of 2 separate phase 3 trials showed that a 14-day course of rifaximin, 550 mg three times daily, resulted in significant improvement compared with placebo in patients with IBS without constipation.³⁸ Improvements included a significant increase in the percentage of patients who had adequate relief of global IBS-D symptoms (40.7% vs 31.7% at 4 weeks; $P < .001$), improved IBS-related bloating (40.2% vs 30.3% at 4 weeks; $P < .001$), and relief in the composite endpoint of abdominal pain/discomfort and loose or watery stools.³⁸ Rifaximin exhibited favorable durability of effect, with a significantly greater percentage of rifaximin-treated patients than placebo-treated patients reporting adequate relief of global IBS symptoms at 10 weeks posttreatment (42% vs 32% in TARGET 1; 40% vs 32% in TARGET 2, respectively).³⁸ The incidence of adverse effects (headache, upper respiratory infection, nausea, and diarrhea) was comparable with placebo.³⁸ More recently, another randomized, placebo-controlled trial demonstrated that repeat treatment with rifaximin, 550 mg 3 times daily for up to 3 cycles of 2 weeks, in patients with IBS-D was safe, well tolerated, and significantly more effective than placebo (38.1% vs 31.5%, respectively; $P = .03$) in improving IBS symptoms and IBS-related quality of life.^{39,40}

WHAT IF NONE OF THIS WORKS? ARE THERE ANY OTHER OPTIONS?

Beyond agents that target the gut microbiota, other pharmacologic interventions available for management of IBS-D vary from those specifically targeting diarrhea (eg, loperamide) to those addressing multiple symptoms.

Eluxadoline

Eluxadoline is a novel mixed mu- and kappa-opioid receptor agonist and delta-opioid receptor antagonist that reduces contractility and secretion in the GI tract, and has low oral bioavailability.⁴¹ In two phase 3 trials, eluxadoline, 75 mg and 100 mg twice daily, significantly improved the composite endpoint of decrease in abdominal pain and improvement in stool consistency from weeks 1 through 12 compared with placebo (31.0%, 27.7%, 21.9%, respectively) and from weeks 1 through 26 (31.0%, 26.7%, 19.5%, respectively).^{41,42} There was no significant difference compared with placebo with respect to improvement in abdominal pain.⁴² Eluxadoline is contraindicated in patients with cholecystectomy, history of biliary obstruction, alcohol abuse, or pancreatitis.⁴³

Alosetron

Alosetron is a 5-hydroxytryptamine-3 receptor antagonist approved only in women with severe, chronic IBS-D with inadequate response to conventional therapy.⁴⁴ It has demonstrated improvement in stool consistency and frequency (relative risk [RR], 1.59; 95% CI, 1.04-2.41), abdominal pain (RR, 1.24; 95% CI, 1.16-1.33), and overall IBS symptoms (RR, 1.58; 95% CI, 1.42-1.75).⁴⁵ Severe constipation and ischemic colitis have occurred with cumulative incidence rates of 0.25 cases and 1.03 cases per 1000 patient/years, respectively.⁴⁶

Loperamide

Loperamide is a mu-opioid receptor agonist that improves diarrhea by decreasing peristalsis, prolonging GI transit time, and reducing fluid secretion in the intestinal lumen.⁴ Loperamide is not approved for diarrhea related to IBS, and the few controlled trials examining its efficacy for this indication report improvements in individual symptoms of stool frequency, consistency, and urgency, but usually no improvement in bloating or in abdominal pain.⁴⁷⁻⁵⁰ Loperamide, 2 mg/d to 8 mg/d, could be useful in some patients with IBS-D.^{4,7}

Tricyclic antidepressants

Antidepressants have become a widespread treatment option for IBS because of their effects on pain perception, mood, and motility, as well as on the brain-gut axis.^{9,51} A meta-analysis of 17 studies showed a lower risk of remaining symptomatic with antidepressants vs placebo (RR, 0.67; 95% CI, 0.58-0.77), with similar treatment effects for both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors.⁵² The most frequent side effects with TCAs were drowsiness and dry mouth.²⁰ TCAs should be initiated at low dosages (10 to 25 mg) at bedtime and gradually increased based on symptom response and tolerability.⁵¹

Bile acid sequestrants

These agents bind bile acids in the intestine to prevent free bile acid from stimulating electrolyte and water secretion in the colon. Because a subset (approximately 28%) of patients with IBS-D have bile acid malabsorption, an empiric trial of a bile acid sequestrant could be considered for diarrheal symptoms based on evidence of efficacy in recent pilot studies (eg, cholestyramine, 9 g two to three times daily, colestipol, 2 g once or twice daily, or colesevelam, 625 mg once or twice daily).^{1,21,53,54} A bile acid sequestrant could be considered after other therapies targeting diarrhea have not been successful.²³

SUMMARY

An individualized approach to managing patients with IBS-D begins with reassurance, explanation, and a positive diagnosis that includes limited testing to rule out disorders that may mimic IBS-D (eg, IBD or celiac disease). Treatment options should be considered in the context of symptoms, possible etiologic factors, and benefits vs risks. Treatment typically begins with dietary modifications, increased exercise, and stress reduction. A probiotic could be considered, particularly for bloating, and a TCA for pain. Diarrhea might be ameliorated with loperamide or a bile acid sequestrant. For persistent and/or more severe symptoms, rifaximin, eluxadoline, or alosetron could be considered, with the specific choice guided by patient-specific factors. ●

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Differentiating Among the SGLT-2 Inhibitors: Considering Cardiovascular and Other Safety Outcomes

Eden M. Miller, DO; Carol H. Wysham, MD

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- Provide an overview of the rationale and role of SGLT-2 inhibitor therapy
- Describe the results of cardiovascular outcome trials with canagliflozin and empagliflozin
- Describe the evidence related to the safety of available SGLT-2 inhibitors

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The availability of several new classes of medications for diabetes over the past decade or so provides greater opportunity to individualize treatment based on a patient's needs and characteristics. Among these new options, the effect of the sodium glucose cotransporter-2 inhibitors (SGLT-2i) on the kidney to lower blood glucose offers a unique, yet complementary mechanism of action to all other classes of medications, including basal insulin. This benefit, coupled with important glycemic and nonglycemic effects that include modest weight loss and an incidence of hypoglycemia similar to metformin, dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and thiazolidinediones (**TABLE 1**),¹⁻³ makes the SGLT-2i class of medications an important option for type 2 diabetes mellitus (T2DM) as an alternative to metformin⁴⁻⁷ or as part of dual and triple therapy.^{1,2} Four SGLT-2i are currently available in the United States: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

CARDIOVASCULAR SAFETY TRIALS

Historical overview

A cardiovascular (CV) event is the leading cause of death among persons with T2DM, serving to underscore the importance of managing other CV risk factors beyond blood glucose, including blood pressure, blood lipids, and body weight. More than a decade ago, evidence emerged indicating an elevated risk of myocardial infarction with rosiglitazone.⁸⁻¹⁰ Although further investigation allayed some concerns, the US Food and Drug Administration issued guidance in 2008 requiring industry sponsors of new medications for T2DM to demonstrate in a clinical trial that a new medication is not associated with an unacceptable increase in CV risk relative to a control group at higher risk of a CV event.¹¹ A finding of noninferiority, ie, similarity, is demonstrated if the upper limit of the two-sided 95% confidence interval (CI) for the estimated risk ratio is less than 1.8, indicating that the new medication poses no increased CV risk versus the control (usually placebo as part of standard care). A risk ratio of less than 1 indicates superiority, demonstrating that the new medication reduces CV risk.

Nine CV safety trials investigating a DPP-4i, GLP-1 RA, or SGLT-2i have been completed. Additional trials are ongoing with other DPP-4i, GLP-1RA, and SGLT-2i, including dapagliflozin and ertugliflozin, with results available over the next 1 to 3 years. All 9 completed trials demonstrated the CV safety of the DPP-4i (alogliptin, saxagliptin, sitagliptin), GLP-1RA (exenatide once-weekly, liraglutide, lixisenatide, semaglutide), or SGLT-2i (canagliflozin, empagliflozin) to be noninferior to placebo as part of standard care.¹²⁻²⁰ In other words, the

CV safety of each of these 9 medications is similar to placebo as part of standard care. However, canagliflozin and empagliflozin, as well as the GLP-1RA liraglutide and semaglutide, were shown to reduce CV risk compared to placebo as part of standard care (**TABLE 2**).^{16,18-20} The CV safety trials for these 4 medications involved patients with a history or at high risk of CV disease, except empagliflozin, which involved only patients with a history of CV disease (**TABLE 3**).^{16,18-20}

Canagliflozin

The CV benefit observed with canagliflozin appears to be a cumulative effect of the 3 components of the primary composite outcome, ie, CV death, nonfatal myocardial infarction, and nonfatal stroke, since changes in these components did not reach statistical significance individually.¹⁹ The CV benefits were generally consistent across a wide range of subgroups at baseline, including age, HbA_{1c}, duration of T2DM, estimated glomerular filtration rate, and history of CV disease, but not beta-blocker or diuretic use. Post hoc analysis suggests that the CV benefits may result from reductions in one or more of the following: systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial pressure, and double product.²¹

The risk of hospitalization for heart failure alone (hazard ratio [HR], 0.67; 95% CI, 0.52-0.87), as well as combined with CV death (HR, 0.78; 95% CI, 0.67-0.91), was significantly reduced with canagliflozin compared with placebo. Of key importance is that renal outcomes were significantly improved with canagliflozin compared with placebo. These included lower risk of progression of albuminuria (HR 0.73; 95% CI, 0.67-0.79), as well as the composite of a 40% reduction in the estimated glomerular filtration rate, initiation of renal-replacement therapy, or renal death (HR, 0.60; 95% CI, 0.47-0.77).

There was a significantly higher risk of amputation of toes, feet, or legs with canagliflozin than with placebo (6.3 vs 3.4 persons with amputation/1000 patient-years; HR 1.97; 95% CI, 1.41-2.75).¹⁹ Nearly three-quarters (71%) of the amputations were at the level of the toe or metatarsal. The highest absolute risk of amputation occurred among patients who had a history of amputation or peripheral vascular disease. The etiology for amputation is uncertain but may involve poor perfusion due to osmotic diuresis and lower blood pressure in compromised patients.

Empagliflozin

Among patients with T2DM and established CV disease, the CV benefit in the composite endpoint observed with empagliflozin was primarily due to a significant reduction in CV death compared with placebo (HR, 0.62; 95% CI, 0.49-0.77), with no significant between-group differences in the risks of myocardial infarction or stroke.²⁰ The reductions in the risk

TABLE 1 Key glycemc and nonglycemc effects of sodium glucose cotransporter-2 inhibitors^{1-3,26}

HbA _{1c} lowering*	FPG:PPG lowering	Hypoglycemia	Weight change*	SBP	CV effects		DKD
					ASCVD	HF	
-0.35% to -0.77%	FPG<PPG	No	-1.37 to -2.9 kg	-2.4 to -8.5 mm Hg	Benefit: canagliflozin, empagliflozin		

Abbreviations: HbA_{1c}, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DKD, diabetic kidney disease; FPG, fasting plasma glucose; HF, heart failure; PPG, postprandial glucose; SBP, systolic blood pressure.

*As add-on to metformin vs metformin; data are from trials involving canagliflozin, dapagliflozin, or empagliflozin.

TABLE 2 Medications for type 2 diabetes mellitus that have been shown to offer a cardiovascular benefit vs placebo as part of standard care^{16,18-20}

Endpoint	Rate/100 patient-years		Hazard ratio (95% CI)
	Medication	Placebo	
Canagliflozin			
CV death, nonfatal MI, nonfatal stroke ^a	2.69	3.15	0.86 (0.75-0.97)
HF hospitalization	0.55	0.87	0.67 (0.52-0.87)
CV death or HF hospitalization	1.63	2.08	0.78 (0.67-0.91)
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)
40% reduction of eGFR, renal dialysis or transplantation, renal death	0.55	0.9	0.60 (0.47-0.77)
Empagliflozin			
CV death, nonfatal MI, nonfatal stroke ^a	3.74	4.39	0.86 (0.74-0.99)
All-cause death ^b	1.94	2.86	0.68 (0.57-0.82)
CV death	1.24	2.02	0.62 (0.49-0.77)
HF hospitalization	0.94	1.45	0.65 (0.50-0.85)
HF hospitalization or CV death (excluding fatal stroke)	1.97	3.01	0.66 (0.55-0.79)
Liraglutide			
CV death, nonfatal MI, nonfatal stroke ^{a,c}	3.4	3.9	0.87 (0.78-0.97)
CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for UA or HF	5.3	6	0.88 (0.81-0.96)
All-cause death ^d	2.1	2.5	0.85 (0.74-0.97)
CV death	1.2	1.6	0.78 (0.66-0.93)
Microvascular event	2	2.3	0.84 (0.73-0.97)
Nephropathy	1.5	1.9	0.78 (0.67-0.92)
Semaglutide			
CV death, nonfatal MI, nonfatal stroke ^{a,e}	3.24	4.44	0.74 (0.58-0.95)
CV death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for UA or HF	6.17	8.36	0.74 (0.62-0.89)
All-cause death, nonfatal MI, nonfatal stroke	3.66	4.81	0.77 (0.61-0.97)
Nonfatal stroke	0.8	1.31	0.61 (0.38-0.99)
Revascularization	2.5	3.85	0.65 (0.50-0.86)
New or worsening nephropathy	1.86	3.06	0.64 (0.46-0.88)

Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; UA, unstable angina.

^aPrimary endpoint.

^bNumber needed to treat = 39 over 3 years.

^cNumber needed to treat = 66 over 3 years.

^dNumber needed to treat = 98 over 3 years.

^eNumber needed to treat = 45 over 2 years.

TABLE 3 Key methodologic features and baseline characteristics of cardiovascular safety trials of sodium glucose cotransporter-2 inhibitors that have been shown to offer a cardiovascular benefit vs placebo as part of standard care^{16,18-20}

Medication (Trial)	Participants	Randomization/treatment	Notes
Canagliflozin (CANVAS & CANVAS-R)	Men, women with T2DM; age ≥ 30 y with symptomatic ASCVD ^a or age ≥ 50 y with ≥ 2 CVD risk factors ^b HbA _{1c} $\geq 7\%$ to $\leq 10.5\%$	2-wk single-blind, placebo-run-in Background glucose-lowering treatment allowed <u>CANVAS</u> Cana 300 mg/d or Cana 100 mg/d or Placebo OR <u>CANVAS-R</u> Cana 100 mg/d (optional increase to 300 mg/d at wk 13) or Placebo	N=10,142 (CANVAS 4330; CANVAS-R 5812) Age (mean) ^c : 63.3 y T2DM duration (mean) ^c : 13.5 y CVD history ^c : 65.6% HbA _{1c} (mean) ^c : 8.2% Treatment D/C rate ^d : cana 29.2%, placebo 29.9% Follow-up: 188.2 wks (mean); 126.1 wks (median)
Empagliflozin (EMPA-REG OUTCOME)	Men, women with T2DM and established CVD ^e HbA _{1c} $\geq 7\%$ to $\leq 10\%$	2-wk single-blind, placebo-run-in Background glucose-lowering treatment allowed Empa 10 mg/d or Empa 25 mg/d or Placebo	N=7020 Age (mean) ^c : 63.1 y T2DM duration >10 y ^c : 57% CVD history ^c : 99% HbA _{1c} (mean) ^c : 8.1% Treatment D/C rate: empa 10 mg 23.7%, empa 25 mg 23.1%, placebo 29.3% Follow-up (median): 3.1 y

Abbreviations: HbA_{1c}, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; Cana, canagliflozin; CVD, cardiovascular disease; D/C, discontinuation; Empa, empagliflozin; T2DM, type 2 diabetes mellitus.

^aStroke; myocardial infarction; hospitalization for unstable angina; coronary artery bypass graft; percutaneous coronary intervention; peripheral revascularization; symptomatic with hemodynamically-significant carotid or peripheral vascular disease; amputation secondary to vascular disease.

^bT2DM duration ≥ 10 y; systolic blood pressure >140 mmHg while receiving ≥ 1 blood pressure-lowering medication; current smoking; microalbuminuria or macroalbuminuria; high-density lipoprotein cholesterol <38.7 mg/dL.

^cBaseline.

^dCanvas: canagliflozin 41.1%, placebo 49%; CANVAS-R: canagliflozin 17.4%, placebo 20.4%.

^eCoronary artery disease; history of myocardial infarction or stroke; coronary artery bypass graft; peripheral artery disease; cardiac failure.

of CV death in the empagliflozin group were independent of baseline characteristics, including age, body mass index, estimated glomerular filtration rate, and history of CV disease.

The reductions in the risks of CV death and all-cause death occurred early in the trial (within 12 months) and continued thereafter. A dose-response effect, which has been observed for metabolic responses, was not evident with respect to CV outcomes. Of note, the adjusted mean HbA_{1c} at week 206 was 7.81% in the pooled empagliflozin group and 8.16% in the placebo group, suggesting that mechanisms beyond glucose-lowering contributed to the CV benefits observed with empagliflozin.

Additional analysis revealed that patients treated with

empagliflozin had a significantly lower risk of a composite microvascular outcome than did those who received placebo (HR, 0.61; 95% CI, 0.55-0.69).²² Approximately 80% of patients in both groups received concomitant renin-angiotensin-aldosterone system inhibitors at baseline. The between-group difference in the composite microvascular outcome was primarily due to a lower risk of progression of kidney disease with empagliflozin. New or worsening nephropathy occurred in 12.7% of empagliflozin and 18.8% of placebo patients (HR, 0.61; 95% CI, 0.53-0.70). Although empagliflozin did not prevent new albuminuria, patients treated with empagliflozin had a significantly lower risk of progression to macroalbuminuria (11.2% vs 16.2%), doubling of the serum creatinine (1.5% vs 2.6%), or initiation of renal-

TABLE 4 Key safety outcomes with SGLT-2 inhibitors^{3,23-26}

Safety outcome	FDA drug safety communication	Included in product labeling			
		Cana	Dapa	Empa	Ertu
Blood pressure reduction		X	X	X	X
Genital mycotic infection		X	X	X	X
Acute kidney injury	Cana, Dapa	X	X	X	X
Urosepsis, pyelonephritis		X	X	X	X
Leg/foot amputation	Cana	X			X
Bone fracture	Cana	X			
Ketoacidosis	Cana, Dapa, Empa	X	X	X	X
Bladder cancer			X		

Abbreviations: Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Ertu, ertugliflozin; FDA, US Food and Drug Administration.

replacement therapy (0.3% vs 0.6%) than patients in the placebo group, respectively.

OTHER SAFETY CONSIDERATIONS

The SGLT-2i are generally well tolerated with small increases in treatment-related adverse events (see below) compared with placebo.²³⁻²⁵ When compared to metformin, a meta-analysis of 7 short-term trials as add-on therapy to metformin showed a similar risk of total hypoglycemia compared to metformin monotherapy.³

Genital mycotic and urinary tract infection

The unique mechanism of action to increase urinary glucose excretion results in a variety of adverse events, including genital mycotic infection (6% to 13%) and urinary tract infection (0% to 2%), particularly in females who have had a previous infection (TABLE 4).^{3,23-26} Urinary tract infection may progress to urosepsis and pyelonephritis; hydration can aid in preventing progression.²⁷ To minimize the risk of genital mycotic infection, patients should be advised to keep the genital area clean and dry and, if necessary, apply topical antifungal, A+D ointment, zinc oxide ointment, or similar barrier method.

Blood pressure

The increased urinary glucose excretion caused by SGLT-2i results in an osmotic diuresis and increased urinary frequency. As a consequence, volume depletion may occur in <1% to 4%, lowering systolic blood pressure, which may result in postural hypotension and dizziness. Volume-depletion-related falls have been reported in 1.9%, 3.3%, and 1.5% of patients treated with canagliflozin 100 mg and 300 mg and placebo, respectively.²⁸ Therefore, it is especially important that patients maintain adequate hydration. In addition, patients should be advised to avoid bending at the waist and

to rise slowly from sitting or lying down. Caution is advised with concomitant use with medications that lower blood pressure, especially diuretics; adjustment of antihypertensive therapy may be necessary based on clinical judgment.

Kidney function

Kidney-related adverse events, eg, acute kidney injury and impaired renal function, may occur with SGLT-2i therapy in 1% to 3% of patients with normal renal function and up to 5% to 6% with moderate renal impairment at baseline.^{4-7,29} Although renal function generally improves after discontinuation or hydration, hospitalization and dialysis may occur.²⁹ Caution is advised with concomitant use of a diuretic, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or nonsteroidal anti-inflammatory drug.²⁹

Diabetic ketoacidosis

Diabetic ketoacidosis with SGLT-2i therapy also may occur, although rare in patients with T2DM.^{4-7,27} Factors predisposing to ketoacidosis include insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency, and alcohol abuse.⁴⁻⁷ Treatment in an emergency department or hospitalization may be required. In some cases, the diabetic ketoacidosis was present with only modestly elevated blood glucose.

Fractures

The incidence of fractures has been reported to be significantly higher with canagliflozin compared to other medications for T2DM.³⁰ A pooled analysis showed that the incidence rates were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator (placebo and active comparators), canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively.²⁸ Fractures were observed as early as 12 weeks after treatment initiation, were more likely to result from minimal trauma, and predominately affected the hands, humerus, ankles, and feet.^{28,30} The increased fracture risk was driven primarily by the results of the Canagliflozin Cardiovascular Assessment Study (CANVAS), which involved older patients with a prior history or risk of CV disease and with lower baseline renal function and higher diuretic use. While uncertain, it is possible that the increased risk of fracture in CANVAS may have resulted from volume depletion-related falls, although no adverse events of volume depletion (including syncope and

presyncope) were reported in patients just before or within 30 days of experiencing a fracture.²⁸ Additional investigation showed that canagliflozin caused significantly greater loss of bone mineral density at the hip (~1%) but not femoral neck, lumbar spine, or distal forearm, compared with placebo over 104 weeks of treatment.³¹

Leg and foot amputation

In the CANVAS program, leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to placebo.^{19,32} Over 1 year, the risk of amputation ranged from 5.9 to 7.5 per 1000 patients treated with canagliflozin and 2.8 to 4.2 per 1000 patients treated with placebo. Amputation of the toe and middle of the foot were the most common. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.⁵ The etiology for amputation is uncertain, but may involve poor perfusion due to osmotic diuresis and lower blood pressure in compromised patients.

Bladder cancer

Dapagliflozin is associated with an increased incidence of cancer. During the FDA review for the approval of dapagliflozin, the possibility of increased risks of breast and bladder cancers were identified.³³ Further investigation revealed no increased risk for breast cancer, but an imbalance in bladder cancer with dapagliflozin remained. Therefore, dapagliflozin should not be used in patients with active bladder cancer and used with caution in patients with a history of bladder cancer.⁴

IMPLICATIONS FOR PRACTICE

The SGLT-2i class of medications possesses many glycemic and nonglycemic characteristics that make them an important option for individualizing therapy in patients with T2DM. SGLT-2i are generally well-tolerated, with a low incidence of hypoglycemia. Adverse events related to osmotic diuresis and volume depletion are among the most common. A key benefit of canagliflozin and empagliflozin is their ability to reduce CV risk compared to placebo as part of standard care. Whether this is a class effect, eg, that dapagliflozin and ertugliflozin may demonstrate a similar CV risk reduction, is not yet known. Therefore, it remains unclear if patients should be switched from another medication not shown to provide CV risk reduction to a medication with demonstrated CV risk reduction, eg, canagliflozin and empagliflozin. At the very least, the CV benefits observed thus far with canagliflozin and empagliflozin are important to consider when initiating glucose-lowering therapy in patients with T2DM. ●

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Individualizing Treatment with Statin Therapy

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LEARNING OBJECTIVES

After participating, the clinician will be able to:

- Clarify the role of statins in the treatment of elevated low-density lipoprotein cholesterol (LDL-C) according to current guidelines and other recommendations
- Individualize statin therapy based on patient needs and characteristics

INTRODUCTION

Statin therapy remains the pharmacological foundation for the management of elevated low-density lipoprotein cholesterol (LDL-C). This is due to an established record of safety with lowering LDL-C, and supported by a host of outcome trials indicating a significant reduction in major cardiovascular (CV) events.¹ Yet, many challenges and questions still

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exist in clinical practice. To aid in the optimal management of elevated LDL-C levels, medical associations have developed guidelines or recommendations with a focus on patient-centric care (**TABLE 1**).¹⁻⁴

A key challenge for any target condition is individual risk assessment of patients for primary prevention. Performing risk scoring to estimate 10-year atherosclerotic cardiovascular disease (ASCVD) risk helps stratify patients in determining appropriate lipid targets and statin intensity. Most notable is the American College of Cardiology (ACC) ASCVD risk estimator,¹ which recommends moderate- to high-intensity statin (**TABLE 2**) therapy for those with 10-year ASCVD risk of $\geq 7.5\%$. Such recommendations align with the general principles that the intensity of risk-reduction therapy should be adjusted to the patient's absolute ASCVD risk and that the benefit of risk reduction is proportional to the extent of LDL-C reduction.^{1,2} Moreover, limited data exist on managing certain complex populations. For example, individuals with human immunodeficiency syndrome (HIV) have inherently high CV risk, yet remain understudied.

Three decades of statin data and guideline revisions have shown how critically important it is to take a patient-centric approach by individualizing treatment so as to improve adherence and, ultimately, patient care.

DIFFERENTIATING AMONG STATINS

Effectiveness in LDL-C lowering

It is imperative to assess individual patient characteristics and needs when prescribing statins. Selecting among the statins, as well as the statin dose, requires the clinician to find the "best fit" to limit adverse effects (AEs), improve long-term adherence, and ultimately reduce ASCVD events. A key differentiation among the statins is their effectiveness in lowering LDL-C, with dose intensity based on desired percent LDL-C reduction (**TABLE 2**) and corresponding to the overall 10-year ASCVD risk.^{1,2} In general, moderate- to high-intensity statins are recommended for patients with a 10-year ASCVD risk score $\geq 7.5\%$ or who have previously experienced a CV event. Moderate-intensity statins can also be considered for patients with a 10-year ASCVD risk score of 5% to $< 7.5\%$. Moderate-intensity statins result in a 30% to $< 50\%$ reduction in LDL-C, whereas high-intensity agents reduce LDL-C by $\geq 50\%$. The National Lipid Association (NLA) also stresses the importance of non-high-density lipoprotein cholesterol

TABLE 1 Comparative highlights of major lipid guidelines and recommendations

ACC/AHA ¹ 2013	NLA ² 2014	USPSTF ⁴ 2016	AACE/ACE ³ 2017																									
All guidelines recommend lifestyle as the foundation for ASCVD risk reduction																												
Shifted away from LDL-C goals Statin-intensity categories <ul style="list-style-type: none"> • High-intensity $\geq 50\%$ LDL-C \downarrow • Moderate-intensity 30 to $<50\%$ LDL-C \downarrow • Low-intensity $<30\%$ LDL-C \downarrow Four statin benefit groups – patients with: <ol style="list-style-type: none"> 1. Any form of clinical ASCVD <i>Primary prevention</i> <ol style="list-style-type: none"> 2. LDL-C $\geq 190^a$ 3. (+) DM, 40-75 yrs of age with LDL-C 70-189^a 4. (-) DM, 40-75 yrs of age + estimated 10-y ASCVD risk $\geq 7.5\%$ Introduced ASCVD risk calculator <ul style="list-style-type: none"> • Added race, gender, presence of DM, and treatment for hypertension to risk calculation; along with lifetime risk of ASCVD • Predicts 10-y ASCVD risk for primary prevention patients • Guides statin intensity for patients with 10-y risk of 5 to $<7.5\%$ and $\geq 7.5\%$ 	Primary targets: non-HDL-C^c and LDL-C Recommended moderate- or high-intensity statin Treatment goals: (mg/dL) <table border="1"> <thead> <tr> <th>Risk</th> <th>non-HDL-C^{a,c}</th> <th>LDL-C^a</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td><130</td> <td><100</td> </tr> <tr> <td>Moderate</td> <td><130</td> <td><100</td> </tr> <tr> <td>High</td> <td><130</td> <td><100</td> </tr> <tr> <td>Very high</td> <td><100</td> <td><70</td> </tr> </tbody> </table> Criteria for ASCVD risk assessment <table border="1"> <thead> <tr> <th>Risk</th> <th>Criteria</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td>0-1 ASCVD RFs^b</td> </tr> <tr> <td>Moderate</td> <td>2 ASCVD RFs^b</td> </tr> <tr> <td>High</td> <td>≥ 3 ASCVD RFs^b or DM + (0-1 ASCVD RFs^b or stage 3B/4 CKD or LDL-C ≥ 190 mg/dL)</td> </tr> <tr> <td>Very high</td> <td>ASCVD DM + (≥ 2 ASCVD RFs^b or end organ damage)</td> </tr> </tbody> </table>	Risk	non-HDL-C ^{a,c}	LDL-C ^a	Low	<130	<100	Moderate	<130	<100	High	<130	<100	Very high	<100	<70	Risk	Criteria	Low	0-1 ASCVD RFs ^b	Moderate	2 ASCVD RFs ^b	High	≥ 3 ASCVD RFs ^b or DM + (0-1 ASCVD RFs ^b or stage 3B/4 CKD or LDL-C ≥ 190 mg/dL)	Very high	ASCVD DM + (≥ 2 ASCVD RFs ^b or end organ damage)	<i>Primary prevention</i> Age 40-75 y with no history of CVD, ≥ 1 CVD risk factor, and estimated 10-y ASCVD risk 7.5%-10%: selectively offer low- to moderate-dose statin Age 40-75 y with no history of CVD, ≥ 1 CVD risk factor, and estimated 10-y ASCVD risk $\geq 10\%$: initiate low- to moderate-dose statin Age ≥ 76 y with no history of CVD: no recommendation due to insufficient evidence LDL-C >190 mg/dL: may require statin use Familial hypercholesterolemia: may require statin use	Primary targets: LDL-C and non-HDL-C^c Endorsed 10-yr ASCVD risk prediction using various assessment calculators Statins are recommended as the primary drug therapy for achieving LDL-C goals Introduced 'extreme risk' category and aggressive lipid targets – patients with: <ul style="list-style-type: none"> • Progressive ASCVD despite LDL-C $<70^a$ • ASCVD + DM, CKD (Stages 3/4) or HeFH • History of premature ASCVD Lipid targets: <ul style="list-style-type: none"> • LDL-C $<55^a$ • Non-HDL-C $<80^{a,c}$
Risk	non-HDL-C ^{a,c}	LDL-C ^a																										
Low	<130	<100																										
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^amg/dL^bMajor risk factors = age (male ≥ 45 y, female ≥ 55 y), family history of early ASCVD (<55 y of age in a male first-degree relative or <65 y in a female first-degree relative), (+) cigarette smoking, high blood pressure ($\geq 140/90$ mm Hg, or on blood pressure medication), and low HDL-C (male <40 mg/dL, female <50 mg/dL).^cnon-HDL-C = total cholesterol – HDL-C

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetSyn, metabolic syndrome; NLA, National Lipid Association; REs, risk equivalents; RFs, risk factors; y, year.

(non-HDL-C) and LDL-C, both of which are considered the root cause of atherosclerosis. Consequently, the NLA recommends both as primary targets of therapy (TABLE 1).² Although the non-HDL-C target is 30 mg/dL higher than the LDL-C goal, non-HDL-C reduction is typically proportional to statin intensity and achieved LDL-C reduction.

Importantly, the American College of Cardiology/American Heart Association (ACC/AHA) notes numerous intensity-modifying factors that can be considered for those who are otherwise candidates for a high-intensity statin.¹ These include patients with multiple or serious comorbidities such as impaired renal or hepatic function, a history of statin intolerance or muscle disorders, unexplained liver function test (LFT) elevations, concomitant drug interactions (DIs), age >75 years, and Asian ancestry. In such patients, moderate-intensity statin therapy may be a better choice for overall safety and tolerability.

STATIN SAFETY

Treatment safety and patient tolerability are key considerations in developing a treatment plan. Differences among the statins provides an opportunity to individualize therapy and give patients the best chance of staying on lifelong treatment to prevent ASCVD. When safety or tolerability issues preclude continued use of one statin, switching to another statin with attributes that are aligned with the individual patient should be considered before leaving the statin class for other lipid-modifying agents. For example, switching to a statin with low potential for DIs in a patient with polypharmacy limits safety concerns and the likelihood of concentration-dependent AEs.

Safety and tolerability

Although numerous factors can affect statin safety and tolerability, statins have an overall favorable safety profile. Severe

TABLE 2 Statin-intensity categories¹

High-intensity — dosed daily (↓ LDL-C ≥50%)	Moderate-intensity — dosed daily (↓ LDL-C 30 to <50%)	Low-intensity — dosed daily (↓ LDL-C <30%)
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 40 mg bid Fluvastatin XL 80 mg Lovastatin 40 mg Pitavastatin 2-4 mg Pravastatin 40-80 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Abbreviations: bid, twice daily; LDL-C, low-density lipoprotein-cholesterol.

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AEs resulting in hospitalizations (ie, rhabdomyolysis) are very rare with an estimated annual incidence of 0.44 per 10,000 person-years with statin monotherapy.^{5,6} Safety and tolerability are important considerations for statin therapy since, whether real or perceived, AEs are the primary reason for statin discontinuation.⁷ This is important since statin discontinuation is associated with higher rates of ASCVD.⁸ Statin safety and potential AEs are common topics in the medical literature and mainstream media. As such, the US Food and Drug Administration (FDA) and the NLA have provided updates including potential risks of statin use.^{9,10}

When statin therapy results in a major AE, an underlying DI is frequently implicated. Drug interactions are well established with the individual statins.^{11,12} Most worrisome are concomitant medications that may increase statin levels by several-fold, resulting in concentration-dependent AEs (**FIGURE**) (see Drug Interactions on page S46).¹² Those with advanced age are perhaps most at risk for DIs due to polypharmacy and comorbidities, and AEs may be most debilitating in patients age ≥65 years.¹²

Statin intolerance

One limitation of statin therapy is statin intolerance. Although there is no universally agreed upon definition, the NLA defines statin intolerance as “adverse symptoms, signs, or laboratory abnormalities attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living, leading to a decision to stop or reduce statin therapy.”¹³ Switching to another statin is also an option.

Statin intolerance due to musculoskeletal complaints typically involves myalgias or myopathy, with the latter being associated with elevated creatine kinase (CK) levels. In most instances, patients report myalgias, with normal CK values.¹⁴ The incidence of statin-associated muscle symptoms (SAMS)

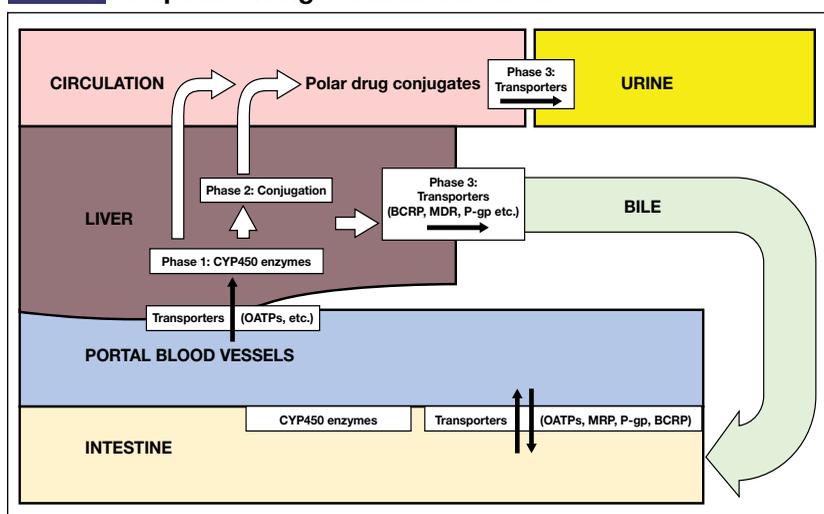
is widely variable and not well-defined, but is estimated to affect approximately 15% of statin users.¹³

Statin intolerance can frequently be attributed to patient perception or other underlying medical conditions, comorbidities, and concomitant therapies. Nonetheless, there are certain patients that have a true sensitivity and are unable to tolerate any level of statin therapy.⁵ However, before a patient is considered statin intolerant, the exclusion of other potential causes of muscle-related symptoms (eg, hyperuricemia, hypothyroidism, vitamin B₁₂ and/or D deficiency, inflammatory diseases, and non-statin-related musculoskeletal disorders)¹⁴ is warranted.

Muscle-associated symptoms or injury

The primary barrier to statin therapy is patient-reported musculoskeletal complaints.¹⁴ The clinical presentation of SAMS is highly subjective, as CK levels are typically normal, and involves a spectrum of symptoms, which overlap with common musculoskeletal conditions. Moreover, SAMS negatively impacts outcomes as discontinuation or down-titration of statin therapy is associated with higher rates of ASCVD.¹⁵ Various tools and approaches have been developed to determine if symptoms are statin-related and to assist with management.

One such tool is the Statin Myalgia Clinical Index (SMCI),¹⁴ which has recently been revised.¹⁶ Key features of the SMCI suggesting statin etiology include symmetric distribution of unexplained muscle symptoms, symptom onset shortly after initiation, improvement within 2 weeks after dechallenge, and symptom reoccurrence within 4 weeks of rechallenge. If the symptoms are determined to be statin-related, numerous approaches can be utilized including trying a different statin, implementing an alternate dosing strategy (such as once-weekly dosing) with a statin that has a long half-life (ie, ator-

FIGURE Steps involving statin metabolism.

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Phase 1 drug metabolism: Oxidation, reduction, and/or hydrolysis via cytochrome P450 enzymes

Phase 2 drug metabolism: Conjugation via glucuronidation, acetylation, glutathione conjugation, sulfate conjugation, methylation

Phase 3 drug metabolism: Distribution and elimination of drugs mediated by transporters

Cytochrome P450 enzymes (CYP450) = via microsomal/endoplasmic reticulum; most common CYP450 isoenzyme for drug metabolism is CYP450 3A4

Organic Anion-Transporting Polypeptides (OATP) = Organic anion-transporting polypeptides, including OATP1B1, facilitate drug movement in and out of intestinal cells and into liver cells; organic cationic transporters facilitate drugs movement in and out of the intestinal cells, and from the blood into the intestine and into the liver

Multidrug-Resistant-associated Proteins (MRP) = facilitate drug movement from intestinal cells into the blood

P-glycoproteins (P-gp) = facilitate drug movement from intestinal cells into the intestinal lumen, and from the liver into the bile

Breast Cancer-Resistant Proteins (BCRP) = facilitates drug movement from intestinal cells into the intestinal lumen, and from the liver into the bile

astatin, rosuvastatin, pitavastatin), and gradually titrating as tolerated from once-weekly to every other day dosing.⁵ Finally, having frank discussions and incorporating shared decision-making when rechallenging patients with an alternative statin or dosing strategy are essential.⁵

Hepatotoxicity

The potential for hepatotoxicity with lipid-altering agents has historically been a concern for clinicians and, more recently, patients.¹⁷ However, in 2012, the FDA removed the need for routine periodic monitoring of hepatic enzymes in all statin labeling.⁹ Instead, the FDA recommended that LFTs only need to be performed prior to initiating statin therapy, and as clinically indicated thereafter.

Statins have been implicated in cases of severe hepatotoxicity, but the incidence is exceedingly rare. A population-based study evaluated the incidence of hospitalization due to drug-induced acute liver failure among ~5.5 million patients.¹⁸ Of 32 cases identified over a 6-year period, nearly 80% implicated either acetaminophen or dietary supplements, while two involved statin therapy, along with other

concomitant agents. For managing potential statin-associated hepatotoxicity, repeating LFTs to confirm persistent elevations and using sound clinical judgment are the most critical.¹⁷

CASE SCENARIO #1

JS is a 63-year-old male being seen for a follow-up visit. He has been taking simvastatin 20 mg/day for the past year; LDL-C is now 105 mg/dL. At last visit 3 months ago, he was started on verapamil for hypertension, which is now controlled. His 10-year ASCVD risk score is 16.6%, but he is otherwise healthy. Today, he is complaining of achy muscles that make it hard for him as a custodian at a local school. JS notes that he is not sure he wants to continue statin therapy and is uncertain whether he really needs it.

DRUG INTERACTIONS

A key step to individualizing statin therapy is awareness of potential DIs. Multiple steps are involved in statin metabolism (FIGURE). In addition to the well-described cytochrome P450 (CYP) enzyme system, numerous drug transporters are involved in statin metabolism, including multidrug-resistant-associated proteins, breast cancer-resistant proteins, P-glycoproteins,

and organic anion-transporting polypeptides (OATPs), particularly OATP1B1. Statins are potential substrates for such pathways, but the affinity for specific transporters and CYP450 isoenzymes vary greatly among medications. Several commonly prescribed medications can interfere with one or more of the transporters or enzymatic pathways, and markedly increase statin serum concentrations and the risk for statin-related AEs.¹²

Approximately 75% of all medications are metabolized via the CYP450 system, with 50% of these agents having affinity for the CYP3A4 isoenzyme.¹¹ Lovastatin, simvastatin, and to a lesser extent, atorvastatin, are metabolized via CYP3A4. Concomitant use of strong CYP3A4 inhibitors, including azole antifungals, amiodarone, HIV protease inhibitors, certain macrolides (clarithromycin) and calcium channel blockers (amlodipine, diltiazem, and verapamil), and grapefruit juice, have the potential to markedly increase the serum concentrations of these statins.¹² Conversely, the statins that do not utilize the CYP3A4 isoenzyme for metabolism include fluvastatin, rosuvastatin, pitavastatin, and pravastatin. Moreover, the statins that are not dependent on the CYP450 system

for their metabolism are pitavastatin and pravastatin and thus, may have a reduced potential for significant DIs.¹²

CASE SCENARIO #1 (CONTINUED)

This case presents a common scenario in which a DI may have occurred with the addition of verapamil to simvastatin, which may have contributed to the patient's subsequent hesitancy to continue statin therapy. It also underscores the patient's limited understanding of his ASCVD risk. Discussing his 10-year risk score can be used to improve his understanding and hopefully motivate him to agree to further treatment for his elevated LDL-C. Verapamil could be discontinued and the patient switched to another antihypertensive medication that is not metabolized via CYP3A4. If this is done, the dose of simvastatin should be increased to provide additional LDL-C reduction. Alternatively, the simvastatin could be discontinued and the patient switched to another statin that is not metabolized via CYP3A4 at a dose that would provide additional LDL-C reduction.

Another key metabolic step with statins is hepatic uptake with OATPs, especially OATP1B1.¹² All statins are substrates for OATP1B1 (**FIGURE**). Common inhibitors of OATP1B1 include cyclosporine, erythromycin, and gemfibrozil. Cyclosporine not only inhibits OATP1B1 but other statin metabolic pathways and may increase statin concentrations several-fold. As such, cyclosporine should generally be avoided with statins. Although statin concentrations are only modestly increased (1-2-fold) with gemfibrozil, concomitant use of statins and gemfibrozil should be avoided or recommended dose limits should be followed for certain agents.¹²

CASE SCENARIO #2

MR is a 46-year-old male presenting for follow-up. His past medical history is significant for HIV, poorly controlled type 2 diabetes mellitus (DM), hypertension, atrial fibrillation, and depression. Other notable information is a family history of premature ASCVD, current tobacco use (1 pack/day), no alcohol intake, and a 10-year ASCVD risk score of 24%. MR reports no recent hospitalizations but admits that he is concerned regarding his future health, given his HIV status and family history of early ASCVD. Current labs indicate a mixed dyslipidemic pattern with an LDL-C of 110 mg/dL; C-reactive protein is moderately elevated. Medications of interest include his HIV protease inhibitors lopinavir + ritonavir, amlodipine, warfarin, but no antihyperlipidemic agents.

Certain populations are prone to DIs and potential statin-related AEs. These include patients taking multiple medications or conditions requiring complex drug regimens such as HIV infection and solid organ transplants.¹ For those with HIV and taking protease inhibitors, the FDA has provided guidance

on the use of statins to limit DIs.¹⁹ Most statins have dose limits (rosuvastatin, atorvastatin), are contraindicated (lovastatin, simvastatin), have no data available (fluvastatin), or should be avoided with certain HIV protease inhibitors (atorvastatin). Conversely, pitavastatin and pravastatin have no dose limits or additional precautions with concomitant use of HIV protease inhibitors. The HIV population is also at significant risk for ASCVD secondary to HIV, comorbid dyslipidemia, and chronic inflammation.²⁰ Epidemiologic data indicate that those with HIV infection have a 2-fold increased rate of CV events relative to non-infected patients.²⁰ To best answer the question of the benefit of statins in preventing ASCVD in this understudied population at high risk for ASCVD, the National Institute of Allergy and Infectious Diseases and Division of AIDS is currently conducting a landmark outcome trial comparing the effects of pitavastatin versus placebo on composite CV events (REPRIEVE).²¹

CASE SCENARIO #2 (CONTINUED)

MR is an example of a patient with significant ASCVD risk and requiring a complicated medication regimen. His 10-year ASCVD risk score of 24% may be underestimated since most risk calculators do not factor in premature family history of ASCVD and inflammatory measures,^{1,2} nor do they factor in HIV infection. The clinician must recognize the need for statin therapy and the need to stop smoking, but also be aware of the potential for major DIs and severe AEs. Given his ASCVD risk, implementing a safe, moderate-intensity statin for LDL-C reduction of 30% to 49% may be considered.

Clinicians must understand statin-related DIs, especially among populations requiring complex drug regimens. It is imperative to avoid critical combinations of the statins most prone to DIs (ie, lovastatin, simvastatin, atorvastatin) with specific agents having the highest potential for increasing statin concentrations (eg, azole antifungals, macrolides, cyclosporine, gemfibrozil, HIV protease inhibitors). Further, certain statins (eg, rosuvastatin, simvastatin) inhibit warfarin clearance, thus increasing the potential for bleeding during statin treatment initiation.¹² Awareness of such interactions may limit statin-related AEs and potentially improve adherence and long-term outcomes.

New onset diabetes

Consistent with earlier observations, a small but significant association between new onset diabetes (NOD) and rosuvastatin therapy was observed in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study.²² A subsequent meta-analysis confirmed this small but significant link as statin therapy was associated with a 9% increased risk for incident DM.²³ An additional analysis by Preiss et al evaluated statin dose and

determined that high-dose statin therapy was associated with a 12% greater likelihood of NOD compared to moderate dose therapy.²⁴ In 2013, a comprehensive meta-analysis further confirmed a dose-dependent link with NOD and a gradient of risk across many different individual statins.²⁵ Overall, most data indicate a modest increase in NOD (10%-12%) with several statin therapies, particularly among those at risk for DM.²⁶ In terms of number needed to harm, one meta-analysis of randomized controlled trials (RCTs) (N=91,140) found that treating 255 patients with statin therapy for 4 years would yield one additional case of DM.²³ Conversely, a few observational studies note higher rates and a stronger correlation, suggesting that deprescribing statin therapy in certain populations (ie, women age >75 years) may be advisable.^{27,28}

The FDA considers statin-associated NOD a class effect,⁹ but most data suggest the link is secondary to dose and each statin.²⁶ Zaharan et al found significantly higher rates of NOD with atorvastatin (HR, 1.25; $P<.0001$), rosuvastatin (HR, 1.42; $P<.0001$) and simvastatin (HR, 1.14; $P=.0005$) compared to pravastatin (HR, 1.02; $P=NS$) and fluvastatin (HR, 1.04; $P=NS$).²⁹ A meta-analysis of pitavastatin RCTs, including doses up to 8 mg daily, found no adverse effect on glucose metabolism or NOD.³⁰

Cognition

Limited data have suggested an association between statins and cognitive impairment (CI), prompting labeling changes to all statins in 2012. The FDA indicated that post-marketing AE reports "...described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy."⁹

The FDA stressed the rarity of these events and that there is no evidence to indicate progression to dementia. At worst, a weak causal effect is suggested. Conversely, other data have suggested a neutral or protective effect on cognition with statin therapy.^{31,32} For example, an analysis of a possible association between statins and Alzheimer's disease among Medicare beneficiaries (N=399,979)³² showed that patients with high statin exposure had a significantly lower risk of developing Alzheimer's disease (HR, 0.85-0.88; $P<0.01$) compared to those with minimal statin exposure.

Overall findings involving statin therapy and cognitive effects are mixed. If statin associated CI is suspected, ruling out other causes is warranted. If symptoms persist following statin discontinuation, neuropsychological testing can be considered.

SUMMARY

Statins are endorsed as first-line therapy by numerous authorities for LDL-C reduction and prevention of ASCVD. For optimal management, statin intensity should provide the LDL-C reduction needed based on the patient's overall ASCVD risk. Statins possess a favorable safety profile, yet musculoskeletal com-

plaints are a major barrier, often resulting in discontinuation of statin therapy. Certain statins are prone to significantly more severe DIs based on metabolism and can result in dose-dependent AEs. Clinicians must be aware of these factors to appropriately individualize therapy for optimal patient outcomes. ●

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Advances in Type 2 Diabetes: Focus on Basal Insulin/Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy

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INTRODUCTION

Despite a greater understanding of pathophysiologic processes of type 2 diabetes mellitus (T2DM) and new classes of medications targeting these processes, the treatment of persons with T2DM remains a formidable challenge. Recent evidence suggests that one-third to one-half of patients with T2DM have not achieved target glycemic control, that is, a glycosylated hemoglobin (A1c) <7%.^{1,2} A key reason appears to be a low rate of timely treatment intensification. Among patients with A1c >7% on metformin monotherapy, recent data indicate that only 38% had evidence of addition of a second glucose-lowering medication during the subsequent 12 months.³

Patients treated with basal insulin fare no better. Blonde et al found that 19% achieved A1c control 6 months after initiating basal insulin therapy and 31% after 12 months.⁴ Other investigators showed that after initiation of basal insulin, an A1c level \leq 7% was achieved in 21% to 27% of patients at 3 months and 28% at 24 months.^{5,6} Individuals who do not have early treatment intensification are less likely to have any treatment intensification at all. For example, failure to achieve A1c \leq 7% at 3 months was found to be associated with an increased risk of failing to achieve the A1c target at 24 months (odds ratio [OR] 3.7; 95% confidence interval [CI], 3.41-4).⁶ Recent evidence indicates that in patients with inadequate glycemic control taking basal insulin, treatment intensification with prandial or premix insulin or a glucagon-

like peptide-1 receptor agonist (GLP-1RA) took an average 4.3 years and happened in 31% of eligible patients.⁷

In patients treated with basal insulin, markers indicating the need to consider additional therapy include (1) an elevated A1c and persistent postprandial hyperglycemia despite a normal or near-normal fasting plasma glucose (FPG) concentration; (2) a total daily dose of basal insulin >0.5 units/kg; (3) severe, nocturnal, or frequent symptomatic hypoglycemia; and (4) persistent difference between bedtime and before-breakfast blood glucose >55 mg/dL.^{8,9} An even lower total daily dose of basal insulin as a marker for dose intensification has been suggested by a post hoc analysis of 3 insulin glargine titration studies of at least 24 weeks' duration (N=458).¹⁰ The analysis found that reduction in the FPG begins to slow at \sim 0.3 units/kg, leveling at \sim 0.5 units/kg.

These findings are a concern and emphasize the importance of staying ahead of this progressive disease through timely, individualized treatment intensification. Recommendations for intensifying glycemic control over time vary between the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE), although both recommend using a patient-centric approach to treatment and intensifying every 2 to 3 months.^{8,11} The 2018 ADA/EASD guideline recommends a sequential approach to treatment, generally beginning with metformin monotherapy.⁸ If the A1c target is not achieved after 3 months of metformin monotherapy, and adherence is assured, treatment should be intensified based on patient factors, including cardiovascular risk. Options include sodium-glucose cotransporter-2 inhibitors (SGLT-2is), GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4is), thiazolidinediones (TZDs), sulfonylureas, and basal insulin. For patients with A1c \geq 10%, blood glucose \geq 300 mg/dL, or markedly symptomatic, combination injectable therapy (basal insulin in combination with a GLP-1RA or prandial insulin) should be considered.

In contrast, the 2018 AAACE/ACE guideline stratifies therapy based on A1c (<7.5%, 7.5%-9%, >9%).¹¹ The AAACE/ACE guideline recommends the following hierarchy of usage

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for addition to metformin monotherapy: GLP-1RA, SGLT-2i, DPP-4i, TZD, basal insulin, and others. Each of these classes of agents has benefits and limitations to be considered when individualizing treatment. For patients with A1c >9%, basal insulin alone or in combination with other agents should be used if the patient is symptomatic; if not, metformin-based dual or triple therapy should be considered. No matter the treatment chosen, the treatment plan should be assessed every 2 to 3 months and treatment intensified if target glucose goals are not achieved. The remainder of this article will discuss the use of basal insulin and GLP-1RAs, focusing on their combined use.

EFFECTS OF BASAL INSULIN AND GLP-1RAS ON THE GLYCEMIC PROFILE

Long-acting basal insulins are intended to reduce the FPG level by mimicking the nonmeal secretion of insulin over the 24-hour day, which in turn suppresses hepatic glucose production. This mechanism of action is in contrast to bolus or prandial insulins, which are intended to lower the postprandial rise in glucose level after nutrient ingestion. People who are using insulin alone for the treatment of their diabetes will often need both insulin components for target glucose control. However, the use of basal insulin is much more common than meal-time insulin in primary care for the treatment of patients with T2DM. If basal insulin at a daily dose ≥ 0.5 units/kg is needed to normalize the FPG, close blood glucose monitoring is advised because of an increasing risk of hypoglycemia, especially if a meal is missed or a person is more active on a given day.

A key feature of the GLP-1RAs is their ability to stimulate insulin secretion and suppress glucagon secretion, both in a glucose-dependent manner, thus exerting greater effect when the blood glucose level is elevated and minimal effect as the blood glucose level approaches normal, thereby reducing the risk of hypoglycemia. The long-acting GLP-1RAs (albiglutide, dulaglutide, exenatide once-weekly, liraglutide, and semaglutide), which have a greater effect on stimulating insulin secretion and inhibiting glucagon secretion, produce strong reduction of FPG and modest reduction of postprandial glucose (PPG).¹²⁻¹⁸ The short-acting GLP-1RAs (exenatide twice-daily and lixisenatide), which slow gastric emptying, produce strong reduction of PPG and modest reduction of FPG.^{12,13,19} The GLP-1RAs also suppress appetite, producing modest weight loss of 1 to 2 kg in most patients with T2DM.^{20,21}

EARLY USE OF BASAL INSULIN AND GLP-1RAS

Among the attributes of an ideal medication for T2DM is the ability to achieve and maintain long-term glycemic-lowering effectiveness. The early addition of basal insulin to metformin improves glycemic control and lowers the risk of hypoglycemia compared with later addition of a sulfonylurea

to metformin.²² Moreover, as a natural hormone, insulin is effective long-term, with the magnitude of glycemic lowering dependent on dose and limited by the risk of hypoglycemia.

The GLP-1RAs serve to normalize the impaired incretin effect observed in patients with T2DM, providing an additional 0.5% to 1.3% A1c lowering when added to metformin.²³ Clinical investigation shows that GLP-1RAs improve various markers of beta-cell function, including homeostatic model assessment of β -cell function (HOMA-B), thus suggesting long-term effectiveness.²⁴ Further support for long-term glycemic effectiveness for GLP-1RAs stems from a network meta-analysis of 301 clinical trials (118,000 patient-years of treatment). The analysis yielded an intermediate OR for treatment failure for a GLP-1RA in combination with metformin. Treatment failure was defined as lack of efficacy or need for additional glucose-lowering therapy. Using the sulfonylureas as the reference class (treatment failure OR = 1), the order of treatment failure (ORs least to greatest) was estimated to be basal insulin (0.1); SGLT-2i (0.68); GLP-1RA (0.84); sulfonylurea (1); TZD (1.18); and DPP-4i (1.37).²⁵

COMBINATION OF BASAL INSULIN WITH A GLP-1RA

As suggested above, patients who do not achieve adequate A1c control despite basal insulin therapy often have postprandial hyperglycemia.^{26,27} Historically, to normalize the PPG, rapid- or short-acting prandial insulin has been added to basal insulin.^{28,29} Although generally effective in improving postprandial hyperglycemia and achieving A1c <7%, the addition of prandial insulin to basal insulin is often limited by weight gain and more frequent symptomatic hypoglycemia.⁸ Further, prandial insulin is a dosing challenge unless the person is willing to be carbohydrate consistent. Otherwise, matching the dose with food intake is difficult. In addition, the general need for multiple injections per day usually requires people to carry their “diabetes supplies” with them to work, school, or eating out. This can be a substantial burden that adversely affects patient adherence.

In contrast, the complementary glycemic effects of a GLP-1RA with basal insulin, coupled with their low incidence of hypoglycemia and their weight-loss effects, provide a strong rationale for using a GLP-1RA in place of prandial insulin for use in combination with basal insulin. They can be taken less often (twice daily to once weekly) and often do not need to be taken outside the home.

Comparison of GLP-1RA vs prandial insulin

Diamant et al compared a GLP-1RA vs prandial insulin, both in combination with basal insulin and metformin.³⁰ After a 12-week period to optimize the dose of insulin glargine

(mean dose 61 units/d), patients with A1c >7.0% (N=627) were randomized to exenatide 5 to 10 mcg twice daily or insulin lispro 3 times per day titrated to achieve a premeal glucose concentration of 100 to 108 mg/dL. After 30 weeks, the A1c was reduced to 7.2% and 7.1% in the exenatide and lispro groups, respectively, down from randomization A1c values of 8.3% and 8.2% (end of treatment difference -0.04%; 95% CI, -0.18-0.11). From a randomized FPG of 128 mg/dL for both groups, the FPG was 117 and 130 mg/dL at study end in the exenatide and lispro groups, respectively ($P=$.002). Reductions in PPG were similar in both groups except after lunch, in which the reduction with lispro was greater than with exenatide (-56 vs -39 mg/dL; $P<$.001).

Other randomized controlled trials investigating the addition of albiglutide or lixisenatide to basal insulin have shown similar results when compared with the addition of prandial insulin.^{31,32}

Combination of insulin with a GLP-1RA

The complementary glycemic and nonglycemic effects of basal insulin and GLP-1RAs provide a strong rationale for their combined use. The benefits of the combination were demonstrated by a systematic review of 14 observational/real-world studies and 5 clinical trials involving approximately 5000 patients with T2DM for 7 to 15 years and treated with the combination of GLP-1RA and basal insulin with or without prandial insulin.³³ Across the 19 studies, the combination of a GLP-1RA with insulin improved glycemic control without weight gain or an increased risk of hypoglycemia. Weight loss was commonly observed. The addition of a GLP-1RA to basal insulin therapy allowed for a reduction of the total daily insulin dose without a loss of glucose control. The most commonly reported adverse events were gastrointestinal, but were generally mild or moderate in severity and decreased in occurrence with continued dosing.

Similar results were reported in a more recent meta-analysis of 26 randomized clinical trials involving 11,425 patients treated for 12 to 52 weeks.³⁴ Compared with patients treated with a variety of regimens consisting of basal insulin with or without prandial insulin, patients treated with the combination of basal insulin and GLP-1RA had significantly greater reductions in A1c (weighted mean difference [WMD], -0.47%; 95% CI, -0.59 to -0.35) and body weight (WMD, -2.5 kg; 95% CI, -3.3 to -1.7 kg), were more likely to achieve the A1c target (relative risk [RR], 1.65; 95% CI, 1.44-1.88), and had similar rates of hypoglycemia (RR, 1.14; 95% CI, 0.93-1.39).

Fixed-ratio combination products of basal insulin and GLP-1RA

The glycemic and nonglycemic benefits observed with the

combination of basal insulin and a GLP-1RA as individual medications led to the development of fixed-ratio combination products. An advantage of these combination products for patients is that they avoid the need for 2 separate injections and 2 copays.

One fixed-ratio product combines insulin glargine U-100 with lixisenatide (IGlarLixi) and the other combines insulin degludec U-100 with liraglutide (IDegLira).^{35,36} Both products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin or GLP-1RA therapy. Both are titrated based on the basal insulin component, allowing for a slow increase in the GLP-1RA dose, thereby minimizing the frequency and severity of nausea and vomiting. IGlarLixi can be titrated over the range of 15 to 60 units, in which 1 unit of IGlarLixi equals 1 unit of glargine and 0.33 mcg of lixisenatide. The maximum dose of lixisenatide is 20 mcg. IDegLira can be titrated over the range of 10 to 50 units, in which 1 unit of IDegLira equals 1 unit of degludec and 0.036 mg of liraglutide. The maximum dose of liraglutide is 1.8 mg. Both are available only in pen devices.

INSULIN GLARGINE/LIXISENATIDE

LixiLan-O trial

The LixiLan-O trial compared the individual components of glargine U-100 and lixisenatide with the fixed-ratio product IGlarLixi in patients with T2DM inadequately controlled with metformin with or without a second oral medication (N=1170).³⁷ At the end of 30 weeks, from a baseline of 8.1%, the A1c was reduced -1.6% with IGlarLixi compared with -1.3% for glargine and -0.9% for lixisenatide 20 mcg/d ($P<$.0001 IGlarLixi vs comparators). The reduction in FPG was similar with IGlarLixi (-63 mg/dL) and glargine (-59 mg/dL) and smaller with lixisenatide 20 mcg/d (-27 mg/dL; $P<$.0001 vs IGlarLixi). The reduction in PPG was greater with IGlarLixi (-103 mg/dL) than glargine (-59 mg/dL; 95% CI, -2.8 to -2.0) or lixisenatide (-83 mg/dL; 95% CI, -1.6 to -0.6). The total daily dose of insulin at study end was 39.8 units with IGlarLixi and 40.3 units with glargine.

Changes in body weight were as expected, with a -0.3 kg loss with IGlarLixi. The rate of symptomatic hypoglycemia (\leq 70 mg/dL) was highest with IGlarLixi at 1.4 events/patient-year, compared with glargine at 1.2 events/patient-year and lixisenatide at 0.3 events/patient-year. Nausea (9.6% vs 24.0%) and vomiting (3.2% vs 6.4%) occurred less frequently with IGlarLixi than lixisenatide, respectively, likely due to the slow increase in lixisenatide dose due to titration of the insulin dose. A positively adjudicated major adverse cardiovascular event occurred in 2 patients in the IGlarLixi group, 7 patients in the glargine group, and 2

patients in the lixisenatide group. No cases of pancreatitis occurred.³⁷

LixiLan-L trial

The LixiLan-L trial compared IGLarLixi with up-titrated glargine U-100 in patients who had inadequate glycemic control while using glargine 15 to 40 units/d plus oral agents (N=736).³⁸ After a 6-week run-in during which oral agents other than metformin were stopped, patients were treated for 30 weeks with doses of IGLarLixi and up-titrated glargine capped at 60 units/d. From a baseline A1c of 8.1%, the A1c was reduced -1.1% in the IGLarLixi group and -0.6% in the glargine group ($P<.0001$). A post hoc analysis demonstrated that the reductions in A1c were greater for IGLarLixi than glargine for each of 3 groups of patients based on screening A1c level (A1c \leq 8%, 8%-9%, and $>$ 9%) (all $P<.0001$).³⁹

Although the reduction in FPG was small (-7 mg/dL with IGLarLixi and -9 mg/dL with glargine), the PPG reduction was significantly greater with IGLarLixi than glargine (-85 vs -25 mg/dL, respectively; 95% CI, -3.9 to -2.8). The mean final total daily dose of insulin was 47 units in both groups.

More patients in the IGLarLixi group than the glargine group achieved several composite endpoints that consisted of glycemic control, no weight gain, and/or no hypoglycemia. These benefits were independent of baseline A1c, body mass index, and duration of T2DM.^{40,41} For example, 20% of patients treated with IGLarLixi achieved A1c $<$ 7% without weight gain and documented symptomatic hypoglycemia, compared with 9% of glargine patients ($P<.0001$).³⁸

Post hoc analyses

Further analyses of LixiLan-O, LixiLan-L, and other trials demonstrated additional benefits of IGLarLixi compared with glargine. In LixiLan-L, an A1c $<$ 7% was achieved by 50% of IGLarLixi patients at a median of 153 days, but was never reached by 50% of patients with glargine.⁴² In patients treated with IGLarLixi in LixiLan-O, the change from baseline in PPG excursion was -29, -36, and -52 mg/dL for the lixisenatide dose groups of 5 to 10, 10 to 15, and 15 to 20 mcg, respectively.⁴³ Glycemic and nonglycemic outcomes with IGLarLixi have been found to be generally similar in patients \geq 65 years of age compared with patients $<$ 65 years, with no increased risk of hypoglycemia.⁴⁴ Modest weight loss was observed in patients \geq 65 years of age.

INSULIN DEGLUDEEC/LIRAGLUTIDE

DUAL-I trial

The DUAL-I trial compared the individual components of degludec U-100 and liraglutide 1.8 mg/d with the fixed-ratio product IDegLira in patients with T2DM inadequately

controlled with metformin with or without pioglitazone (N=1660).⁴⁵ Patients were treated for 26 weeks, after which approximately three-quarters of patients continued treatment for an additional 26 weeks. After 52 weeks, from a baseline A1c of 8.3%, the A1c reduction was greatest with IDegLira than degludec or liraglutide (1.8% vs 1.4% vs 1.3%; both $P<.0001$ vs IDegLira). The reduction in FPG was similar with IDegLira (-62 mg/dL) and degludec (-61 mg/dL), and smaller with liraglutide (-30 mg/dL; $P<.0001$ vs IDegLira). The total daily dose of insulin at study end was 39 units with IDegLira and 62 units with degludec. Substudy analysis showed the decrease in the PPG increment was similar with IDegLira and liraglutide, both of which were greater than with degludec.⁴⁶

Changes in body weight were as expected, with a -0.4 kg loss with IDegLira. The rate of confirmed hypoglycemia (requiring assistance or $<$ 56 mg/dL with or without symptoms) was highest with degludec (2.6 events/patient-year) and least with liraglutide (0.2 events/patient-year). Nausea occurred less frequently with IDegLira than liraglutide (9% vs 20%), likely because of the slow increase in liraglutide dose due to titration of the insulin dose. A positively adjudicated major adverse cardiovascular event occurred in 4 patients in the IDegLira group and 1 in each of the degludec and liraglutide groups. Two cases of treatment-emergent pancreatitis occurred in the liraglutide group, but were judged as unlikely to be treatment-related.

DUAL-II trial

The DUAL-II trial compared IDegLira with degludec, both once daily with the maximum degludec dose capped at 50 units.⁴⁷ Patients (N=413) had inadequate glycemic control despite basal insulin 20 to 40 units/d in combination with metformin with or without a sulfonylurea or meglitinide. At randomization to IDegLira or degludec, patients were continued on metformin alone. Insulin doses were titrated to achieve a FPG of 72 to 90 mg/dL. After 26 weeks, from a baseline A1c of 8.7% to 8.8%, the A1c was reduced -1.9% in the IDegLira group and -0.9% in the degludec group ($P<.0001$). Similarly, the FPG reduction was greater with IDegLira than with degludec (-62 vs -46 mg/dL, respectively; $P=.0019$). The 2-hour PPG excursion was similar (40 vs 43 mg/dL, respectively). The mean total daily degludec dose was 45 units in each group.

More patients in the IDegLira group than the degludec group achieved several composite endpoints that consisted of glycemic control, no weight gain, and/or no hypoglycemia. The rates of confirmed and nocturnal hypoglycemia were similar in both groups. Similar to DUAL-I, nausea occurred more frequently with IDegLira than with degludec (6.5% vs 3.5%). One positively adjudicated major adverse cardiovas-

cular event occurred with IDegLira and 2 with degludec. No cases of pancreatitis were observed.

Post hoc analyses

Further analyses of DUAL-I and DUAL-II and other DUAL trials have provided additional insight regarding the benefits of IDegLira compared with degludec. As expected, the magnitude of A1c lowering increased with increasing A1c at baseline.⁴⁸ However, A1c reductions with IDegLira were significantly greater than with degludec or liraglutide in all baseline A1c categories ($P < .01$) ($\leq 7.5\%$, $> 7.5\% - 8.5\%$, $> 8.5\% - 9\%$, $> 9\%$), except for no difference in the lowest A1c category in DUAL-II. The DUAL-V trial, which compared IDegLira with glargine, also showed IDegLira to be significantly more effective than glargine for reducing A1c across all baseline A1c categories ($P < .0001$) ($\leq 7.5\%$, $> 7.5\% - 8.5\%$, $> 8.5\%$).⁴⁹ Similarly, IDegLira was significantly more effective than glargine for reducing A1c irrespective of baseline FPG ($P < .0001$) (< 130 and ≥ 130 mg/dL) or body mass index ($P < .0001$) (< 30 , 30 to < 35 , and ≥ 35 kg/m²).

Additional analysis of DUAL-I and DUAL-II showed the mean A1c to be significantly lower and the proportion of patients achieving A1c $< 7\%$ significantly greater at weeks 8 and 12 with IDegLira (all $P < .0001$).⁵⁰ Reductions in A1c also have been shown to be significantly greater with IDegLira vs comparators (basal insulin, GLP-1RA, placebo) in patients with mildly or moderately impaired renal function (estimated glomerular filtration rate ≥ 90 , ≥ 60 to < 90 , ≥ 30 to < 60 mL/min/1.73 m²).⁵¹

In DUAL-I, a subset of patients underwent continuous glucose monitoring after meal tests.⁴⁶ Results showed a reduction in the PPG increment after all 3 main meals. The reduction was similar for IDegLira and liraglutide, both significantly greater than for degludec. Additional data suggested that the improvement was partially explained by higher endogenous insulin secretion and improved β -cell function due to liraglutide.

The data from DUAL-I, as well as 9-point self-monitored blood glucose (SMBG) profiles from DUAL-I and DUAL-II, showed that IDegLira resulted in a higher proportion of patients with SMBG values within the target range (70-162 mg/dL) for all pre- and postprandial values, as well as for the full 9-point profile ($P < .01$ for all).⁵² Moreover, reduction in the fluctuation of interstitial glucose was significantly greater with IDegLira than liraglutide ($P = .0072$).

DOSING AND TITRATION

Before initiating IGLarLixi or IDegLira, basal insulin and GLP-1RA therapy must be discontinued.³⁵ IGLarLixi is initiated at a dose of 15 units (15 units glargine and 5 mcg lixisenatide) for

patients taking basal insulin < 30 units/d or taking lixisenatide, or at a dose of 30 units (30 units glargine and 10 mcg lixisenatide) for patients taking basal insulin 30 to 60 units/d.³⁵ The dose of IGLarLixi is administered once daily prior to the first meal of the day and should be titrated up or down by 2 to 4 units between 15 and 60 units every week.

IDegLira is initiated at a dose of 16 units (16 units degludec and 0.58 mg liraglutide).³⁶ The dose of IDegLira is administered at the same time each day and should be titrated up or down by 2 units between 10 and 50 units every 3 to 4 days.

The pen devices for IGLarLixi and IDegLira are similar to the pen devices for their respective insulin products, which should simplify transitioning patients from the insulin product to the fixed-ratio combination product.

CLINICAL IMPLICATIONS OF FIXED-RATIO BASAL INSULIN/GLP-1RAS

The fixed-ratio basal insulin/GLP-1RA combination products combine 2 important patient-centered features: high levels of efficacy as represented by most patients achieving target treatment goals and superior glucose control compared with insulin. Furthermore, a single daily injection with no substantial dosing preparation should seem simple for patients. However, the use of these agents as the first injectable treatment may be limited by insurance coverage and cost, likely because this use is outside the currently approved indication. If these agents are added after basal insulin or GLP-1 RA, the provider should be mindful of the starting dose and discuss the expected glucose changes and common adverse reactions during titration. ●

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From Randomized Controlled Trials to the Real World: Putting Evidence into Context

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How often have you treated a patient with a medication for type 2 diabetes mellitus (T2DM) and found that the patient didn't achieve the benefits you expected based on the results of a phase 3 randomized controlled clinical trial (RCT)? Perhaps your patient had a 0.6% reduction in glycated hemoglobin (HbA_{1c}) instead of 1% as reported in the RCT. Or maybe you found that hypoglycemia

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occurs in 20% of your patients treated with a specific medication per month rather than the 3% reported in the latest RCT of that medication. Such differences between RCTs and real life are common.

A recent analysis of an observational cohort of 917,440 adults with diabetes in the Surveillance, Prevention, and Management of Diabetes Mellitus network showed that the rate of severe hypoglycemia ranged from 1.4 to 1.6 events per 100 person-years.¹ In contrast, a systematic review of 216 RCTs in patients with T2DM by Bolen et al found that few RCTs reported even 1 case of severe hypoglycemia for most classes of medications (except sulfonylureas or insulin for which hypoglycemia is very common) as mono-, dual, or triple therapy.²

Why are there differences between the results observed in RCTs and those achieved in real-world clinical practice? Do these different data sets serve different purposes? If so, what? What are the benefits and limitations of each? Before we begin answering these questions, it is important to become familiar with key terminology (**TABLE 1**).³⁻⁵ The primary source for these definitions is the US Food and Drug Administration's (FDA) 2017 *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*; universal acceptance is not implied. Nonetheless, the definitions provided here can be used for a general understanding. Two particularly important terms are real-world data (RWD) and real-world evidence (RWE). RWD are data collected from a variety of sources outside of an RCT that relate to patient health status and/or delivery of health care. RWE is clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of RWD.³

RANDOMIZED CLINICAL TRIALS

Traditional RCTs are the "gold standard" for clinical research because they enable a direct comparison of the impact of ≥ 2 interventions on ≥ 1 outcomes, often efficacy and safety. To do this, an RCT is designed to minimize the impact of external factors on outcomes by strictly controlling the study methods, ie, setting, characteristics of the patient population, interventions, the primary and secondary outcomes, as well as the statistical analyses. Typical—but not universal—

TABLE 1 Glossary of terms³⁻⁵

Term	Definition
Average treatment effect	The average effect of treatment on those participants who received the treatment ⁵
Effectiveness trial	Also called a pragmatic trial, measures the degree of beneficial effect under real-world clinical settings ⁴
Efficacy trial	Also called an explanatory trial, determines whether an intervention produces the expected result under ideal circumstances. ⁴ Most randomized controlled trials are efficacy trials
Medical administrative claims data	Claims arising from a person's use of the health care system (and reimbursement of health care professionals for that care)
Observational study	A study that does not involve any interventions (experimental or otherwise) on the part of the investigator, eg, a population study in which changes in health status are studied in relation to changes in other characteristics. Most analytical epidemiologic designs (notably, case-control and cohort studies) are called observational because investigators observe without intervening other than to record, classify, count, and analyze results
Post-marketing surveillance	Collection, analysis, and interpretation of data or other information about a marketed device or drug
Propensity score	The probability of treatment assignment conditional on observed baseline characteristics. It allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial. This is achieved by balancing the distribution of observed covariates between treated and untreated subjects so that they are similar at baseline ⁵
Propensity score matching	The formation of matched sets of treated and untreated subjects who share a similar value of the propensity score. This enables the estimation of the average treatment effect for the treated. The most common is 1-to-1 pair matching, in which pairs of treated and untreated subjects are formed, such that matched subjects have similar values of the propensity score ⁵
Prospective study	Also called a concurrent cohort study, defines the original population of interest at the start of the study and collects exposure/treatment and outcome data from that time point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated
Randomized or traditional clinical trial	Typically conducted in specialized research settings with a specific population. These studies often utilize measures designed to control variability and ensure data quality, such as detailed eligibility criteria, detailed case report forms that exist apart from medical records, and intensive monitoring and auditing designed to ensure precise adherence to study procedures and rigorous precision in data collection. They typically also include substantial efforts to ensure compliance with treatments and to avoid concomitant treatments that might influence the randomized treatment effect
Real-world data	Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (outside of a randomized controlled trial)
Real-world evidence	Clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of real-world data
Registry	An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves ≥ 1 predetermined scientific, clinical, or policy purposes
Retrospective analysis	Also called an historical cohort study, defines the population and determines the exposure/treatment from historical data. The variables and outcomes of interest are determined at the time the study is initiated

features of RCTs involving medications are⁴:

- prospective design
- randomization of study participants between/among treatment arms
- strict inclusion and exclusion criteria
- specific use and dose(s) of interventions
- extensive, regimented monitoring that often involves more frequent patient visits than would occur in usual clinical practice
- extensive patient support and education

- relatively short follow-up (weeks, months, 1 to 2 years)

RCTs or safety/efficacy trials often compare the interventions of interest, such as an investigational medication or biologic, with placebo or sometimes with an established drug to determine whether the medication produces the expected result under ideal conditions.⁴ Although valuable for research and required for regulatory purposes, such a comparison might not be entirely helpful to a clinician who often is more

interested in the effectiveness and safety in patients who are more similar to those he or she sees and relative to best current or most common practice.⁶

Therefore, RCTs assess the efficacy and safety of the medication, whereas real-world studies evaluate the effectiveness of the medication, including the degree of beneficial effect under real clinical practice conditions.⁴ Differences between efficacy and effectiveness might be larger for medications that produce benefits over many years such as for a chronic disease, but smaller for an acute disease where benefits are observed more quickly.⁷ Differences between efficacy and effectiveness also might be larger for medications used in a diverse population because of the wide heterogeneity of patient characteristics that might impact outcomes.⁷

As noted above, a key characteristic of an RCT is the use of strict inclusion and exclusion criteria. This creates a well-defined patient population that generally is younger and healthier and whose sociodemographic characteristics are more homogeneous than patients treated with the medication in the real world.^{4,6,8} Furthermore, non-white races, women, and older adults often are underrepresented in RCTs, while pregnant women and children often are excluded in pre-approval clinical trials. Previous and concomitant treatment often is limited. Consequently, the narrowly defined population in an RCT could represent only a small percentage of patients expected to be treated with the medication in the real world. Thus, the internal validity attained in RCTs often limits the generalizability or relevance of the RCT results to other patient populations.⁹ Because of the highly selected population, careful clinical management, and relatively short trial period, patients in RCTs might be less likely to experience adverse events and clinical outcomes than real-world populations, which may lead to an underestimation of a medication's adverse outcomes in clinical practice.⁴

Another limitation of RCTs is that patients who elect to participate in RCTs often are highly motivated, although motivating factors can vary significantly by condition.¹⁰⁻¹³ High rates of treatment adherence generally are observed in RCTs because of extensive patient support and education with frequent patient visits. For example, retrospective analysis of the Optum/Humedica claims database showed that only 29% and 37% of patients treated with a glucagon-like peptide-1 receptor agonist or dipeptidyl peptidase-4 inhibitor, respectively, were adherent over 1 year.¹⁴ By comparison, investigators estimated the adherence rate to be 95% in RCTs of these agents.¹⁴

Historically, RCTs have not assessed health care resource utilization or direct and indirect costs because the types of primary clinical endpoints used are less likely to correspond with the optimal endpoint for economic evaluation, such as

quality-adjusted life years, hospitalization or office visit costs, medication costs, and missed work time.⁶ Moreover, the use of a composite of several endpoints as is sometimes done in an RCT, generally does not lend itself to cost per composite clinical endpoint. In contrast, clinical endpoints that focus on the treatment's impact on how a patient feels, functions, or survives are useful for economic evaluation.^{6,15}

SHIFTING FOCUS

Increasing recognition of the limitations of RCTs, particularly their limited generalizability to real-world clinical practice, has been paralleled by decades of concerns about escalating health care costs with only modest improvements in health care quality.⁹ The shift from volume-based to value-based payment has stimulated further interest in estimating how a medication or intervention affects care quality and spending in the real world. It also has stimulated interest in treatment decision-making for and by an individual patient.

Making these value-based estimates is not new; they have been done for decades using population health data, usually on a national or regional level through the use of insurance claims databases or registries.¹⁶ On a local level, hospitals and clinicians have used patient level data for quality and safety monitoring via chart audit.

Now the availability of patient-level data in electronic health records that includes data across the health care system has not only streamlined the collection and analysis processes, it often provides a more complete picture of the patient experience. When it doesn't, claims databases can be used to provide missing data elements. There has been expansion in the size and types of databases available; therefore, the term "big data" often is used when referring to some RWD sources.¹⁷ Databases commonly used for real-world studies of patients with diabetes include Truven Health Analytics MarketScan, Optum Humedica SmartFile, GE Healthcare Centricity Practice Solution, IBM Explorys, and Kaiser Permanente. In some countries, health data of nearly the entire population is available for analysis from resources such as the United Kingdom Clinical Practice Research Datalink.

REAL-WORLD EVIDENCE

The role of RWE in health care decision making, as well as regulatory affairs and drug development, is expanding. Current and evolving uses of RWE include changes in product labeling by the FDA, the development of a personalized treatment plan by patients and physicians, use as a tool for quality improvement, and measurement of health care resource utilization and associated costs.¹⁷ RWE also can be used to provide information about clinical questions when RCTs would be impractical to conduct because they might require

TABLE 2 Example of benefits and uses of real-world data¹⁸

- Estimates of effectiveness in a variety of typical practice settings
- Comparison of multiple alternative interventions (eg, older vs newer drugs) or clinical strategies to inform optimal therapy choices beyond placebo comparators
- Estimates of the evolving risk-benefit profile of a new intervention, including long-term and rare clinical benefits and harms
- Examination of clinical outcomes in a diverse study population that reflects the range and distribution of patients observed in clinical practice
- Results on a broader range of outcomes, eg, patient-reported outcomes, health-related quality of life, and symptoms, than traditionally have been collected in RCTs, ie, major morbidity and short-term mortality
- Data on resource use for the cost of health care services and economic evaluation
- Information on how a product is dosed and applied in clinical practice and on levels of compliance and adherence to therapy
- Data in situations where it is not possible to conduct an RCT
- Substantiation of data collected in more controlled settings
- Data in circumstances where there is an urgency to provide reimbursement for some therapies because it is the only therapy available and might be life-saving
- Interim evidence—in the absence of RCT data—upon which preliminary decisions can be made
- Data on the net clinical, economic, and patient-reported outcome impacts following implementation of coverage or payment policies or other health management programs

Abbreviation: RCT, randomized controlled trial.

Creative Commons License (<https://creativecommons.org/licenses/by/4.0/legalcode>) from: Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: The ISPOR Real-World Data Task Force Report. *Value Health*. 2007;10(5):326-335.

too many patients over too long a period of time and be too expensive. Other uses and benefits of RWD are shown in **TABLE 2**.¹⁸

There is no universally accepted definition of RWD. In its broadest terms, RWD refers to data obtained outside of an RCT.¹⁹ RWD can be gathered retrospectively, as commonly used for health outcomes research, or prospectively, as may be used for safety monitoring or a pragmatic trial.²⁰

As with RCTs, data quality is of paramount importance. The RWD used to develop RWE must be high quality. Because RWD often are taken from multiple but heterogeneous sources, it is important that RWD is refined before analysis and interpretation as RWE.^{19,20} For example, a HbA_{1c} level might be documented using a procedure code as well as in a clinician note. Steps must be taken to ensure the data are

consistent. Another example is where information is absent in 1 data source, eg, electronic health record, and might need to be filled from another source, eg, claims database.

The length of an RWE trial sometimes is longer than an RCT so that accurate assessment of health outcomes can be made.⁴ RWE trials generally involve a simple design and include a large sample size, often tens of thousands patients, from diverse settings. Application of exclusion criteria and techniques such as propensity score matching (see **TABLE 1**) could reduce the number of patients. Large datasets allow the use of novel data analytics such as machine learning and predictive modelling.

In RWE trials, standard treatment or current practice is a typical comparator, although new treatments could be used. Consequently, similar to RCTs, RWE trials of medications could include patient populations or indications not approved by the FDA. In contrast to RCTs, RWE trials allow patients and their clinicians to choose treatments based on clinician preference, as well as the patient's characteristics and preferences.⁴

There are many potential limitations to RWE trials.¹⁸ Most RWE trials involve nonrandomized patients where it often is not known why patients were assigned to a particular treatment or intervention, which can introduce confounding. To correct for nonrandomization, patient groups might be matched using covariate adjustment, propensity scores, etc; nonetheless, selection bias and other confounders could remain. Patient accrual over a reasonable period of time might be difficult, particularly for a medication with low usage or rare condition. Data may be of poor or unknown quality or missing leading to random or systematic bias.²¹ The collection and analysis of RWD can be costly.¹⁷

Limitations among RWD sources are common as well.⁹ For example, electronic medical record data and patient registries could consist of variable types and quality of information. Some data elements might be missing from these sources as well as from claims data and there may be limited follow up of some patients.²¹ Moreover, the reasons patients initiate or change treatments often are not available. These limitations should not exclude the use of these sources, but should be documented so that their impact on analysis and interpretation can be understood.²⁰

The challenges presented with the limitations of RWD are a focus of active efforts by the FDA, National Institutes of Health, pharmaceutical manufacturers, and other stakeholders.^{9,22,23}

CASE EXAMPLES

Beta-blocker therapy post-myocardial infarction

An early example of how RWD can lead to practice change

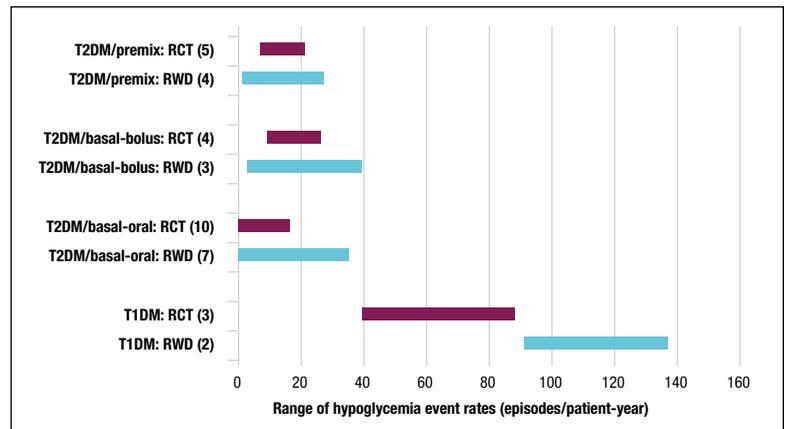
involves the use of beta-blockers in patients who had experienced a myocardial infarction (MI). In the 1990s, Medicare sponsored the Cooperative Cardiovascular Project, which analyzed medical records of >200,000 people who had experienced an MI. The analysis showed that patients who had vs those who had not received a beta-blocker following an MI, including those with a contraindication to beta-blocker therapy, experienced a substantial reduction in mortality (relative risk, 0.67; 95% CI, 0.62 to 0.72).²⁴ These results supported similar evidence from some earlier clinical trials, helping to make beta-blocker therapy standard care in patients with an MI.

Insulin glargine 300 units/mL

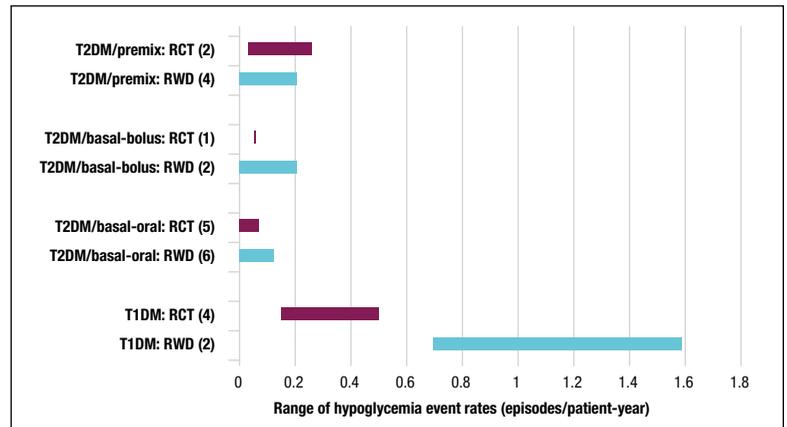
Differentiate Gla-300 clinical and Economic in real-world Via EMR Data study (DELIVER 2) was a retrospective analysis of the Predictive Health Intelligence Environmental database.²⁵ The purpose of the analysis was to evaluate clinical outcomes of patients with T2DM currently using basal insulin who were then switched to either insulin glargine, 300 units/mL, or other basal insulins in real-world practice. (The reason for the switch is not included in the dataset.) Patients who switched to insulin glargine, 300 units/mL, (N = 2196) or other basal insulins (N = 3837) were compared following 1:1 ratio propensity score matching (N = 1819 in each cohort). From a baseline of 8.95% and 8.93%, HbA_{1c} reductions were comparable in both cohorts (−0.51% vs −0.51%, respectively; *P* = .928). At 6 months, fewer patients who switched to insulin glargine, 300 units/mL, experienced hypoglycemia compared with those who switched to other basal insulins (15.4% vs 18.1%, respectively; *P* = .015). After adjusting for baseline hypoglycemia, switching to insulin glargine, 300 units/mL, was associated with a significantly lower rate of hypoglycemia compared with switching to other basal insulins (difference between least squares means of 0.15 events/patient-year; *P* = .041 favoring insulin glargine, 300 units/mL). Incidence and event rates of hypoglycemia requiring hospitalization or emergency care also were significantly lower with insulin glargine, 300 units/mL, contributing to an overall savings of \$1439 per patient per year. In a real-world setting, switching to insulin

FIGURE Hypoglycemia event rates in randomized controlled trials vs real-world data studies²⁶

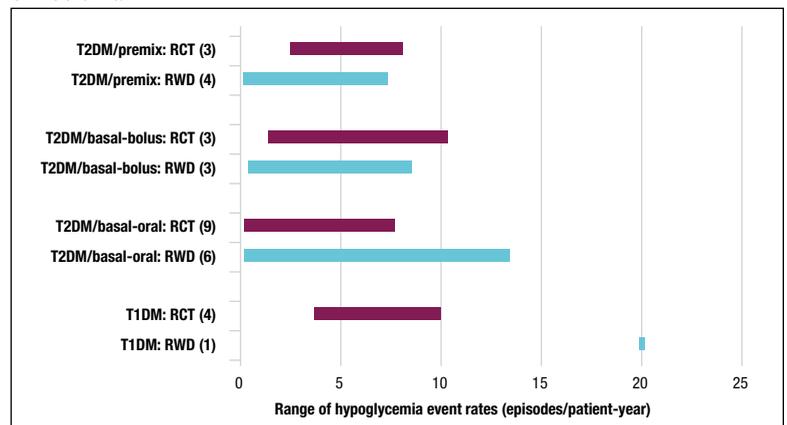
a. Nonsevere/confirmed



b. Severe



c. Nocturnal



Abbreviations: RCT, randomized controlled trial; RWD, real-world data; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The number of studies in each subgroup is shown in parentheses.

Reprinted by permission from Springer Nature, Diabetes Therapy: Research, Education, and Treatment of Diabetes and Related Disorders, Hypoglycemia event rates: A comparison between real-world data and randomized controlled trial populations in insulin-treated diabetes., Elliott L, Fidler C, Ditchfield A, Stissing T, Copyright (C) 2016.

glargine, 300 units/mL, was associated with a significantly lower risk of hypoglycemia, including hypoglycemia associated with hospitalization or emergency department visit, than switching to other basal insulins, while delivering comparable glycemic control.

Hypoglycemia in insulin-treated diabetes

The frequency of hypoglycemia in patients with type 1 diabetes mellitus (T1DM) or T2DM has been compared in real-world settings vs RCTs.²⁶ A structured literature review of studies from 2010 to 2014 identified 6 involving patients with T1DM (4 RCTs, 2 RWDs) and 25 involving patients with T2DM (15 RCTs, 10 RWDs). The minimum study duration was 26 weeks for RCTs; there was no minimum for RWD studies. A minimum of 400 patients were required in each study. Case study reports and database studies were excluded from the RWD studies, the latter because the investigators felt they do not provide an accurate representation of overall hypoglycemia.

Higher rates of hypoglycemia generally were observed in RWD studies vs RCTs in patients with T1DM or patients with T2DM treated with basal-bolus or basal-oral therapy, although there was some overlap in the range of reported event rates (FIGURE, see previous page).²⁶ These findings indicate that the true burden of hypoglycemia might be underestimated in RCTs, probably resulting from carefully selected patients, carefully titrated dosing using a treat-to-target approach, closer supervision and blood glucose monitoring, and typically shorter duration. In interpreting these results, one must keep in mind that RWD studies also might underestimate the true burden of hypoglycemia because blood glucose monitoring from self-monitoring or continuous glucose monitoring might not be available or collected as frequently as occurs in RCTs.

IMPLICATIONS OF REAL-WORLD DATA

RWE based on RWD is gaining importance as a complement to randomized controlled trials. The primary attribute that distinguishes RWE from other kinds of evidence is the clinical care and community settings as opposed to research-intensive or academic environments. The premise is that real-world data can be collected from multiple sources that include extremely large samples of patients in real-world clinical practice, then appropriately analyzed and evaluated to yield RWE that can be generalized to a broader population of patients treated with the medications, devices, or other interventions. This may include patient subgroups often excluded in RCTs, eg, older patients, children, those with renal impairment, etc. Therefore, RWE likely could facilitate improved management of patients. Barriers and limitations

to RWE studies exist, however. But as these are increasingly addressed, RWE likely will have wider application in clinical research, regulatory review and approval, postapproval outcomes, and post-marketing surveillance. ●

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Weight Management for Patients with Type 2 Diabetes: Impact of Newer Antidiabetic Therapies on Body Weight

Carlos Campos, MD, MPH, CDE

CASE STUDY

JB is a 61-year-old, non-Hispanic Caucasian man diagnosed with type 2 diabetes (T2D) in June 2015. His body mass index (BMI) at diagnosis was 31.* To control his blood glucose, JB was prescribed metformin combined with a sulfonyleurea, which has reduced his fasting plasma glucose and glycated hemoglobin (HbA_{1c}) levels. He received dietary advice to help him lose weight; however, after initial success, JB has been unable to keep the weight off in the long term. Although he felt well, he also had elevated blood cholesterol and is receiving a statin.

In March 2018, JB attended a scheduled clinic appointment. His HbA_{1c} was 7.6% and his BMI was 30.8. JB tells you he has read that some diabetes medicines can cause weight gain, and he is concerned that the drugs he is taking are making it more difficult for him to lose weight.

What advice would you give him, and would you make any changes to his diabetes medications?

*Calculated as weight in kilograms divided by height in meters squared.

Note: This is a hypothetical case study for educational purposes.

INTRODUCTION

Obesity is linked to insulin resistance, development of metabolic syndrome, and progression to diabetes, as well as increased risk of morbidity, including cardiovascular disease,

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and mortality in patients with T2D.¹⁻³ Even modest weight loss (~5% of body weight) in overweight or obese patients with T2D has been shown to improve blood glucose control as well as blood pressure and lipid levels, delay progression of diabetes, and reduce the need for glucose-lowering medication.⁴⁻⁷ Consequently, guidelines from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend that weight loss should be considered for any patient with T2D who is overweight or obese.^{4,5} However, patients with diabetes who are overweight or obese often struggle to achieve sustained weight loss with lifestyle modification alone. In the opinion of the author, this is because the body has a goal to return to its maximal weight, and these patients must constantly work against this goal to first reduce and then maintain a lower weight.

Maintenance of weight reduction was assessed in the Action for Health in Diabetes (Look AHEAD) study, which compared intensive lifestyle intervention with usual care in a large cohort of overweight and obese patients with T2D.^{6,7} Although weight loss was significantly greater in the group receiving intensive intervention at all time-points up to 8 years, weight loss started to drop off after the first year, even in this group. At 1 year, there was a mean 8.6% reduction from baseline in weight in the intensive lifestyle intervention group, declining to 4.7% at year 8.^{6,7} The tendency for weight regain is likely to be at least partly due to physiological adaptations that favor weight gain in response to a reduced-calorie and reduced-fat diet.⁸ Therefore, primary care physicians should consider the psychological implications associated with advising their patients on losing weight and ensure that realistic expectations are set. Physicians should also encourage improved health and lifestyle rather than making weight loss the main focus.

Moreover, for many patients with T2D, lifestyle modifications are unlikely to be enough to achieve glycemic targets, and guidelines recommend that pharmacotherapy should also be employed to improve glycemic control.^{4,5} With a wealth of different agents available, it is now possible to tailor therapy to the needs of the individual. This is particu-

larly important for patients who are struggling to lose weight, because several commonly used antidiabetic medications can actually promote weight gain: namely, insulin, sulfonylureas, and thiazolidinediones.^{4,5,9} In addition, concomitant medications may also be associated with an increase in body weight. For example, antipsychotic and antiepileptic medications, including some that are used to manage diabetic neuropathy, may contribute to an increase in weight.¹⁰⁻¹² Furthermore, other medications commonly prescribed in primary care, such as beta-blockers and selective serotonin reuptake inhibitors, may also lead to weight gain.^{13,14}

The aim of this article is to review the impact on body weight of new classes of antiglycemic therapies and provide practical guidance on the most appropriate strategies for glycemic control in the overweight or obese patient with T2D.

EFFECT OF TYPE 2 DIABETES THERAPIES ON BODY WEIGHT

Therapies associated with weight gain

Sulfonylureas and thiazolidinediones effectively reduce blood glucose and HbA_{1c} levels, and may be used as add-on therapy in patients with T2D who do not achieve targets with metformin alone. However, they are also associated with weight gain.⁹ In addition, insulins, which may be used in patients with T2D who require additional control, are also associated with weight gain. For example, in the United Kingdom Prospective Diabetes Study (UKPDS), insulin therapy was associated with a 4-kg increase in weight, and sulfonylureas with an increase of 1.7 to 2.6 kg, over 10 years.¹⁵ Similar results were observed in other prospective studies involving patients with T2D,^{16,17} with treatment combinations containing insulin associated with a mean 3.2-kg increase in weight; thiazolidinediones, with a 3.1-kg increase; and sulfonylureas, with a 0.7-kg increase, over 5 years.¹⁶ Moreover, weight gain can be additive when different agents are used. Pioglitazone was associated with an increase in body weight of 0.9 to 2.6 kg, depending on dosage, in monotherapy studies (16 to 26 weeks), with larger increases seen when used in combination with insulin (2.3 to 4.1 kg) and sulfonylureas (2 to 4.1 kg).¹⁷ Insulin acts through a number of mechanisms, including lowering blood glucose levels by increasing uptake of glucose into fat and muscle cells.⁹ Sulfonylureas promote the release of insulin from beta cells in the pancreas. These mechanisms of action by insulin and sulfonylureas improve glycemic control, but can also lead to weight gain by decreasing excretion of glucose in the urine (glycosuria).⁹ In addition, insulin and sulfonylureas are associated with a risk of hypoglycemia, and patients concerned about this may increase food intake as a protective

strategy.⁹ Unlike other insulins, insulin detemir is associated with modest weight loss (~0.5 kg over 26 weeks) rather than weight gain.¹⁸ Weight increase with pioglitazone may result from increases in both water retention and fat storage.¹⁷

Therapies associated with weight neutrality or loss

Metformin is usually the first-line treatment option for T2D, due to its well-established efficacy and safety profile determined through decades of use in Europe and since 1995 in the United States.^{5,19} Metformin is generally considered to have a neutral effect on weight,⁹ although in the Diabetes Prevention Program Outcomes Study, it was found to induce weight loss over the trial period (2 years; mean 2.1% decrease from baseline) and the open-label extension period (7 to 8 years; mean 2% decrease from baseline),²⁰ most likely resulting from reduced food intake.²¹ However, if HbA_{1c} targets are not met with lifestyle modifications and metformin alone, additional antihyperglycemic agents may be required.

Newer therapies for T2D, including glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and amylin mimetics, may be considered for overweight and obese patients because they provide glycemic control while having either a neutral effect on body weight or an overall weight reduction effect.^{9,16,17,20,22-28} The effects of the various therapies on body weight are summarized in the **TABLE**.

GLP-1 is an incretin hormone that is secreted from the intestinal L cells and is involved in increasing glucose-dependent insulin secretion as well as the regulation of food intake.^{9,22,29} Native GLP-1 is rapidly (half-life, <2 min) degraded in the body by the enzyme DPP-4.²⁹ Injectable analogs of GLP-1 (GLP-1 receptor agonists) used for T2D treatment are resistant to degradation by DPP-4.²⁹ These include albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide.^{22,30,31} GLP-1 receptor agonists reduce HbA_{1c} by up to 1.9% and also induce weight loss by up to 3.7 kg by promoting reduced food intake^{9,22,30} (in these studies, background medications differed and may have contributed to weight changes). GLP-1 receptor agonists have recently been shown to reduce the risk of cardiovascular events and all-cause mortality in patients with T2D at high risk of cardiovascular events while they were taking standard therapy.³² The most common side effects associated with GLP-1 receptor agonists include gastrointestinal effects, such as nausea, diarrhea, and vomiting.^{19,30}

Decreased food intake with GLP-1 receptor agonists is thought to result from their effects in inhibiting gastric emptying and promoting a feeling of satiety⁹ via a variety of central effects in the hypothalamus. Animal studies have

TABLE Type 2 diabetes therapies and their effects on body weight

Associated with weight gain	Weight-neutral or modest weight decrease	Associated with weight loss
Insulin (3.2-kg increase over 5 years ¹⁶ ; 4-kg increase over 10 years ¹⁵)	MET (~2-kg reduction over 10 years ²⁰)	GLP-1RA (~1- to 4-kg reduction over 26–52 weeks ^{9,22})
SU (0.7-kg increase over 5 years ¹⁶ ; 1.7- to 2.6-kg increase over 10 years ¹⁵)	DPP-4i (overall considered weight-neutral ^{22,23})	SGLT-2i (~2- to 4-kg reduction over 26–52 weeks ^{9,24})
TZD (3.1- to 4-kg increase over 3–5 years ^{16,17})	AGI (no effect ^{25,26} or ≤1.2-kg reduction ²⁷)	Amylin analog (~1- to 2-kg reduction over 26–52 weeks ²⁸)

Abbreviations: AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

indicated that weight loss with GLP-1 receptor agonists is mediated by the arcuate nucleus in the hypothalamus, which is involved in energy intake and expenditure.^{29,33} A separate pathway for increased energy expenditure may involve stimulation of the ventromedial nucleus in the hypothalamus, resulting in increased metabolism in brown adipose tissue.^{29,34} Other proposed mechanisms for weight loss with GLP-1 receptor agonists include increased metabolism in white adipose tissue and neuroprotective effects, including reduction of hypothalamic inflammation induced by a high fat diet.²⁹ Moreover, treatment with a GLP-1 receptor agonist has been shown to inhibit the increase in leptin receptors normally seen during weight loss, resulting in increased circulating levels of leptin, which acts to reduce appetite.³⁵ It should be noted, however, that despite the beneficial effects of the GLP-1 receptor agonists on body weight, they are not approved for weight reduction in patients with T2D.⁴ In 2010, a higher dosage (3 mg daily) of liraglutide was approved by the US Food and Drug Administration (FDA) in combination with a reduced-calorie diet and increased physical exercise for weight management.³⁶ However, this dosage is not indicated for the treatment of T2D (usual dosage in T2D is 1.2 mg daily, to a maximum of 1.8 mg daily).³⁶

SGLT-2 mediates reabsorption of filtered glucose in the kidneys.³⁷ There are several marketed SGLT-2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, and the recently FDA-approved ertugliflozin. These agents are administered orally and promote increased glycosuria, thereby lowering blood glucose.³⁷ SGLT-2 inhibitors are associated with HbA_{1c} reductions of 0.5% to 1%, with additional beneficial effects in patients with T2D, including reductions in blood pressure (placebo- or comparator-corrected decreases: systolic, up to -7 mm Hg; diastolic, up to -3 mm Hg) and body weight (~2 to 4 kg).^{9,24,38} In addition, cardiovascular outcomes studies have shown that, like the GLP-1 receptor agonists, SGLT-2 inhibitors are associated with a reduction in cardiovascular events^{39,40} and have also reduced all-cause mortality in patients with T2D at high risk of cardiovascular events.⁴⁰

Side effects associated with SGLT-2 inhibitors include genital mycotic infection and urinary tract infection.^{9,19,38}

Weight loss associated with SGLT-2 inhibitor therapy is considered to result from increased glucose excretion. However, the typical observed weight loss is less than expected, considering the number of calories excreted.⁴¹ It is thought that glycosuria may promote increased food intake, and combining an SGLT-2 inhibitor with a calorie-restricted diet may provide greater weight loss.⁴¹

DPP-4 inhibitors (including linagliptin, saxagliptin, and sitagliptin) are orally administered agents that reduce DPP-4-mediated degradation of GLP-1, resulting in an increase in endogenous GLP-1 levels.²² Glycemic efficacy of DPP-4 inhibitors (HbA_{1c} reductions of 0.5% to 1%) is typically less than that of GLP-1 receptor agonists.^{22,23} Overall, DPP-4 inhibitors are considered to have a neutral effect on weight.^{22,23} Compared with GLP-1 receptor agonists, DPP-4 inhibitors are associated with fewer gastrointestinal symptoms.²²

Alpha-glucosidase inhibitors (including acarbose and miglitol) delay breakdown of carbohydrates in the small intestine, and lower postprandial glucose and insulin levels.²⁷ HbA_{1c} reductions are typically in the region of 0.5% to 0.8%.^{25–27} Clinical trials have reported no or a moderate (≤1.2-kg reduction) effect on body weight.^{25,27} A reduction in BMI of 0.17 was reported in a meta-analysis of alpha-glucosidase inhibitor trials; however, no significant effect on body weight was found.²⁶ Gastrointestinal effects are typically the most common side effects reported with these drugs.

The pancreatic beta-cell hormone amylin is involved in regulation of food intake, presenting a therapeutic strategy for T2D. The injectable, pramlintide, is currently the only amylin analog available. HbA_{1c} reductions of 0.1% to 0.6% and weight loss ranging from 1 to 2 kg in patients with T2D have been reported with pramlintide.²⁸

GUIDELINE RECOMMENDATIONS FOR BODY WEIGHT MANAGEMENT IN TYPE 2 DIABETES

Overall, guidelines from the ADA and AACE/ACE are similar

in their approach to treatment of patients with T2D who are overweight or obese; however, there are several differences in the proposed treatment algorithms, as noted in the text that follows.

Glycemic targets and treatment algorithms for improving glycemic control

ADA guidelines recommend a HbA_{1c} target of <7% for nonpregnant adults with T2D or a HbA_{1c} target of <6.5% for those who can achieve this target without adverse effects or significant hypoglycemia.⁴² AACE/ACE guidelines suggest an optimal HbA_{1c} target of ≤6.5%; if this is not achievable without adverse outcomes (eg, in patients with concurrent serious illness at risk of hypoglycemia), higher targets should be employed.⁵

The treatment algorithm in the 2018 ADA guidelines suggests 3 starting points for therapy (in addition to lifestyle modification), depending on HbA_{1c} at diagnosis: initiating metformin if HbA_{1c} is <9%; initiating dual therapy with metformin and another agent if HbA_{1c} is ≥9%; and moving directly to metformin plus insulin therapy if HbA_{1c} is ≥10%.¹⁹ If the target is not reached on monotherapy or dual therapy, one of the following treatment options can be considered: sulfonylurea, SGLT-2 inhibitor, thiazolidinedione, GLP-1 receptor agonist, DPP-4 inhibitor, or basal insulin. Rather than stating an order of preference for initiating the additional agents, ADA guidelines leave this to the physician to decide, based on drug-specific effects and patient factors, such as glucose-lowering efficacy, the individual's risk of hypoglycemia, effects on weight, cardiovascular effects, cost, preferred route of administration (oral or subcutaneous injection), and potential adverse effects.¹⁹

In the 2018 AACE/ACE guidelines, in addition to lifestyle therapy, patients with HbA_{1c} <7.5% should be started on monotherapy; those with HbA_{1c} ≥7.5%, on dual or triple therapy; and those with HbA_{1c} >9% and with symptoms at entry, on insulin (with or without an additional agent). The 2018 AACE/ACE guidelines state that the choice of therapies should be individualized.⁵ However, in contrast to ADA guidelines, recommendations are given on the choice of therapeutic options, which are listed in hierarchical order based on strength of recommendations. Metformin is the preferred agent for initiating monotherapy.⁵ For dual therapy, metformin should be used plus another agent, in the following order of preference: GLP-1 receptor agonist, SGLT-2 inhibitor, DPP-4 inhibitor, thiazolidinedione, basal insulin, colesevelam (a bile acid sequestrant), bromocriptine (a dopamine-receptor agonist), alpha-glucosidase inhibitor, and, last, sulfonylurea. Recommendations for triple therapy are similar, except that DPP-4 inhibitors come after basal insulin in order of preference.⁵ Caution is advised with regard

to the use of thiazolidinediones, sulfonylureas, and basal insulin, due to their potential for adverse effects.⁵

Recommended approaches for managing weight loss

Both ADA and AACE/ACE guidelines agree that weight loss management should be employed if patients are overweight or obese, due to the known benefits of weight reduction (eg, improved glycemic control, lipid levels, and blood pressure).^{4,5}

The 2018 ADA recommendations for overweight or obese patients are as follows⁴: At each routine visit, BMI should be calculated. A BMI ≥25 to 29.9 is classified as overweight (≥23 to 27.4 for patients of Asian origin); a BMI above these levels is classified as obesity.^{43,44} All patients with BMI ≥25 (≥23 for patients of Asian origin) who are ready to lose weight should receive advice on lifestyle modification, including dietary, behavioral, and physical exercise recommendations. Weight-loss medications may be considered for selected patients with BMI ≥27, and bariatric surgery may be considered for those with BMI ≥30 (27.5 for patients of Asian origin). Medications approved for weight loss include phentermine, orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide 3 mg daily.⁴

AACE/ACE guidelines are slightly different from ADA guidelines; they propose a “complications-centric” model for weight management, in which weight-loss medications or surgery may be considered for patients with elevated BMI if additional complications (such as diabetes) are present.^{5,45} Addition of weight-loss medication may be considered for patients with BMI ≥27 and complications, and for those with BMI ≥30 regardless of the presence of complications. Bariatric surgery can be used for adults with BMI ≥35 and comorbidities, particularly if therapeutic goals have not been reached using other treatments.

Both ADA and AACE/ACE guidelines highlight that the choice of antidiabetic medications for patients with T2D should involve consideration of the effect of these agents on the patient's weight (**TABLE**).^{4,5} From this perspective, therapies that have a weight-neutral or weight-reducing effect (metformin, GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, alpha-glucosidase inhibitors) are preferred over those that promote weight gain (sulfonylureas, insulin, thiazolidinediones).^{4,5,19} However, the physician should also consider the HbA_{1c} target: if this is not reached with metformin plus 2 other glucose-lowering agents, insulin may need to be employed. The side-effect profiles of the chosen agents should also be considered.^{5,19} Recommendations for weight management in patients with T2D, based on the ADA and AACE/ACE guidelines, are summarized in the **FIGURE**.

FIGURE Approaches for glycemic and weight control for patients with type 2 diabetes, based on ADA and AACE/ACE guidelines^{4,5,19,42}

Guideline:	ADA (2018)	AACE/ACE (2018)	
HbA _{1c} goal:	<7% ^a	≤6.5% ^b	
All patients to receive lifestyle therapy			
Weight-loss program if BMI:	≥25	≥25	Order of preference (based on AACE/ACE recommendations) for dual/triple therapy based on effects on body weight:
Weight-loss medication ^c if BMI:	≥27	≥27	
Bariatric surgery ^c if BMI:	≥30	≥35	
Pharmacotherapy (if HbA _{1c} goal not met with lifestyle therapy alone)			
Monotherapy (MET) Initiate if entry HbA _{1c} :	<9%	<7.5%	Weight loss: GLP-1RA SGLT-2i Weight neutral: DPP-4i AGI Weight gain: TZD Basal insulin SU
If goal not met by 3 months, move to dual therapy			
Dual therapy (MET + 1 agent) Initiate if entry HbA _{1c} :	≥9%	≥7.5%	
If goal not met by 3 months, move to triple therapy			
Triple therapy (MET + 2 agents) Initiate if entry HbA _{1c} :	N/A	>9% (without symptoms)	
If goal not met by 3 months, move to insulin therapy			
Insulin therapy (MET and/or 1 agent) Initiate if entry HbA _{1c} :	≥10% (or BG ≥300 mg/dl, or with symptoms)	>9% (with symptoms)	

Abbreviations: AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; ADA, American Diabetes Association; AGI, alpha-glucosidase inhibitor; BG, blood glucose; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; MET, metformin; N/A, not applicable; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

^aGoal <6.5% for patients without adverse treatment effects or significant hypoglycemia.

^bGoal >6.5% in cases of serious illness and at risk of hypoglycemia.

^cDepending on patient factors.

BMI units are kg/m². Lower BMI thresholds may be appropriate for some ethnicities (eg, patients of Asian origin).

2018 ADA guidelines do not make recommendations about starting with triple therapy.

CASE STUDY FOLLOW-UP

JB’s primary care physician should inform him that although metformin is weight-neutral, sulfonylureas are associated with weight gain. Because JB’s HbA_{1c} level (7.6% at his most recent clinic appointment) has not met the target of ≤7.5% (according to 2018 AACE/ACE guidelines), JB’s physician should consider escalating him to triple therapy. The additional therapeutic agent should be one that is associated with weight loss, such as a GLP-1 receptor agonist or an SGLT-2 inhibitor. According to current guidelines, potential for side effects should also be considered. JB should therefore be advised to visit the clinic in 3 months.

If triple therapy improves JB’s HbA_{1c} level but does not lead to weight loss by the next clinic visit, weight-loss medication

could also be considered. If triple therapy does not control the HbA_{1c} level, JB remains at risk of microvascular and macrovascular complications of diabetes; injectable insulin therapy should be considered.

Note: This is a hypothetical case study for educational purposes.

IMPLICATIONS FOR PRIMARY CARE

T2D remains a significant cause of morbidity and mortality in the United States. Most patients with T2D are overweight or obese, and a weight reduction of even 5% to 10% can have significant health benefits, improving glycemic control, potentially reducing the risk of cardiovascular events, and also reducing pressure on weight-bearing limbs. Primary care

physicians can play a key role both in counseling patients on the benefits of weight reduction and in helping them to find the best approach for them to lose weight. Physiological processes that make the patient's own body want to return to its maximal weight mean that it can be very difficult for a patient to sustain weight loss in the long term. Specific weight-loss medication and bariatric surgery should be considered in a minority of motivated patients if they are really struggling to keep the weight off. Although none of the agents approved for the management of blood glucose levels are indicated to help patients with T2D lose weight, several of the available agents are either weight-neutral or induce weight loss and should be considered when selecting the most appropriate management strategy in overweight or obese patients with T2D. ●

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Managing Patient Pain: A Focus on NSAID OTC Formulations for Relief of Musculoskeletal and Other Common Sources of Pain

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Most Americans use over-the-counter (OTC) analgesics for short-term relief of mild-to-moderate pain. The literature demonstrates the efficacy of these agents through meta-analyses, comparator studies (primarily at prescription dosages), and through trials that have assessed the efficacy of agents at OTC dosages for the management of a variety of common conditions. This article will provide education to better enable clinicians to counsel their patients regarding the use of OTC analgesics and help them appropriately select agents, based on such factors as dosing, duration of action, condition for which pain relief is required, and pharmacologic profile. The safety of these agents has been extensively covered, as have issues that may result from off-label long-term use; therefore, we will not include that information here.

Many Americans experience frequent pain for which OTC pain relievers are commonly used, with demonstrated

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efficacy. A 3-month survey of adults revealed that, during that time, 29% of participants experienced low back pain; 17%, migraine or severe headache; 15%, neck pain; and 5%, face or jaw pain.¹

The importance of OTC analgesics is evidenced by the fact that their sales constitute 16.5% of the US nonprescription drug market.² In 2017, sales of OTC analgesics totaled more than \$4.1 million.³ 86% of Americans believe that responsible use of OTC medications helps lower the cost of health care.⁴ A poll of more than 2000 US adults revealed that approximately 30% regularly use OTC analgesics for arthritis or other pain management needs.⁵

The take-away message for clinicians is that consumers use these products regularly to relieve minor aches and pains due to headache, toothache, musculoskeletal pain, menstrual pain, fever, common cold, and influenza. They believe that they are effective and contribute to their health, well-being, and quality of life.⁶

Based on widespread use of OTC analgesics among consumers and the high level of consumer confidence in these agents, clinicians should be prepared to discuss OTC analgesic use with their patients, both to ensure that patients use these agents safely (see “Safety of OTC nonsteroidal anti-inflammatory drugs [NSAIDs] and analgesic agents,” page S68) and because these agents differ significantly; they are not interchangeable as treatments for all pain. Some have shown greater efficacy in the management of specific pain syndromes but show limited use for other ailments.

Family physicians have an opportunity to help patients use these agents properly, select them appropriately, use them at the correct dosage, understand common side effects, and be aware of any potential drug-drug interactions.⁵ Clinicians in practice often find that patients believe OTC formulations to be less effective than the same drugs provided in prescription formulations. They may also believe that OTC formulations are safer than prescription products because they are available without a prescription.^{7,8}

Safety of OTC nonsteroidal anti-inflammatory drugs and analgesic agents

Gastrointestinal risk factors represent an issue of concern; before recommending a nonsteroidal anti-inflammatory drug (NSAID), clinicians should consider patient risk factors, including longer duration of NSAID use, age 60 years or older, history of peptic ulcer disease, and general frailty, as well as alcohol use and concomitant use of corticosteroids and anti-coagulants.¹ Reports in the medical literature have shown a significant decrease in hospitalization associated with NSAID use, attributable to widespread use of proton pump inhibitors (PPIs), better NSAID prescribing, and decreased prevalence of *Helicobacter pylori* infection. Gastroprotective therapy should be considered with administration of a nonselective NSAID; should dyspepsia occur, PPI co-therapy should be introduced, along with either dosage reduction or a switch to a different NSAID.² It should be noted that PPIs do not protect the lower intestine, which can ulcerate. Naproxen has been cited as the best option in patients with high cardiovascular risk and low or moderate gastrointestinal risk.^{2,3}

Topical and oral NSAIDs have been compared in studies of patients with rheumatoid arthritis. Topical agents showed reduced risk of cardiovascular events, compared with oral agents.⁴

At a joint meeting on April 24 and 25, 2018, the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the US Food and Drug Administration met and reviewed safety data from the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, which evaluated the safety of celecoxib and prescription ibuprofen and naproxen in 24,081 patients. Cardiovascular safety was similar among all 3 agents, with noninferiority noted for celecoxib. The participants discussed findings related to a possible interaction between NSAIDs and low-dose aspirin, based on in vitro platelet aggregation studies; however, the committees concluded that no impact has been demonstrated clinically, and therefore questioned the overall clinical relevance of the findings.⁵

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Clinicians should be able to help patients select the most appropriate OTC agent for specific conditions, using the lowest effective dosage for the minimum duration of time as part of an overall pain management plan for appropriate patients.

EFFICACY OF OTC NSAIDs

NSAIDs and other analgesics, available as OTC formulations, as well as prescription pain relievers, have been evaluated sufficiently for experts to develop recommendations for use (TABLE 1).¹ Significantly, acetaminophen, ibuprofen, and naproxen show sufficient evidence for first-line treatment of acute mild-to-moderate pain.⁹⁻¹²

MECHANISMS OF ACTION

Specific NSAIDs and acetaminophen differ significantly in terms of dosing, half-life, and duration of effect, with implications for effectiveness in addressing specific patient needs for pain relief.

Acetaminophen

Acetaminophen has a mechanism of action similar to that of NSAIDs, particularly selective cyclooxygenase-2 (COX-2) inhibitors. Generally, it provides weaker analgesic activity than NSAIDs or selective COX-2 inhibitors.¹³ It is thought to inhibit cyclooxygenase-1 (COX-1) and COX-2 by metabolizing their peroxidase function. It inhibits phenoxyl radical formation from an essential tyrosine residue and thus inhibits cyclooxygenase activity of COX-1 and COX-2 and prostaglandin synthesis. Acetaminophen shows selectivity for inhibition of the synthesis of prostaglandins and related factors in the presence of low levels of arachidonic acid and peroxides. It demonstrates little activity with high levels of arachidonic acid and peroxides. For these reasons, it does not suppress the severe inflammation of conditions such as rheumatoid arthritis and acute gout, but does inhibit inflammation associated with tooth extraction.¹⁴

Acetaminophen is absorbed rapidly and distributed quickly throughout the body, with peak plasma concentration attained within 30 to 60 minutes; delay may occur with food intake.¹⁴ With repeated doses, plasma concentration reaches steady-state level in 10 to 15 hours. Higher steady-state levels are not achieved with continued dosing. These results are consistent with the short elimination half-life of 2 to 3 hours and the recommended dosing interval of 4 to 6 hours.¹⁵

Over-the-counter NSAIDs

NSAIDs share similar mechanisms of action, inhibiting the synthesis of prostaglandins, fatty acid derivatives that are widely distributed in tissues and are involved in the production of pain, fever, and inflammation.¹⁶ NSAIDs achieve these

TABLE 1 Key recommendations for practice

Recommendation	Rating
Acetaminophen, ibuprofen, and naproxen are good, effective first-line treatments for mild-to-moderate acute pain	A ⁹⁻¹²
Selective COX-2 NSAIDs are second-line medications for mild-to-moderate pain, with similar efficacy to nonselective NSAIDs but at increased cost	A ¹¹

Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

A = consistent, good-quality, patient-oriented evidence.

Adapted from: Blondell et al. *Am Fam Physician*. 2013;87:766-772.¹

effects through inhibition of the cyclo-oxygenase enzymes. Their demonstrated anti-inflammatory and analgesic activities stem from effects on prostaglandins that sensitize tissues to pain and inflammation-producing mediators. It is assumed that, in the presence of infectious states, antipyretic activity also results from inhibition of prostaglandin synthesis.¹⁶

Aspirin is rapidly hydrolyzed, primarily in the liver, to salicylic acid. This is conjugated with glycine, thus forming salicylic acid, and glucuronic acid. Both are excreted primarily by the kidneys. Because of rapid hydrolysis, plasma concentrations of aspirin rarely exceed 20 µg/mL at ordinary therapeutic dosages. The peak salicylate level for uncoated aspirin occurs in about 2 hours but is delayed by enteric coating. The plasma half-life of aspirin is approximately 15 minutes; however, when metabolized to salicylate, half-life increases, particularly with higher dosages.¹⁷

Ibuprofen features a linear blood level dose-response relationship with single doses up to 800 mg. In chronic conditions, a therapeutic response may be observed within a few days; most often, it occurs by 2 weeks.¹⁸ After a satisfactory response is achieved, the clinician should review the dosage and adjust as appropriate. For mild-to-moderate pain, recommended dosing is 400 mg every 4 to 6 hours, as necessary. Trials have shown that exceeding the recommended dosage does not increase efficacy.¹⁸

Naproxen, in low dosages (≤660 mg/d naproxen sodium), features analgesic and antipyretic actions, although a full anti-inflammatory activity response requires higher dosages. Within 20 minutes of intake, significant plasma levels and initiation of pain relief occur. Rapidly and completely absorbed from the gastrointestinal tract, naproxen, at 440 mg, achieves peak plasma level (C_{max}) of 53 to 66 g/mL approximately 1 to 1.5 hours after intake. Food consumption may delay absorption of caplets and will delay absorption of liquid gels. Dose-linear kinetics are observed with use of as much as 550 mg twice daily. Plasma concentrations of the active component, unbound circulating naproxen (about 10 ng/mL), provide analgesic effects; they correspond to a total naproxen plasma concentration of 15 µg/mL. The volume of distribution of naproxen is small, about 0.1 L/kg of

body weight. Within 2 days, steady-state concentrations are observed, with no significant accumulation. More than 99% of circulating naproxen is albumin-bound.¹⁶

NSAIDS AND ACETAMINOPHEN FOR PAIN RELIEF ASSOCIATED WITH COMMON PAIN SYNDROMES

Meta-analyses and comparator studies show evidence for effectiveness of NSAIDs and acetaminophen.

NSAIDs and acetaminophen are somewhat effective in the management of common pain syndromes, such as osteoarthritis. This chronic condition has been estimated to carry an estimated lifetime risk of 45%,¹⁹ underscoring the importance of clinician counseling concerning pain associated with this condition and the need to provide strategies for pain relief. A 2018 meta-analysis¹⁹ investigated the comparative effectiveness of nonsurgical treatment—NSAIDs, acetaminophen, and intra-articular (IA) options (corticosteroids, platelet-rich plasma, and hyaluronic acid [HA])—for management of knee osteoarthritis. In their review of 56 studies, most of which were high-quality, the authors assessed the effect of treatment on pain, via conversion to a 0 to 100 visual analog scale, and function, assessed through conversion to a 0 to 100 Western Ontario and McMaster Universities Osteoarthritis Index.

All active treatment regimens demonstrated significant improvement in pain compared with placebo. For function, only naproxen showed clinically significant improvement. Neither IA interventions nor options available OTC (ibuprofen and acetaminophen) showed improvement over placebo. The authors concluded that naproxen was the most effective single treatment and may produce the greatest likelihood of improvement of both pain and function when combined with an IA corticosteroid. They noted that, although caution should accompany the routine use of NSAIDs in chronic arthritic conditions, evidence indicates that naproxen is less likely than other NSAIDs to be associated with adverse cardiovascular events. Furthermore, the meta-analysis supports the use of naproxen as the conservative treatment of choice, most likely to improve pain and function associated with knee osteoarthritis, followed by IA interventions, ibuprofen, and celecoxib (TABLE 2¹⁹). The authors speculate

TABLE 2 Improvements in pain, function, and pain and function associated with common interventions for knee osteoarthritis¹⁹

Rank	Outcomes		
	Pain and Function	Pain	Function
1	Naproxen	Corticosteroid	Naproxen
2	Corticosteroid	Ibuprofen	Diclofenac
3	IA PRP	IA PRP	Celecoxib
4	Ibuprofen	Naproxen	Ibuprofen
5	Celecoxib	Celecoxib	IA PRP
6	Diclofenac	HA	Corticosteroid
7	HA	Diclofenac	HA
8	IA placebo	IA placebo	Acetaminophen
9	Acetaminophen	Acetaminophen	IA placebo
10	Oral placebo	Oral placebo	Oral placebo

Abbreviations: HA, hyaluronic acid; IA, intra-articular; PRP, platelet-rich plasma.

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that the effect of NSAIDs specifically on function may result from the fact that knee-joint effusion contributes to limited knee-joint function; impaired function often is secondary to inflammatory factors that lead to joint effusion. They note that the limited benefit of acetaminophen for improving pain and function—combined with the potential for hepatic toxicity—make this agent a lower-level treatment choice.¹⁹ A recent Cochrane review of IA steroids as a treatment for knee osteoarthritis showed no benefit compared with placebo.²⁰

Similar findings were reported in a 2015 report seeking to establish rational treatment algorithms for management of knee osteoarthritis. In a meta-analysis of treatments for osteoarthritis, 129 trials (32,129 participants) were assessed in terms of pain-related outcomes. Naproxen, ibuprofen, diclofenac, IA HA, and IA corticosteroids were shown to be significantly statistically superior to acetaminophen, the only agent that did not meet criteria for clinically significant improvement in pain. Seventy-six trials (24,059 participants) were included in the analysis of physical function outcomes; only IA corticosteroids were not statistically significantly superior to oral placebo. Naproxen, ibuprofen, diclofenac, and celecoxib showed greater statistical significance than did acetaminophen. Fifty-five trials (18,267 participants) were analyzed regarding stiffness outcomes. Naproxen, ibuprofen, diclofenac, and celecoxib showed statistically significant improvement over oral placebo and acetaminophen. Acetaminophen was the only agent that showed no clinically significant improvement from baseline.²¹

The benefits of prescription-dosage agents for long-term

use have been established.²¹ In a study of osteoarthritis of the hand, researchers noted that naproxen, which provides the least cardiovascular risk among NSAIDs, may be a beneficial component to pain management. Still, the optimal NSAID likely differs for the individual patient, as these agents have effects on multiple sites as well as both peripheral and central pathways associated with analgesia. It is possible that NSAIDs offer potential benefits for treatment of inflammation associated with various conditions.²²

The effects of dosage escalation also provide important information that may help clinicians individualize treatment. Among agents available in OTC formulations, a significant linear dose effect in treatment was significant only for naproxen, based on a review of 8973 manuscripts, including 76 randomized trials and a total of 58,451 patients.²³

NSAIDS AND ACETAMINOPHEN AT OTC DOSES FOR PAIN RELIEF

These analgesics have also been studied in low-dosage formulations for a variety of conditions.

Osteoarthritis

Studies involving low-dosage OTC formulations provide guidance for clinicians in helping to aid patient selection of pain relief products, as noted in the studies summarized below.

The specific effects of OTC NSAIDs on pain and function were evaluated in a recent post hoc pooled analysis (n = 818). Patients 65 years or younger received naproxen, 660 mg/d. A separate subgroup analysis assessed older patients who received a lower dosage of naproxen (440 mg/d). Compared with placebo, the use of naproxen provided significant improvements in pain and physical function ($P < .05$); efficacy was similar among both younger and older patients. Both investigators and patients rated treatment as "good" to "excellent" significantly more often ($P < .001$).²⁴

Benefits of NSAIDs, including OTC formulations when possible, were also reported in long-term clinical and economic evaluations of patients with osteoarthritis and cardiovascular disease and diabetes. In patients with multiple comorbidities, regimens that included naproxen and ibuprofen were more effective and cost-effective in managing pain than were opioids, celecoxib, or pharmacotherapeutic standard-of-care acetaminophen and corticosteroid injection.²⁵

Multicenter, randomized, double-blind, placebo-controlled trials compared the analgesic efficacy and safety of nonprescription dosages of naproxen, ibuprofen, and placebo in patients with osteoarthritis of the knee. A total of 444 patients were randomized—all for 7 days—to a daily dosage of naproxen sodium, 660 mg; naproxen sodium,

440 mg (patients ≥ 65 years); ibuprofen, 1200 mg; or placebo. Naproxen (440 mg and 660 mg) and ibuprofen were clinically effective at relieving pain compared with placebo, and reduced the mean symptom score by 30% to 45%. Compared with placebo, naproxen (440 mg and 660 mg) significantly improved all 7 symptoms from baseline, and ibuprofen significantly improved 5 symptoms. For patients ≥ 65 years ($n = 183$), naproxen, 440 mg, showed significant superiority in comparison with placebo for all symptoms other than pain on weight-bearing; ibuprofen showed a significant reduction only in day pain. No significant differences in adverse event reporting were noted among groups.²⁶

Acute muscle soreness

OTC formulations are commonly used for relief of acute muscle soreness, a common complaint among consumers. In a study, OTC naproxen, 220 mg for 3 days, was administered to patients who underwent a series of exercises consisting of knee extensions designed to produce muscle soreness and strength loss associated with exercise. Three days after exercise, participants in the placebo group experienced more loss of concentric ($P < .0064$) and isometric ($P = .0213$) strength and greater thigh soreness when rising from a seated position ($P < .0393$). Investigators concluded that naproxen is likely to protect muscle strength and function during early stages of increased physical activity, with less muscle injury and soreness.²⁷ Other investigators have reported similar results.²⁸ It has been suggested that naproxen improves recovery by attenuating expression of the inflammatory response to muscle injury.²⁹ High dosages of ibuprofen have shown similar efficacy; however, moderate dosages have not been shown to alleviate soreness.³⁰

Pain relief following dental procedures

Multiple NSAIDs and acetaminophen have demonstrated efficacy in addressing pain associated with dental procedures. Both OTC and prescription formulations are commonly used to relieve pain. The efficacy of OTC products—along with the efficacy of opioids and prescription NSAIDs—for pain management was assessed in a survey completed by 2765 patients. At 5-day follow-up after a variety of procedures associated with significant pain, both OTC and prescribed NSAIDs demonstrated relief sufficient to manage most postoperative dental pain.³¹

In a study, lower-dosage naproxen submicron particle capsules provided effective analgesia in acute postsurgical dental pain; the authors propose additional studies to assess the utility of this agent as a treatment for other acute pain conditions.³² In a double-blind randomized study ($n = 41$), patients evaluated the efficacy of naproxen gel for relief of

pain resulting from the placement of orthodontic elastic separators. Naproxen was associated with significantly lower mean pain scores at all time points ($P < .001$), compared with placebo.³³

Ibuprofen has also been shown to effectively manage dental pain after removal of the third molar, with administration every 4 to 6 hours. For more severe pain, a combination of 400 to 600 mg ibuprofen with 500 mg acetaminophen, every 6 hours for 24 hours, has been recommended.³⁴ Acetaminophen has been shown to decrease swelling after oral surgery.³⁵

Postoperative pain

The effect of NSAIDs has also been evaluated in multiple studies for postoperative pain. In 9 studies ($n = 784$), naproxen sodium 550 mg (equivalent to 500 mg naproxen) demonstrated that the number needed to treat was 2.7 (95% confidence interval, [CI] 2.3-3.2) for at least 50% pain relief over 4 to 6 hours. The authors concluded that oral administration of naproxen at dosages in the range of 400 mg and 500 mg provided effective analgesia for adults who experience moderate-to-severe postoperative pain.³⁶

Pain associated with headache

NSAIDs provide relief from headache. Ibuprofen has been shown to provide relief from acute migraine in about one half of affected patients, but providing *complete* relief from pain and associated symptoms for a minority. For all efficacy outcomes, the number needed to treat was better with 400 mg than with 200 mg, compared with placebo. More rapid pain relief was seen with the use of soluble formulations.³⁷

Naproxen has been compared with sumatriptan for both initial and recurrent migraine attacks. It has been suggested that naproxen may be useful in combination with sumatriptan for patients with unrelieved recurrent headache because this strategy has been shown to provide more pain relief than either agent alone when used for the initial treatment of acute migraine.³⁸ It may also be useful to add an oral anti-emetic dopamine antagonist to naproxen.³⁸ Clinicians who are called on to decide which medication to prescribe for headache recurrence should be guided by considerations that include cost, contraindications, side effects, and the patient's overall previous experience with the medication.³⁸

Pain associated with dysmenorrhea

Primary dysmenorrhea generally begins within 2 years after onset of menstruation, with symptoms that include low backache, nausea and vomiting, headache, and diarrhea.³⁹ Dysmenorrhea results from withdrawal of progesterone, which activates the COX-2 enzyme and decreases hydroxyprosta-

glandin dehydrogenase. The resulting increased secretion of prostaglandins leads to increased strength of uterine contractions and pain.⁴⁰ NSAIDs are widely used to relieve pain and are significantly more effective than placebo (odds ratio, 7.91; 95% CI, 5.65-11.09). Little evidence suggests superiority of individual NSAIDs, although NSAIDs provide greater pain relief than acetaminophen.³⁹

CONCLUSIONS

Clearly, NSAIDs and acetaminophen differ significantly regarding their utility in managing specific pain conditions. Correct dosing is likely to be important for the individual patient who has difficulty remembering to take medication on schedule or for whom only short-term pain relief is required. Similarly, duration of effect may guide the clinician's and patient's decision-making. However, data clearly show that these agents are effective and safe when used correctly in patients without contraindications. They provide a low-cost option for patients and help empower them to participate in their care and discuss options and treatment goals with their clinicians. ●

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Approaches to Increase Colorectal Cancer Screening Rates: Key Information for the Primary Care Provider

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INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer diagnosed in the United States and, despite its potential for early detection, remains the second most common cause of oncology-related deaths for US men and women combined.¹ An estimated 140,250 patients will be newly diagnosed in 2018, and 50,630 CRC-related deaths will occur.¹ The incidence of and mortality related to CRC are greater in men than women, and CRC affects more non-Hispanic blacks than non-Hispanic whites (males: 56.4 vs 45.2 per 100,000, respectively; females: 41.7 vs 34.5 per 100,000, respectively).² Risk for CRC increases with age, as adults aged 65 to 74 years are most commonly diagnosed.³ Moreover, risk increases in individuals with a family history of CRC (1.9-fold) or inflammatory bowel disease (2.9-fold).⁴ Regardless of risk, screening has improved early detection rates and reduced CRC-related mortality.⁵ Additionally, screening can detect adenomatous polyps and villous adenomas, with malignancy rates of 34.5% for patients with severe atypia, and 48.0% for those with severe atypia and polyp size >2 cm.⁶⁻⁸ Discovery of adenomatous polyps and villous adenomas is key for detecting early-stage CRC, when the potential to treat and cure the disease is greatest.⁵ Five-year survival rates are high with localized disease

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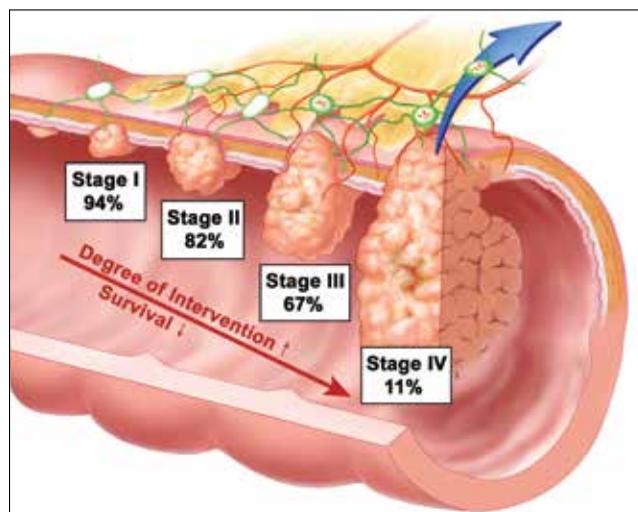
Dr. Mackey was involved with the concept and design of the manuscript, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approved the final draft for submission.

(stage I, 93.9%), but decrease as CRC spreads to lymph nodes and metastasizes (stage IV, 11.4%; **FIGURE 1**).^{9,10} Consequently, encouraging screening for early detection of polyps and localized cancers is an important role for primary care providers.

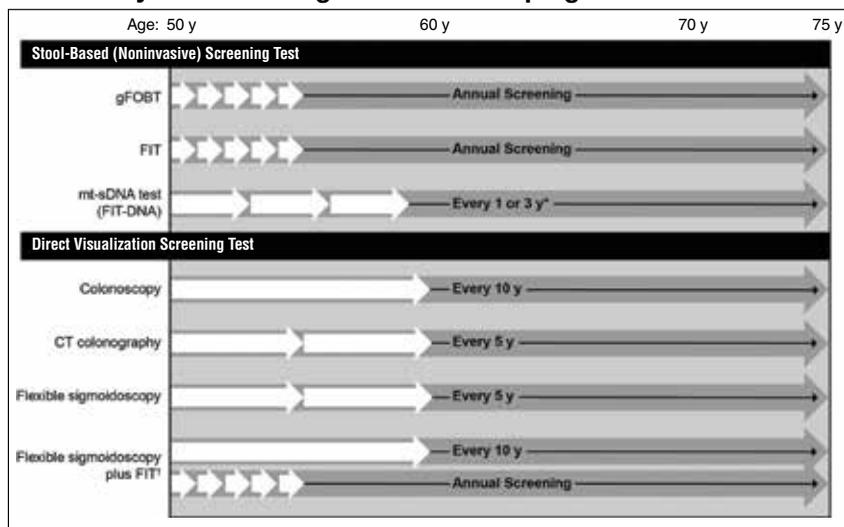
COLORECTAL CANCER SCREENING

The importance of screening to detect and diagnose early-stage CRC,^{11,12} as well as the favorable effect of screening on CRC-related mortality, has been established.¹³ In the United States, CRC-related mortality decreased 51%, from 28.6 to 14.1 per 100,000, from 1976 to 2014, in part related to a 14% decrease attributed to screening.^{14,15} However, according to the findings of a national survey-based study, in 2012, only 65.1% of individuals 50 to 75 years of age in the United States were current with CRC screening recommendations, and 27.7% of individuals had never been screened.¹⁶ In one study (N=9437 diagnoses), screening resulted in the diagnosis of a significantly greater percentage of early-stage CRC diagnoses (stages I and II) than late-stage CRC (stages III and IV; 66.7% vs 39.8%, respectively; $P<.001$).¹¹ A second study (N=1129 patients) reported similar findings, with a significantly greater percentage of CRCs detected in the early stage due to screening versus symptom-based detection (67% vs 45%, respectively; $P<.001$).¹² Screening colonoscopy and guaiac-based fecal occult blood testing (gFOBT) significantly decreased the risk of CRC-related mortality versus symptom-based detection (colonoscopy: hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.21-0.60; gFOBT: HR, 0.47; 95% CI, 0.29-0.77).¹⁷ A 15% reduction in the US incidence of CRC from 2007 to 2020 could save lives (~150,000 life-years saved) and result in a lifetime health care cost savings of approximately \$624 million (2013 dollars).¹⁸ Further, achieving a screening rate of 80% by 2018 in adults aged ≥ 50 years in the United States is projected to result in an estimated 43,000 fewer cases per year by 2030, with a mortality decrease by 203,000 total deaths from 2013 to 2030.¹⁹

For asymptomatic adults aged 50 to 75 years at average risk for CRC, the US Preventive Services Task Force (USPSTF) and American Cancer Society (ACS) clinical practice guidelines recommend routine screening using one of a number

FIGURE 1 Colorectal cancer stages and 5-year survival rates^{9,10}

Adapted from © 2005 Terese Winslow LLC

FIGURE 2 Summary of ACS and USPSTF guideline recommendations for CRC screening for individuals between ages 50 and 75 years at average risk of developing CRC^{3,20}

Abbreviations: ACS, American Cancer Society; CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test; FIT-DNA, fecal immunochemical test-multi-target stool DNA test; gFOBT, guaiac fecal occult blood test; mt-sDNA, multi-target stool DNA; USPSTF, US Preventive Services Task Force.

*Guideline recommendations differ between ACS and USPSTF.

[†]Screening option according to USPSTF, but not ACS.

Adapted from American Cancer Society CRC screening guidelines and Bibbins-Domingo et al.

of stool-based and direct visualization tests (FIGURE 2).^{3,20} The USPSTF guidelines state there is no empirical data to support one screening method over another and, therefore, do not recommend a specific modality.³ Rather, the USPSTF considers

CRC screening for patients aged 50 to 75 years to be an “A” rated process and emphasized choice through shared decision-making, with the goal of increasing the number of individuals who undergo CRC screening.³ Routine screening is appropriate for adults considered healthy enough to undergo treatment if CRC is detected and without comorbidities limiting life expectancy.³ The risk of developing CRC is increased in individuals with a personal or family history of CRC or polyps, a personal history of ulcerative colitis or Crohn’s disease, or a family history of a hereditary CRC syndrome (eg, familial adenomatous polyposis).^{3,20} With that in mind, these individuals may need to initiate screening before age 50 years and/or may require more frequent screening, depending on the specific risk-related factor(s).²⁰

As noted in clinical practice guidelines, several stool-based (noninvasive) and direct visualization methods can be used to accurately detect polyps and early-stage CRC during routine screening (TABLE 1^{3,21-29}). Given detection considerations (eg, polyps and early-stage cancer may only bleed

intermittently),³⁰ guidelines recommend stool-based testing be performed at more frequent intervals than direct visualization methods.^{3,20} A positive result with any stool-based test requires follow-up diagnostic colonoscopy.³ The harms associated with stool-based testing are minimal and primarily result from adverse events related to the diagnostic colonoscopy procedure following a positive stool-based test.³¹ Annual screening using gFOBT, which detects the presence of the heme portion of human hemoglobin in stool,^{32,33} is convenient because 3 stool samples can be collected at home without bowel preparation prior to sample collection.^{3,30} However, dietary and medication restrictions are associated with gFOBT.³⁴ gFOBT was shown to be associated with a 32% decrease in CRC-related mortality compared with no screening (relative risk [RR], 0.68; 95% CI, 0.56-0.82).¹³ The sensitivity of gFOBT for the detection of serrated (pre-malignant) polyps or advanced CRC was low (2.6% and 7.4%, respectively; TABLE 2^{21,35-39}), while specificity was high (98.4% and 98.6%).³⁷ In one study

(N=997 patients), the percentage of patients adherent to CRC screening with annual gFOBT (n=344) over a 3-year period decreased over time, from 67% in year 1 to 27% and 14% in years 2 and 3, respectively.⁴⁰ Similarly, 46.6% of individuals in

TABLE 1 Characteristics of CRC screening methods^{3,21-29}

Parameter	Stool-based (noninvasive) tests					Direct visualization tests			
	gFOBT	FIT	mt-sDNA test	Colonoscopy	CT colonography	Flexible sigmoidoscopy	Flexible sigmoidoscopy with FIT		
Advantages	In-home testing No bowel preparation or sedation required	In-home testing No bowel preparation or sedation required Single stool sample collection No dietary or medication restrictions	In-home testing No bowel preparation or sedation required Single stool sample collection No dietary or medication restrictions Screens for altered DNA biomarkers in stool Embedded patient compliance program Greatest benefits to harms ratio (vs other modalities)	Entire colon examined by imaging Less frequent screening requirement Biopsy or polyp removal during same procedure	Less invasive vs colonoscopy Lower volumes of bowel preparation vs colonoscopy required No sedation required Lower rate of procedural complications vs colonoscopy Detection of extracolonic abnormalities	Less invasive vs colonoscopy Complete bowel preparation not required (eg, enemas) No sedation required Low rate of complications	Less invasive vs colonoscopy Encompasses both stool-based and direct visualization tests		
Disadvantages	Lower sensitivity than mt-sDNA Serial stool sample collection Potential inability to detect carcinomas with little to no bleeding Requires dietary and possible drug administration restrictions prior to testing Lower specificity than FIT Positive findings require diagnostic colonoscopy	Lower sensitivity than mt-sDNA Positive findings require diagnostic colonoscopy Potential inability to detect carcinomas with little to no bleeding	Lower specificity than FIT Positive findings require diagnostic colonoscopy	Bowel preparation and sedation required Potential adverse effects related to bowel preparation, sedation, or procedure Physician skill dependent Patient time requirement (bowel preparation and test) Test performed at health care facility Patient requires transportation home after procedure	Bowel preparation required Requires insufflation* Decreased sensitivity vs colonoscopy for polyp detection Physician skill dependent Patient time requirement (bowel preparation and test) Test performed at health care facility Positive findings require diagnostic colonoscopy Radiation exposure	Restricted to distal colon (lower half) Patient time requirement (bowel preparation and test) Test performed at health care facility Positive findings require diagnostic colonoscopy	Requires 2-step completion by patient (including annual FIT) Patient time requirement (bowel preparation and test) Test performed at health care facility Positive findings require diagnostic colonoscopy		
Adherence or compliance with screening†	—	Adherence FIT vs gFOBT: RR, 1.2 (95% CI: 1.03-1.3)	Compliance 88.3%	Adherence colonoscopy vs gFOBT/FIT: RR, 0.6 (95% CI, 0.4-0.8)	—	—	Adherence flexible sigmoidoscopy plus gFOBT/FIT vs gFOBT/FIT: RR, 0.6 (95% CI, 0.4-0.9)		
Abbreviations: CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; mt-sDNA, multi-target stool DNA; RR, relative risk. *Defined as colonic distension with air or carbon dioxide. †Data presented limited to meta-analysis ²⁷ or study of single screening modality (mt-sDNA). ²⁸	Adherence endoscopy vs stool-based tests: RR, 0.7 (95% CI: 0.6-0.8) Adherence flexible sigmoidoscopy vs stool-based tests: RR, 0.8 (95% CI: 0.6-1.04)								

TABLE 2 Sensitivity of CRC screening methods*^{21,35-39}

Detection parameter	Stool-based (noninvasive) tests			Direct visualization tests			
	gFOBT	FIT	mt-sDNA test	Colonoscopy	CT colonography	Flexible sigmoidoscopy	Flexible sigmoidoscopy with FIT
Any CRC	61.5%-79.4% [¶]	73.8% [†] 62.3%-83.3% [¶]	92.3% [†]	93.1%-99.5% [¶]	75.6%-92.4% [¶]	37.6%	48.6%
Advanced CRC	7.4%	22.3% 15.1%-26.3% [†]	—	—	—	16.3%	31.7%
Advanced adenoma	—	23.8% [†] 20.8%-27% [#]	42.4% [†]	—	—	—	—
Adenoma ≥6 mm	—	—	—	92.3% 75%-93% ^{§,¶}	88.7% 73%-98% [§]	—	—
Adenoma ≥10 mm	17.7%-49.4% [#]	—	—	87.5% 89%-98% [§] 93.1%-99.5% [#]	93.8% 67%-94% [§] 75.6%-92.4% [#]	93.1%-95% [#]	—
Serrated (pre-malignant) polyps	2.6%	4.2%-5.2% [†]	—	—	—	—	—

Abbreviations: CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; mt-sDNA, multi-target stool DNA.

*Sensitivity comparison of method on top row vs method in left column.

[†] $P=.002$ (CRC) and $P<.001$ (advanced adenoma: includes sessile serrated [pre-malignant] polyps ≥ 1 cm) for mt-sDNA vs FIT.

[¶]Sensitivity of InSure FIT and OC FIT-CHEK.

[§]Based on meta-analysis data from 7 studies (CT colonography) or 4 studies (colonoscopy).³⁸

[#]Compared with CT colonography or colonoscopy plus CT colonography.³⁸

[¶]Based on simulation models incorporating multiple screening intervals, different ages at initiation of screening, and different ages at last screening.³⁹

a multicenter health care system returned for annual gFOBT testing, while 35.3% were inconsistent with annual screening and 18.1% did not return for repeat screening.³⁰

Annual fecal immunochemical testing (FIT), which utilizes antibodies to detect the presence of the globin portion of human hemoglobin in stool, may have comparable sensitivity with, but improved specificity for, detection of CRC compared with gFOBT.³² The pooled one-time sensitivity of FIT, determined from a single meta-analysis of FIT studies using colonoscopy as the reference standard, is 71%, with a specificity of 94%.⁴¹ In another study, FIT sensitivity for all stages of CRC was 74%, which decreased to 73% for stages I-III CRC, 46% for high-grade dysplasia, 24% for advanced adenomas measuring 1 cm or greater, and 5% for sessile serrated (flat, pre-malignant) polyps.²¹ Unlike gFOBT, FIT typically requires a single stool sample collected at home, without dietary or medication restrictions prior to sample collection; as with gFOBT, no bowel preparation is needed.^{3,30,34,42} In one study, FIT ($n=4662$) detected a significantly greater percentage of advanced neoplasias (ie, CRC or advanced adenoma) compared with gFOBT ($n=3236$; 0.8% vs 0.3%, respectively; $P=.003$).⁴³ Meta-analysis of 5 randomized studies found FIT detected advanced neoplasia (ie, CRC, or polyp ≥ 10 mm or

with high-grade dysplasia or villous component) and CRC with greater accuracy than gFOBT (advanced neoplasia: RR, 2.3; 95% CI, 1.7-3.1; CRC: RR, 2.0; 95% CI, 1.2-3.2) following adjustment for adherence to screening.²⁷ A meta-analysis of 5 studies demonstrated adherence to FIT was greater than to gFOBT (RR, 1.2; 95% CI, 1.03-1.3).²⁷ However, “real world” year-over-year adherence rates with FIT are often far less than 30%. In one study, only 0.3% of nearly 98,000 individuals were found to have completed 10 consecutive years of FIT testing.⁴⁴ Over a 3-year period, individuals eligible for CRC screening who received annual FIT kits by mail had greater screening completion rates compared with people receiving a screening recommendation during an outpatient visit with their provider (28.0% vs 10.7%, respectively).⁴⁵

In August 2014, the multi-target stool DNA (mt-sDNA) test, which analyzes 11 distinct molecular biomarkers from cells that shed into the intestinal tract to simultaneously detect epigenetic changes in DNA, specific DNA mutations, and human hemoglobin in stool, was introduced as a screening test for adults at average risk of developing CRC.^{21,46} mt-sDNA testing, which is performed at home, requires a single stool sample and no bowel preparation, has no dietary or medication restrictions, and has the greatest benefits-to-harms

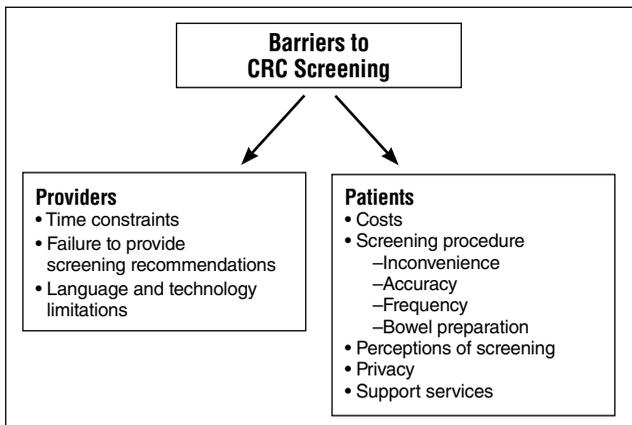
ratio of all CRC screening modalities.^{3,21,46} In asymptomatic individuals at average risk for developing CRC, Imperiale et al²¹ showed mt-sDNA testing had superior sensitivity for detecting CRC (any disease stage) and advanced adenomas versus FIT (CRC: 92.3% vs 73.8%, respectively, $P=.002$; advanced adenomas: 42.4% vs 23.8%, $P<.001$; **TABLE 2**).^{3,21,35-39} Results from Imperiale et al demonstrated false-positive rates of 13% and 8.5% for patients aged 50 to 84 years, and 50 to 64 years, respectively.²¹ For patients previously noncompliant with other screening modalities (ie, >10 years since last colonoscopy and/or >1 year since last gFOBT; N=393), 88.3% completed screening by mt-sDNA testing within 1 year.²⁸ An initial mt-sDNA rescreening interval of 3 years is included in nationally recognized guidelines from ACS²⁰; USPSTF guidelines recommend an interval of either 1 or 3 years.³ The Centers for Medicare and Medicaid Services has approved mt-sDNA reimbursement for a rescreening interval of 3 years.

Direct visualization screening methods include colonoscopy, computed tomography colonography (CTC), and flexible sigmoidoscopy with or without annual FIT. Direct visualization CRC screening modalities are considered more invasive than stool-based tests, typically require bowel preparation, medication and/or dietary changes, anesthesia and subsequent need for transportation following the procedure, time away from work and other responsibilities, and are performed at an outpatient health care facility or hospital.³ Colonoscopy allows for the visualization of the entire colon and rectum through a colonoscope.⁹ CTC, also referred to as virtual or CT colonoscopy, allows for detailed imaging of the entire colon and rectum by inflating the colon with air or carbon dioxide and running the patient through a CT scanner.^{9,47} The recommended CRC screening intervals for colonoscopy and CTC are 10 years and 5 years, respectively.^{3,20} Colonoscopy is the only CRC screening method in which polyps or masses can be identified and removed during the same procedure.⁴⁸⁻⁵⁰ Individuals decline direct visualization screening methods (colonoscopy or CTC; N=151) for a variety of reasons, including time constraints (24%), the belief that screening was unnecessary due to perceived good health (23%), required bowel preparation (8%), discomfort or embarrassment (7%), and concerns regarding complications (7%).⁴⁷ A randomized, controlled study of individuals eligible for CRC screening by colonoscopy (n=5,924) or CTC (n=2,920) found significantly more declined colonoscopy compared with CTC (13% vs 7%, respectively; $P<.001$).⁵¹ The most common reasons cited for declining screening by colonoscopy or CTC included “unpleasantness” of the screening modality (66% vs 30%, respectively; $P<.001$), inconvenience of the test preparation (34% vs 18%; $P<.001$), perception of screening as unnecessary due to lack of symptoms (23% vs 32%; $P=.01$), and time

constraints (14% vs 20%; $P=.04$).⁵¹ Colonoscopy adherence rates at 1 and 3 years have been reported to be 38.2%⁵² and 38.4%⁴⁵, respectively.

In asymptomatic individuals, the sensitivity of CTC to detect adenomas ≥ 6 mm was 88.7%, which was lower than colonoscopy (92.3%; **TABLE 2**).^{21,35-39} However, the sensitivity of CTC to detect large-sized polyps (ie, ≥ 10 mm) was greater than that of colonoscopy (93.8% vs 87.5%, respectively).³⁶ No high-quality studies have validated the sensitivity and specificity of colonoscopy. Colonoscopy and CTC are associated with operator-dependent factors that can affect the quality of the procedure and, in some cases, potentially harm the patient.^{38,48} Factors associated with oversight of polyps during colonoscopy include poor bowel preparation and/or endoscopist training and experience.⁴⁸ Additional considerations specific to CTC include extracolonic findings leading to unnecessary testing and anxiety, and exposure to ionizing radiation during the procedure.^{25,38,49} Meta-analysis of asymptomatic or screening populations showed patients undergoing colonoscopy are at low risk for perforations (n=26 studies; 4 in 10,000 procedures) or major bleeding (n=22 studies; 8 in 10,000 procedures); 36% of perforations and 96% of cases of major bleeding occurred during polyp removal (n=8 studies).³⁸ Similarly, meta-analysis of 11 studies showed the rate of perforation in asymptomatic individuals was low (0.02%; n=6 studies) with CTC; the rate of perforation due to insufflation was 0.03% (n=7 studies).⁵³

Flexible sigmoidoscopy is not commonly used as a CRC screening test in the United States.⁵⁴ Flexible sigmoidoscopy involves endoscopic examination of the distal colon following cleansing by enema⁴⁹ and may not detect polyps and CRC localized to the proximal colon. The limitations of flexible sigmoidoscopy were confirmed in an analysis of US cancer registry data showing CRC occurred more often in the right side (proximal) than the left (distal) side of the colon (43.5% vs 37.7%, respectively).⁵⁵ The overall CRC sensitivity of flexible sigmoidoscopy is limited, but is generally assumed to be comparable to that of colonoscopy for distal colon examination. In one study, 17% of undetected lesions were beyond the reach of flexible sigmoidoscopy.⁵⁶ If the medical professional finds a lesion greater than 1 cm during flexible sigmoidoscopy examination, the patient will need to follow up with a colonoscopic polypectomy to have the lesion removed.^{3,56} Current USPSTF and ACS guidelines recommend screening of asymptomatic individuals in the United States every 5 years when using flexible sigmoidoscopy.^{3,20} Flexible sigmoidoscopy every 10 years, combined with annual FIT, is recommended in USPSTF guidelines (**FIGURE 2**) and demonstrated increased sensitivity for detecting advanced neoplasia or any CRC compared with either screening method alone (**TABLE 2**).^{21,35-39,57}

FIGURE 3 Potential barriers to CRC screening^{28,60-67}

Abbreviation: CRC, colorectal cancer.

The digital rectal exam is not recommended for CRC screening, as testing is limited to the lower rectum.²⁰ Further, any stool found during a digital rectal exam should not be screened for CRC by gFOBT or FIT.²⁰ Recently, the Septin 9 serum assay was approved by the US Food and Drug Administration for the screening of adults aged ≥ 50 years who have been offered, but not completed, CRC screening.⁵⁸ However, current ACS and USPSTF guidelines do not include mention of the Septin serum assay.^{20,59}

POTENTIAL BARRIERS TO CRC SCREENING

Potential barriers to CRC screening include issues relevant to patients and providers (FIGURE 3).^{28,60-67} Prior to implementation of the Affordable Care Act (ACA) in 2010, individuals with coverage through private insurers or Medicare were responsible for a portion of screening-related costs, a potential impediment to CRC screening.⁶⁸ The ACA provides individuals access to preventive care, including CRC screening, with no out-of-pocket costs.⁶⁹ It is unclear if the need for a follow-up diagnostic colonoscopy following a positive stool-based screening test, which may be associated with out-of-pocket costs, is a barrier to CRC screening.⁷⁰

Surprisingly, after ACA implementation, the elimination of cost sharing did not increase the uptake of CRC screening among individuals with private insurance or Medicare (2009 to 2011/2012).⁷¹ Similarly, analysis of a sample of Medicare beneficiaries showed colonoscopy use for CRC screening was unchanged or decreased following ACA implementation compared with the prior 2 years.^{70,72} However, National Health Interview Survey data showed a significant increase in the percentage of adults aged 50 to 75 years undergoing CRC screening from 2008 to 2013 (57.3% to 61.2%; $P < .001$).⁶⁸ Notable increases in CRC screening occurred in individuals classified as low-income ($< \$35,000$ annual household income;

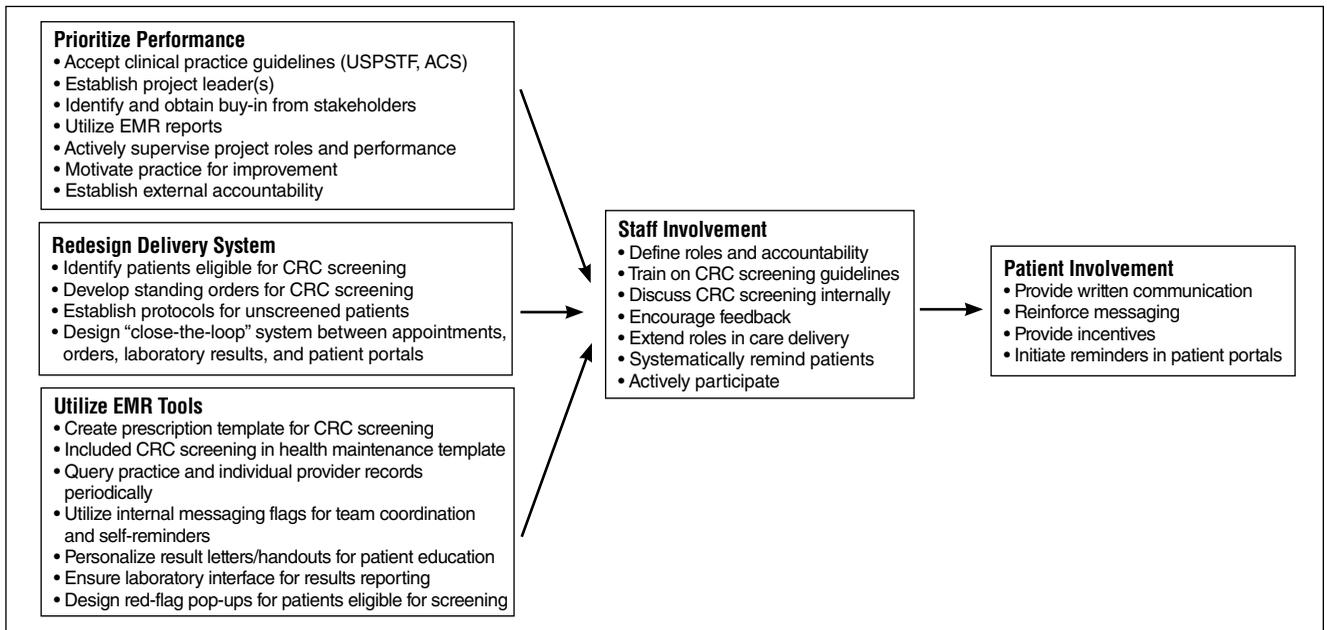
4.3% increase; $P = .02$) and middle-income ($\$35,000$ to $< \$75,000$ annual household income; 3.5% increase; $P = .04$), and in adults with Medicare coverage (9.8% increase; $P < .001$) and Medicare plus private insurance (5.9% increase; $P = .002$); 61.8% of adults included in the dataset were covered by private insurance.⁶⁸ Thus, elimination of patient economic barriers is one factor of importance for increasing CRC screening in some individuals.⁶⁸

For some patients, the invasive nature of a colonoscopy presents a significant barrier. Data suggest there are 2 distinct groups: individuals who prefer colonoscopy and individuals who prefer noninvasive (stool-based) testing.³⁴ Another potential barrier is the role of patient perceptions, as 80.6% of 175 providers surveyed “sometimes” or “usually” encountered individuals unaware of the seriousness of CRC.⁷³ Additional barriers for individuals eligible for CRC screening include issues regarding privacy, inconvenience of testing, concerns with accuracy of testing, frequency of screening required, bowel preparation requirements, invasiveness of testing, and availability of patient support services.^{28,61,62}

Primary care providers play an important role in preventive screening.⁷⁴ In one study, individuals with ≥ 1 primary care visit in 1 year were more likely to have completed CRC screening compared with patients with no annual provider contact (63.1% vs 42.2%, respectively; odds ratio [OR], 2.3; 95% CI, 2.3-2.4).⁷⁵ The substantial demand on a provider’s time may also play a role in the stagnant rates of CRC screening in the United States; providers would have to work an estimated 21.7 hours per day to address all acute and chronic disease and preventive care guideline recommendations.⁶⁷ Provider time constraints are anticipated to increase as a result of expanded health care access through the ACA; thus, the role of nurse practitioners and physician assistants in preventive care, including CRC screening, is likely to expand.⁷⁶

Shared decision-making regarding CRC screening methods is an important factor in adherence.⁵² In a 2016 longitudinal study of more than 150,000 eligible adults older than 50 years of age, one-third failed to adhere to current USPSTF CRC screening recommendations over a 10-year period, whether they underwent colonoscopy, flexible sigmoidoscopy, FIT, or gFOBT.⁴⁴ However, in one study, individuals 50 to 79 years of age at average risk of developing CRC were significantly more likely to adhere to screening when permitted to choose the method (eg, colonoscopy, gFOBT) compared with individuals recommended colonoscopy only (68.8% vs 38.2%, respectively; $P < .001$).⁵² Barriers primary care providers may encounter in shared decision making include language^{65,66} and technological limitations, as some patients lack internet access or the skills required to navigate internet-based educational tools.^{66,77}

Increasing screening rates with stool-based testing may require increased patient navigation. In a study of eligible

FIGURE 4 Suggestions for improvements to CRC screening processes in primary care

Abbreviations: ACS, American Cancer Society; CRC, colorectal cancer; EMR, electronic medical record; USPSTF, US Preventive Services Task Force.

individuals randomly assigned to receive usual care (ie, screening method recommended during outpatient visit; $n=1199$), reminder mailings for colonoscopy ($n=2400$), or FIT kits sent by mail annually ($n=2400$), outreach led to greater screening completion rates versus usual care over a 3-year period (colonoscopy, 38.4% and annual FIT, 28.0%, vs usual care, 10.7%).⁴⁵ However, a greater percentage of individuals in the colonoscopy group never initiated screening compared with the FIT group (44.0% vs 30.2%, respectively).⁴⁵ These findings are consistent with data from another study, in which only 25.5% of 2010 individuals receiving FIT kits in the mail completed testing; patients were 50% more likely to complete FIT testing when reminded by a live phone call compared with a mailed letter.⁷⁸

However, while adherence rates for stool-based CRC screening may be low in some studies,^{30,40} results of a meta-analysis indicated direct visualization screening tests had significantly lower adherence rates than stool-based testing (RR, 0.67; 95% CI, 0.56-0.80; **TABLE 1**).^{3,21-28} Thus, while USPSTF guidelines do not recommend one screening modality over another,³ stool-based (noninvasive) screening methods may be an option for patients who are nonadherent to direct visualization methods or indicate a preference for noninvasive testing modalities.

SUGGESTED PRACTICE IMPROVEMENTS FOR CRC SCREENING

Practice improvements to ensure CRC screening adherence for eligible individuals requires a team effort.⁷⁹ Higher CRC

screening rates have been associated with a number of practice improvement programs, such as engaging patients in shared decision-making and targeting interventions to specific groups.^{79,80} Indeed, practices with a commitment to CRC screening, including use of a script, have been shown to have significantly greater screening rates compared with practices less dedicated to providing CRC screening (57.2% vs 27.6%, respectively; $P<.001$).⁸⁰

Common threads across successful programs include prioritizing CRC screening performance, redesigning the care delivery system, utilizing electronic medical record tools, involving all clinic staff, and engaging patients (**FIGURE 4**). Clinic staff should have defined roles, with accountability, in the process of improving CRC screening rates. Utilizing the medical assistant to review patients' CRC screening status increased the monthly referral rate for colonoscopy by 85% (from 6.0% to 11.1%) at a regional network of 7 community clinics in 2005.⁸¹ At one community practice, CRC screening rates increased from 28% to 80% during a 2-year period, following reevaluation of testing used (eg, replacing gFOBT with FIT) and a redesign of the primary care team (eg, expanding the role of the medical assistant to include obtaining CRC screening status from patients, increasing outreach efforts).⁸² In a single Veteran's Administration health care system (ie, multiple primary care clinics, hospital), replacing gFOBT with FIT resulted in a significantly greater percentage of patients completing testing (FIT, 42.6%; gFOBT, 33.4%; $P<.001$), which suggests that minor changes in processes, including changes

to more convenient methods of stool-based (noninvasive) testing, are effective in improving CRC screening rates.⁴³

Patient care delivery system redesign may be needed to increase CRC screening rates, including determining individuals eligible for CRC screening prior to scheduled appointments, empowering clinic staff with standing orders, and establishing protocols for individuals who are nonadherent to CRC screening. For direct visualization screening, primary care clinic and specialty practice coordination may need to be implemented to ensure timely follow-up with individuals who miss testing or need assistance coordinating medications in advance of screening (eg, patients with diabetes).⁸³ Further, close coordination between the primary care provider and specialist can help improve scheduling, bowel preparation, and adherence with follow-up procedures.⁸³ While not yet documented in the literature, according to Curtis Gattis (Founder and CEO, LeadingReach, Austin, TX; written communication April 24, 2018, unreferenced), adoption of referral management software may improve accountability on both sides of the referral. By tracking and monitoring compliance, referral software can highlight at-risk patients not completing screening. Such simple but effective solutions help both primary care providers and large hospital systems to streamline referral relationships and processes, leading to better compliance and adherence to CRC screening guidelines.

Survey data indicate providers consider alerts in the electronic medical records database to be “somewhat” or “very” helpful interventions for support staff (93.7%; n=174 respondents) and providers (87.9%; n=174).⁷³ Additionally, generating a daily list of individuals eligible for CRC screening has been helpful for increasing screening rates (77.7%; n=175).⁷³ Periodic review of patients’ electronic medical records (eg, every 6 months) may be used to identify individuals eligible for CRC screening based on age or family history of CRC. Additionally, inclusion of all guideline-recommended screening modalities in the health maintenance template could increase CRC screening rates.

Finally, outreach efforts to engage patients in CRC screening by initiating contact through mail, phone, emails, or patient portals have the potential to increase CRC screening rates. Upon arrival at the clinic, patients could be greeted with educational information related to CRC screening methods. However, some individuals might appreciate further discussion with their provider regarding CRC screening.⁶² Reinforcing the importance of regular CRC screening with posters or written information is another suggestion for improving screening rates. At one health center, efforts to improve the convenience of CRC screening included mailing a FIT kit around the time of the patient’s birthday and providing at-home screening kits when individuals arrived for other clinic visits (eg, flu shots).³⁰

The mt-sDNA test is currently the only USPSTF-recommended screening modality offering a patient compliance program and a multilingual (ie, 70 languages), US-based 24/7 customer support call center to address questions from patients and providers.²⁹ The patient compliance program proactively establishes contact before the test is shipped to a patient’s home and continues communication via a series of phone calls and mailings to encourage completion of testing.²⁹ Thus, improving uptake of CRC screening in primary care will involve participation across the entire health care continuum.

CONCLUSIONS

Colorectal cancer is a leading cause of cancer-related deaths in the United States, yet approximately one-third of individuals eligible for CRC screening remain unscreened according to recommended clinical practice guidelines. For individuals at average risk for developing CRC, guidelines recommend screenings begin at age 50 years. Providers and patients are encouraged to use shared decision-making to choose a patient’s preferred CRC screening option, ranging from noninvasive, convenient, at-home stool-based testing (eg, mt-sDNA, FIT, gFOBt) to more invasive, direct visualization methods (eg, colonoscopy, CTC), as screening by any modality is better than no screening at all. Practice improvements have been shown to increase uptake of CRC screening in clinical settings and may include replacing one method of screening with another or redesigning the patient care delivery system to increase CRC screening rates. Regardless of the screening modality used, there is a need to improve CRC screening rates in the general population by improving patient adherence to guideline recommendations and to continue to reduce CRC-related morbidity and mortality. ●

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